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Take it or leave it: prefrontal control in recreational cocaine users

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Abstract

Though stimulant drugs such as cocaine are considered highly addictive, some individuals report recreational use over long periods without developing dependence. Difficulties in response inhibition have been hypothesized to contribute to dependence, but previous studies investigating response inhibition in recreational cocaine users have reported conflicting results.

Performance on a stop-signal task was examined in 24 recreational cocaine users and 32 healthy non-drug using control participants matched for age, gender and verbal intelligence during functional magnetic resonance imaging (fMRI) scanning. The two groups were further matched on traumatic childhood histories and the absence of family histories of addiction. Results revealed that recreational cocaine users did not significantly differ from controls on any index of task performance, including response execution and stop-signal reaction time, with the latter averaging 198 milliseconds in both groups. Functional MRI analyses indicated that, compared with controls, stopping in the recreational users was associated with increased activation in the pre-supplementary motor area but not the right inferior frontal cortex. Thus, findings imply intact response inhibition abilities in recreational cocaine users, though the distinct pattern of accompanying activation suggest increased recruitment of brain areas implicated in response inhibition. This increased recruitment could be attributed to compensatory mechanisms that enable preserved cognitive control in this group, possibly relating to their hypothetical resilience to stimulant drug dependence. Such over-activation, alternatively, may be attributable to prolonged cocaine use leading to neuroplastic adaptations.

Key words: stimulant dependence, stop-signal, cognitive control; recreational cocaine use, fMRI

Introduction

Use and abuse of cocaine is considered a major public health issue with prevalence estimates ranging from 14 to 21 million globally ¹. Hallmarks of cocaine dependence include lack of control underlying the compulsive persistence in drug-taking with larger amounts consumed for longer than intended, despite adverse personal and social consequences ². Cognitive control involves elements of both self- and emotion-regulation, as well as top-down intentional suppression of maladaptive actions and responses. Poor cognitive control likely contributes to multiple aspects of drug abuse, including initial usage and escalation to dependence, and subsequent maintenance ³. Stimulant-dependent individuals exhibit behavioral impairments in self-control and inhibition often accompanied by decreased or ineffective prefrontal cortical recruitment ^{4,5}. Moreover, the fronto-striatal systems affected by cocaine use ⁶ and compromised in chronic drug users overlap considerably with those mediating cognitive control and executive functioning in healthy individuals ³.

A commonly held view suggests that along with ongoing cocaine use, its reinforcing nature leads to eventual escalation of intake ⁷. Nevertheless, intact or even enhanced control may enable some individuals to regulate cocaine use, enabling them to curtail such escalation. Cognitive control could thus be important in allowing those individuals who engage in prolonged occasional use to escape transition to abuse and dependence. These recreational cocaine users fail to satisfy the criteria for cocaine dependence or abuse and do not seek treatment. There is indeed some evidence that cognitive control may not be impaired in some recreational users, especially socially integrated consumers who use the drug infrequently, in small amounts, and typically in social contexts ⁸. These individuals appear to differ substantially from cocaine dependent users, not only in their tightly regulated patterns of use ⁹, but also in their apparent absence of psychological or physiological signs associated with cocaine abuse ¹⁰. Their anecdotal ability to prioritize work or school above drug taking

suggests they may have enhanced capacities for self-control and future planning even compared to the general population.

Another likely factor at play in recreational users is their apparent lack of vulnerability factors characterizing stimulant-dependent individuals such as early life trauma, increased impulsivity and compulsivity, and early drug exposure⁸. This is consistent with evidence that patterns of use and the effects of stimulants may interact extensively with pre-existing individual genetic and psychosocial characteristics¹¹. Therefore, individual traits and early environment together with intact, or even enhanced, cognitive control may curb the transition to dependence. By investigating recreational cocaine users, better identification of those likely to transition to dependence can be achieved, allowing for more effective risk markers and interventions. Examining those who do not transition can also elucidate the mechanisms of resilience and compensatory processes to the aversive effects of cocaine. Moreover, such research could offer evidence regarding the cognitive effects of protracted cocaine in humans, as these remain controversial^{12, 13}.

One key aspect of cognitive control is response inhibition, or the ability to intentionally stop planned or ongoing actions when they are no longer appropriate. Difficulties in stopping are believed to contribute to impulsivity, a construct tightly linked with maladaptive cocaine use¹⁴. The ability to stop and not escalate stimulant drug seeking or taking, despite their positive reinforcing actions, could typify recreational users. Response inhibition constitutes a particularly useful assay of cognitive control and is mediated by defined fronto-striatal circuits with prefrontal cortical involvement specifically including the pre-supplementary motor area (SMA) in the dorsomedial prefrontal cortex (dmPFC), and the ventrolateral PFC (vlPFC)^{15, 16}. Previous evidence has indicated impaired response inhibition in chronic stimulant drug users, accompanied by reduced vlPFC recruitment^{17, 18}. The unaffected biological siblings of these stimulant drug users also exhibited difficulties in

stopping prepotent responses, but rather than showing concomitantly reduced vIPFC activity, this difficulty was accompanied by increased dmPFC recruitment suggestive of compensatory mechanisms for pre-existing vulnerability factors ¹⁸.

Reports on response inhibition in non-dependent stimulant drug users have been mixed with one initial small study showing inhibitory impairment ¹⁹ but subsequent studies indicating no performance difficulties, and only negligible functional activation alterations compared to healthy controls being occasionally noted ^{20, 21}. Such results are reminiscent of the mixed results of studies investigating other, prefrontal cortex mediated, top-down functions such as working memory, selective attention and planning ²²⁻²⁵. Some degree of impairment may be consistent with the notion that occasional users are at different points along a trajectory towards dependence. Accordingly, there is evidence that intense recreational cocaine users show high levels of impulsivity ²¹ and lower cognitive performance ²⁶, though less severe compared to dependent cocaine users. The mixed findings also highlight the challenge of characterizing this population given the current lack of clear criteria or clinical guidelines for classifying recreational and occasional use of cocaine ²⁷.

The present study examined performance during a stop-signal task to assess response inhibition and its neural correlates using functional magnetic resonance imaging (fMRI) in suitably large numbers of recreational cocaine users and healthy controls. The stop-signal task requires cancellation of a planned response in a neutral setting, despite a strong tendency to carry it out to completion. We employed the same paradigm used in a previous study of chronic stimulant users and their unaffected biological siblings ¹⁸, hypothesizing that brain functioning might provide a more sensitive measure to any possible aberrations in response inhibition.

The recreational users were a relatively homogeneous group with no family history of abuse, no psychiatric comorbidities, who reported controlled recreational use with no

interference in daily functioning, although they had been using cocaine for at least 2 years. Data from this group have already suggested a markedly different neurobiological phenotype from that found in stimulant-dependent users, with unimpaired attentional bias to cocaine-related stimuli accompanied by reduced prefrontal activation compared to stimulant-dependent and control individuals ²⁷. Moreover, divergent prefrontal structural abnormalities between recreational and stimulant-dependent users have been reported with *increased* rather than decreased orbitofrontal gray matter in the former, (though some commonalities in brain abnormalities were also noted) ⁸. Thus, we hypothesized that response inhibition may be a factor contributing to apparent resilience in recreational users. We investigated whether or not they would demonstrate difficulties suppressing actions and whether this would be accompanied by aberrations in key prefrontal regions, including the dmPFC and vlPFC.

Materials and Methods

Participants

Recruitment and screening procedures have been described in detail elsewhere ^{8, 27}. All participants were aged 18-55, with no history or current psychiatric, neurological or neurodevelopmental disorder or traumatic brain injury. Inclusion criteria included no family history of substance dependence, with the exception of nicotine, and no current psychotropic medication. All participants were evaluated using the Structured Clinical Interview for DSM-IV ²⁸ augmented with a semi-structured interview to ascertain history of drug use, mental and physical health. Recreational drug users used cocaine for at least 2 years without experiencing physiological or psychological symptoms of dependence as described in the DSM-IV and did not use stimulant drugs for medical reasons. Recreational users had never developed DSM-IV criteria for substance dependence, having used cocaine in relatively small amounts in powdered forms in social settings infrequently (see Table 1). Their occasional use

did not interfere with work, school, family, or social obligations and they never considered seeking any treatment (see SI for further details). Twenty-seven recreational users were recruited from the community by local advertisements, though 3 were excluded (see SI). A sample of 32 controls was matched in age, gender and education.

Drug urinalysis was collected on testing day and results were negative for all participants. Verbal IQ was assessed by the National Adult Reading Test (NART) ²⁹, depressive mood by the Beck Depression Inventory (BDI-II) ³⁰, impulsivity by the Barratt Impulsiveness Scale (BIS-11) ³¹ and sensation seeking traits by the Sensation-Seeking Scale-Form V ³². Alcohol use was quantified by the Alcohol Use Identification Test (AUDIT) ³³ and obsessive-compulsive tendencies by the Padua Inventory-Revised (PI-R) ³⁴. In the recreational users compulsive drug-taking was further assessed with the Obsessive-Compulsive Drug Use Score (OCDUS) (Franken et al., 2002). The study was approved by the Cambridge Research Ethics Committee (REC08/H0308/310; PI KD Ersche) and prior to participation, volunteers provided written informed consent.

Stop-signal task

The task was identical to that reported in a previous study ¹⁸. Participants viewed the task stimuli via a mirror as they lay in the scanner. On go trials participants pressed left and right buttons, in response to go stimuli (left and right pointing white arrows, 1000 msec). On stop trials, the go stimulus was followed by a visual stop-signal (orange arrow pointing upwards, 300 msec) and participants had to withhold responding. There were 48 stop trials and 240 go trials, presented intermixed and counterbalanced with left and right, in a single block with three to seven go trials between stop trials. The delay between go and stop stimuli, initially set to 250 msec, was adjusted individually by a tracking algorithm in 50 msec steps to allow 50% successful stopping ³⁵. If a response was recorded prior to stop-signal onset, it

did not appear and the trial was repeated (less than 1% of trials). Inter-trial-intervals were randomly jittered between 700 and 1100 msec.

Scanning Acquisition

Whole-brain echo planer images (EPI) were collected in one run on a Siemens TIM Trio 3-Tesla scanner with the following parameters: repetition time (TR)=2000 msec; echo time (TE)=30 msec; flip angle=78°; 32 slices with slice thickness 3 mm, 0.75 mm gap; matrix=64x64; field-of-view (FOV)=192 x192 mm yielding 3x3 mm in-plane resolution, and the number of volumes ranging from 274 to 299. T1-weighted scans were acquired for registration (176 slices of 1 mm thickness, TR=2300 msec; TE=2.98 msec, TI=900 msec, flip angle=9°, FOV=240x256 mm).

Data Analysis

Behavioral analyses compared recreational users and controls in mean go reaction time (RT) and stop-signal RT (SSRT). SSRT was estimated by subtracting mean stop-signal delay from correct go RT in accordance with the race-model³⁶. Additionally, percent unsuccessful stopping was computed and unsuccessful stop RT was compared to go RT. Exclusion criteria to ensure the race-model were adopted¹⁸ resulted in the exclusion of 3 recreational users. Behavioral and demographic data were analyzed using chi-squared and t-tests and significant group differences are followed by Cohen d's effect-size.

Imaging data were processed and analyzed using Statistical Parametric Mapping 8 (SPM, <http://www.fil.ion.ucl.ac.uk/spm/>). The first five volumes were discarded due to T1-equilibrium effects. Images were realigned and mean EPI image was co-registered to the T1-weighted image, which was segmented and warped to the Montreal Neurological Institute (MNI) template using New Segment and the deformations applied to the EPI volumes which were resampled to 2x2x2mm. Finally, images were smoothed with a Gaussian kernel of 8-mm FWHM.

First level analyses were performed using the general linear model (GLM) in SPM8. Individual design matrixes modeled successful stop, unsuccessful stop and erroneous go trials by convolving onset times with a canonical hemodynamic response function (HRF) with temporal and dispersion derivatives. Correct go trials occurred frequently, comprising the GLM baseline. First level contrasts were computed for stop relative to baseline, and failed versus successful stops. Anatomical ROIs examining group differences associated with stopping, included the right anterior Insula/frontal Operculum (aIfO; comprising pars opercularis, pars triangularis and anterior insula with $y > 0$) and right and left pre-SMA ($y > 0$) and ACC from the automated anatomical labeling (AAL) atlas (see Figure S1) ³⁷. All results reported were significant at $p < 0.05$ corrected for family-wise error (FWE) with small volume correction, and peak voxels in MNI coordinates. Where significant between-group differences were found, eigenvariates were extracted from 8-mm spheres surrounding peak coordinates for each individual, and were correlated with task performance using Pearson correlation coefficients. Results were further examined while covarying for tobacco and alcohol consumption. To investigate the broader set of regions associated with overriding prepotent responses, group differences in mean activation were computed for an independent search area ROI constructed from all 8-mm spheres surrounding the coordinates derived from a meta-analysis ³⁸ using MarsBar ³⁹ (see also SI).

Results

Demographic and Clinical Measures

The groups did not differ on gender distribution, age, education and verbal IQ (see Table 1). Recreational users scored higher than controls on self-reported measures of sensation-seeking and alcohol use and marginally higher on impulsivity. They also scored somewhat lower on obsessive-compulsive and higher on depression severity measures

compared to controls, though scores in both groups were very low. Whilst recreational cocaine use duration was approximately eight years, their OCDUS indicated very low compulsive use, consistent with their low obsessive-compulsive severity.

Behavioral Measures

As seen in Table 2, there were no significant group differences on any task performance indices, with SSRTs being nearly identical. In keeping with the assumptions of the race model, both recreational users ($t(23)=5.08, p<0.01$) and controls ($t(31)=2.93, p<0.01$) had faster unsuccessful stop than go latencies.

Neuroimaging

Each group demonstrated activation in regions commonly observed in this task for stopping in whole brain analyses corrected for family wise error, $p<0.05$. These included the vlPFC, encompassing the anterior insula and IFG predominantly on the right, in addition to the dmPFC, superior inferior parietal cortex and occipital cortex bilaterally (see Figure 1). Visual inspection suggested greater and more extensive activation in recreational users compared to controls during stopping. In accordance with this conclusion the anatomical ROI analyses indicated over-activation in recreational users compared with the controls in stopping versus going in the right pre-SMA ($p=0.048, [10,20,46]$, cluster extent(K_E)=8, $Z=3.23$). Additionally, there was increased activation in the right ACC ($p=0.028, [-2,26,30]$, $K_E=24, Z=3.58$) and left ACC ($p=0.047, [4,24,18]$, $K_E=14, Z=3.58$) for stopping. These results remained when covarying for alcohol and tobacco consumption (see SI for additional details). There was no significant group difference in the vlPFC ROI. Additionally, no group differences were noted in failed versus successful stopping (see SI for additional details). Recreational drug users showed increased activation in the response override search area ($t(54)=1.86$, Contrast Value 0.96, $p=0.034$), though both groups showed significant activation compared to the go baseline ($t(31)=4.43, p<0.001$ and $t(23)=6.45, p<0.001$ for controls and

recreational users, respectively). SSRT did not correlate significantly with any functional activation or group characteristic. In sum, recreational users showed increased activation not only in the pre-SMA but also more general widespread activation in areas associated with suppressing prepotent responses compared with controls.

Discussion

This study examined response inhibition, as gauged by the stop-signal task and its neural correlates using fMRI, in well-characterized recreational cocaine users and matched controls. The behavioral performance in the recreational group was on par with that of the healthy controls, with no difference on any task measure, including response execution and SSRT. At the same time, within the neural circuitry normally activated by stop-signal and response override tasks, recreational users showed significantly increased activation, including the dmPFC and ACC.

These findings reinforce the notion of a neurobehavioral phenotype in the recreational cocaine users that is distinct from that shown in chronic stimulant-dependent users, who demonstrate performance difficulties in response inhibition along with reduced vlPFC recruitment^{17, 18}. Similarly, recreational users did not show evidence for altered error-processing as previously reported in stimulant dependent individuals^{18, 40, 41}. Previously, it was shown that recreational users also exhibit increases rather than the decreases in orbitofrontal gray matter that characterize stimulant-dependent individuals⁸. In contrast to stimulant-dependent individuals, recreational users also did not exhibit attentional bias to cocaine-related stimuli in conjunction with reduced prefrontal and orbitofrontal activations²⁷. Thus, prefrontal cortical and control processes do not appear to be impaired in the same way in these two cocaine-using groups, with several apparently opposed patterns of abnormalities evident, compatible with their divergent usage patterns. This conclusion dovetails with the findings that the underlying substrates of response inhibition such as the dmPFC and vlPFC

show no overlapping abnormalities in structure between these two groups, though abnormally increased gray matter volume in the parahippocampus gyrus has been reported for both groups ⁸.

Increased recruitment of areas key to response inhibition in the presence of equivalent performance suggests compensatory or protective neural mechanisms at play in the recreational users. Moreover, it is strongly reminiscent of (though not identical to) the findings reported for the unaffected siblings of stimulant-dependent individuals ¹⁸. In both cases, adequate performance was accompanied by increased dmPFC but no abnormalities in vIPFC functional activation. Present results also add to the similarity between the two groups in increased cerebellar gray matter ⁸. These similarities between the non-dependent siblings and recreational drug users and the differences between these two groups on the one hand and the drug dependent individuals on the other, strengthen the notion that, unlike measures of brain structure, functional activations during response inhibition may not be a suitable endophenotype for drug dependence ¹⁸, although they could provide a marker for the capacity for functional compensation. The present fMRI data alone do not distinguish between results indicating inefficient neural recruitment, as opposed to marking the resilience that allows individuals to avoid cocaine dependence (akin to the unaffected siblings avoiding cocaine altogether). However, PFC hyperactivation reminiscent of the present findings has been reported during stop-signal task performance in OCD patients, their unaffected first-degree siblings and in adolescents reporting limited use of illicit substances ^{42, 43}. Taken together, such hyperactivation in the absence of performance difficulties may be markers of general compensatory mechanisms. Thus some level of vulnerability or compromise to the system, from preexisting susceptibility or from limited drug exposure, can be gauged by the apparently greater functional recruitment. However, such compensation may only be possible to a certain extent, as with increasing usage or with greater vulnerability, it becomes no

longer viable, resulting in reduced neural recruitment and disrupted performance. An alternative account might suggest that behavioral measures are less sensitive than brain activations and that current findings might point to reduced neural recruitment in controls. This would be congruent with the notion of resilience in the present recreational users who may have exceptional capacities for cognitive control. Further, the chronic, though limited, use of cocaine in this group could have eroded their potentially superior performance. However, considering increased recruitment of key prefrontal regions in absence of behavioral differences in the unaffected siblings and other groups, we believe the former interpretation of compensatory recruitment to be more parsimonious. Future functional studies examining recreational cocaine users longitudinally or their first degree non-using relatives may elucidate the issue. Increased activation in the response override search area is suggestive of broad compensatory recruitment. However, the contrast between stop and go engages not only response inhibition but also attentional orienting as the stop signal occurs infrequently³⁸, and both processes have been associated with the IFC^{38, 44}. Nonetheless, the pre-SMA is routinely linked to action suppression *per se* in the stop signal task⁴⁵ and more broadly to action control⁴⁶ during response inhibition tasks, suggesting some regional specificity for compensatory recruitment. The recreational users were well-characterized, exhibiting no current or past psychiatric disorders and without a family history of dependence. Further, the two groups were matched for childhood trauma⁸. Most investigations of occasional cocaine users likely include variable mixtures of stable recreational users and individuals on a trajectory to dependence, leading to difficulties in integrating findings across studies. Some recreational user studies have included primarily males or individuals who may have previous psychiatric comorbidities such as ADHD or alcohol abuse which increase the likelihood of transition to dependence^{19, 21}. Moreover, male recreational users may be particularly prone to poorer cognitive performance⁴⁷. The average

age of participants is considerably lower in some studies as is duration of usage (e.g., minimum of 6 versus 24 months) allowing a substantial proportion of individuals who may subsequently escalate²⁰. Finally, our sample of recreational users included individuals with higher levels of education, IQ and disposable income than those reported for stimulant users⁸, in other studies the two groups were more comparable with high levels of craving and impulsivity. Indeed, a proportion of recreational cocaine users in a longitudinal study subsequently increased their usage^{13, 21}. Nevertheless, in accordance with present findings, two previous studies reported no differences in performance on the stop-signal task, reinforcing the conclusion that cocaine use in humans does not necessarily lead to inhibition performance deficits^{20, 21}, although detrimental effects on other domains such as working memory may be apparent²⁶. At the same time a study using a mixed group of young cocaine and prescription stimulant users reported weaker recruitment during stopping compared to controls of parietal and cingulate regions, at odds with the present findings²⁰. Should increased activation in parts of the response override network be indicative of preliminary compensatory recruitment as suggested above, it is predicted that longitudinal studies would reveal initial over-activation to be followed by hypoactivation and performance difficulties. Such longitudinal studies of recreational users are particularly important as they can address the extent to which compensatory strategies may be successful and provide insight into how such strategies fail. Possibilities include the accumulation of the drugs consumed or interference from environmental stressors that could interfere with the cognitive resources necessary for compensatory strategies. Better insight into such issues would have important implications for preventative strategies. In any case, we argue that finer distinctions should be adopted to better characterize what are potentially non-overlapping populations of recreational users. It would also be of use to compare performance and neural activation in recreational users to that of abstinent users as inhibitory control may contribute in a similar

fashion to relapse avoidance. Evidence regarding performance in abstinent users typically encompasses a range of abstinence durations, and is limited in part due to the challenges of conducting such studies. Response inhibition appears impaired in some studies⁴⁸ but not others⁴¹. Though hyperactivation of some PFC regions was initially reported in one small study⁴⁹, this was not replicated subsequently^{50, 51}, while ACC hypoactivation akin to drug users has also been noted⁴¹. Thus, on the whole it remains to be determined if successful abstainers can recruit additional prefrontal resources as present recreational users, although such mechanisms may be exploited more effectively with the adoption of training regimes to bolster response inhibition. As a psychological construct, response inhibition is believed to contribute to cognitive control and executive functioning⁵². As such, it may interact in complex ways with overlapping factors implicated in promotion of stimulant dependence. Familial vulnerability plays a key role as does age of initial use, with greater likelihood of transition to dependence with earlier exposure⁵³. This account is consistent with response inhibition and its mediating neural structures still undergoing maturation until early adulthood^{54, 55}. Disruptions of behavioral inhibition and top-down control may be a key mechanism by which additional factors such as the socio-demographic environment and intelligence contribute to the likelihood of becoming dependent^{56, 57}. Hence, response inhibition and controlled intake may mutually promote one another, reducing the likelihood of transitioning to dependency. Sensation-seeking, whilst being a strong predictor for drug use^{8, 58}, appears to be orthogonal both to response inhibition and to the likelihood of escalation to dependence. This is because increased sensation-seeking characterizes the recreational users in addition to the stimulant-dependent individuals but not their unaffected siblings. As such it would be useful to investigate reward processes more closely in recreational users⁵⁹.

Study limitations include the cross-sectional design and the lack of clinical guidelines defining controlled or recreational cocaine use. Nevertheless, the two groups were well-matched for age, gender, childhood adversity, education and intelligence levels. The task did not model Go trials separately and so was probably insensitive to striatal involvement in response control, although its use enabled opportunities to integrate both present and previous results^{18,43}. Whilst we utilized urine analysis and comprehensive psychiatric diagnostics, cocaine use rested largely on self-report. Future studies should quantify longer-term cocaine use with objective measures such as hair toxicology. We did not seek estimates for the amount of cocaine used as this may be confounded with purity in addition to the usual shortcomings of relying on retrospective reporting. The present findings also do not preclude significant difficulties in other domains of top-down control in the recreational cocaine users such as working memory, or other cognitive domains mediated by neural structures showing similar abnormalities in recreational users and stimulant-dependent individuals such as the hippocampus⁸.

In summary, response inhibition performance of recreational cocaine users who had been using cocaine for at least 2 years with no family history of abuse or psychiatric comorbidities was on par with matched controls. Nevertheless, intact stopping in the recreational users was accompanied by over-activation of the dmPFC, reminiscent of the unaffected siblings of stimulant-dependent individuals. A parsimonious account favors the increased activity as indicative of compensatory recruitment of key response override brain regions. The results suggest that fostering cognitive control in occasional cocaine users may enable such individuals to delay or avoid possible transition to dependence.

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Conflict of Interest:

The authors report no financial interests or conflicts of interest. TWR consults for Cambridge Cognition, Lilly, Lundbeck and GlaxoSmithKline and also holds research grants from those companies. ETB is employed part-time by GlaxoSmithKline and part-time by the University of Cambridge.

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Table 1. Demographic information and group differences for recreational stimulant users and healthy control subjects.

	Recreational Users		Control Subjects		t/χ^2	p
	Mean	SD	Mean	SD		
Characteristic						
Male: female	12:12		18:14		0.22	0.64
Age (years)	28.54	6.78	30.91	8.14	1.15	0.25
Education (years)	13.29	1.78	13.03	1.99	0.51	0.61
Verbal IQ (National Adult Reading Test)	116.32	5.25	113.58	8.12	1.39	0.17
Impulsivity (BIS-11)	62.92	10.68	58.44	7.25	1.87	0.07
Sensation seeking	23.04	5.13	18.28	5.91	3.15	<0.01
Compulsivity (Padua Inventory)	4.33	2.82	7.72	7.45	2.11	0.04
Depression (BDI-II)	4.04	4.43	2.47	2.18	1.75	0.09
Mean number of cigarettes	5.17	5.78	4.25	6.59	0.34	0.74
Alcohol use (AUDIT)	5.79	1.56	3.00	2.31	5.10	<0.01
Compulsivity (OCDUS)	1.25	1.67				
Duration of stimulant use (years)	8.08	6.18				

Age of	20.42	3.39
Stimulant Use		
Onset (years)		

Note. NART: National Adult Reading Test; BIS-11P: Barratt Impulsivity Scale Version 11; BDI-II: Beck Depression Inventory–II; AUDIT: Alcohol Use Disorders Identification Test, cut-off score for alcohol abuse: >8; OCDUS: Stimulant-related Obsessive Compulsive Drug Use Scale.

Table 2. Stop-signal task performance measures

Task Measure	Recreational		Control Subjects		<i>t</i>	<i>p</i>
	Mean	SD	Mean	SD		
Go RT (msec)	386.53	46.30	410.91	76.17	1.38	0.17
SSRT (msec)	198.36	36.92	198.38	59.12	0.01	0.99
Percent errors (on go trials)	3.71	3.19	3.17	2.43	0.72	0.47
Percent unsuccessful stopping	50.13	1.70	49.11	2.18	1.91	0.06
Go SD (msec)	90.81	24.69	91.54	34.71	0.09	0.93
Slowing following an unsuccessful stop (msec)	22.82	36.21	30.04	54.82	1.13	0.26

Note. RT= Reaction time (in msec); SSRT = stop signal reaction time (in msec); Go SD (standard deviation) denotes the individual standard deviation of go RT.

Figure Legends

Figure 1. Significant brain activation maps associated with stopping in each group separately ($p < 0.001$, uncorrected for illustration purposes only). Figure 1a denotes lateral and medial views of recreational cocaine users. Figure 1b denotes lateral and medial views of healthy volunteers.

Figure 1a

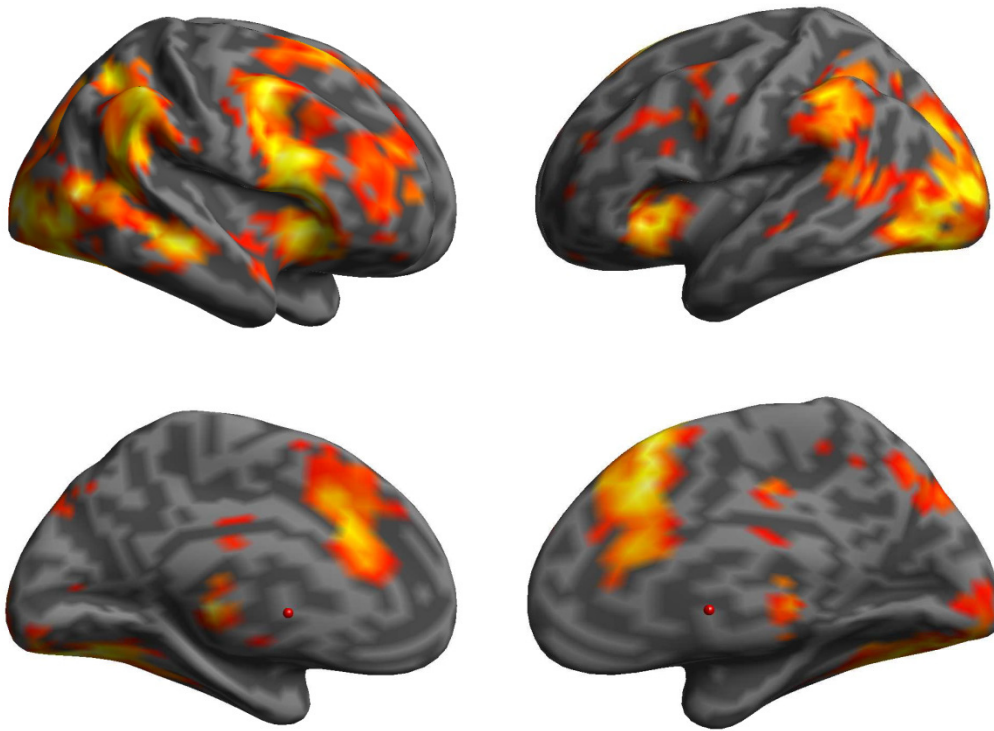
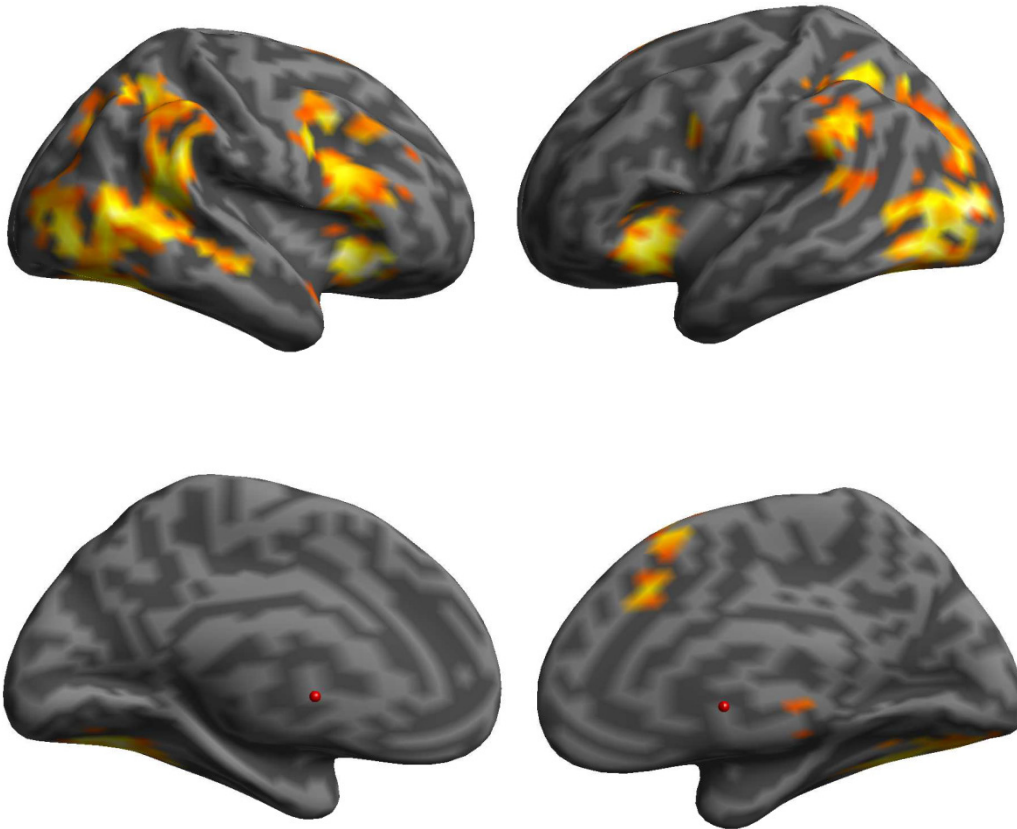


Figure 1b



Supplementary Materials

Additional details about the recreational cocaine users

The recreational users almost all (96%) reported a lifetime history of sporadic, controlled experimentation with illicit drugs other than cocaine, including hallucinogens (50%), amphetamine (58%), ecstasy (87%) and cannabis (100%), but never fulfilled the DSM-IV-TR criteria of substance dependence. None reported any use of opiates, steroids or Gamma Hydroxybutyrate. This pattern of experimentation was consistent with their overall selective and controlled experimentation and usage in social settings with friends and their high sensation seeking (see also low DAST scores in Table 1).

Adult ADHD comorbidity was not ascertained explicitly, but it is highly unlikely that any individuals qualified for ADHD as: a) none reported a childhood history or diagnosis, b) none reported being prescribed ADHD medications, c) none reported using stimulant drugs to ‘calm down’, and d) present results did not find evidence for common findings in ADHD such as elevated impulsivity, increased depression or impaired performance on stop-signal task measures ¹. Moreover, individuals with ADHD are typically characterized by underactivation of prefrontal areas accompanied by overactivation of more posterior regions, which is considerably different from the present profile ².

Stop signal task and analysis

The key dependent measures in the stop signal task are go reaction time (RT), which provides a measure of motor initiation, and stop signal RT (SSRT), which provides a measure of response inhibition. When using the tracking algorithm, convergence around 50% success rate on stop trials together with the race model allows for estimation of SSRT by subtracting mean stop signal delay from go RT. Secondary measures include individual go standard deviation (SD) as an attentional measure and slowing following unsuccessful stop as a measure of error monitoring. Criteria adopted to uphold the race-model were identical to

those previously used in our group ³, These included: a) 0.4 to 0.6 successful inhibition, b) a difference between unsuccessful stop and go RT below 1 SD of the sample, c) less than 30 trials where a response occurred prior to a planned stop-signal (the stop-signal was present in 15.1% to 16.6% of trials).

Additional fMRI analyses

We investigated whether recreational users differed from controls in the amount of head motion in the scanner. There was no significant difference in frame displacement (dvars, <http://fsl.fmrib.ox.ac.uk/>) between the two groups ($t(1,53)=1.3$, $p=0.18$).

Figure S1 conveys the anatomical ROIs used in the main text. An independent region of interest to examine frontal activation associated with response inhibition was derived based on coordinates from a meta-analysis ⁴. The activation likelihood estimation analyses comprised motor inhibition tasks specifically where the motor tasks were prepared or initiated prior to stimulus onset (response override tasks), indicating the need to suppress a prepotent response. For each of the coordinates reported in the analysis (based on Table 5 in the original publication, and presented in Table S1) an 8-mm sphere was created in MarsBar ⁵ and the resulting regions of interest were combined to create the search area.

The recreational users had slightly higher verbal intelligence and levels of self-reported impulsivity (see Table 1). Analyses of stop signal performance covarying for these two factors revealed the same results reported in the main text. Similarly, analyses of eigenvariate values when covarying for the BIS (Barratt Impulsiveness Scale) and verbal IQ again did not alter the results reported in the main text, with increased activations associated with stopping in recreational users compared to controls in the right pre-SMA ($F(1,53)=10.70$, $p=0.002$), and right and left ACC ($F(1,53)=8.35$, $p=0.006$ and $F(1,53)=9.41$, $p=0.004$, respectively).

Comparing unsuccessful to successful stops in the ACC ROI revealed significant activation across all participants when correcting for family wise error ($p=0.005$, [0, 34,8], $K_E=70$, $Z=4.28$, and $p=0.025$, [2,54,12], $K_E=35$, $Z=3.87$). However, there was no evidence for significant differences between the two groups, even at a threshold of $p<0.001$ uncorrected. Similarly, whole brain analyses at the threshold of $p<0.001$ uncorrected did not detect any group differences. Along with the absence of group differences in behavioral indices relating to monitoring following unsuccessful stops (see Table 1), present data do not support abnormal error monitoring in the recreational cocaine.

To further explore potential differences between the groups, we conducted whole brain analyses at a more liberal threshold of $p<0.001$ uncorrected. The results, reported in Table S2, indicated scattered foci of increased activation associated with stopping in the recreational users compared to the control participants. These primarily centered on the prefrontal cortex (including the pre-SMA and anterior cingulate as reported in the main text). Additional foci were noted in the occipital cortex and fusiform gyrus, likely stemming from the visual nature of the stop signal.

Tobacco and Alcohol

As noted in Table 1 in the main text, the recreational users reported higher alcohol consumption and controls as assessed by the AUDIT (Alcohol Use Disorders Identification Test), though below the cutoff for abuse, and did not differ in daily cigarette use. Analyses of eigenvariate values when covarying for AUDIT scores indicated that recreational users had increased activations associated with stopping compared to controls in the right pre-SMA ($F(1,53)=5.02$, $p=0.029$). Similarly, increased activation in the right and left ACC remained significant ($F(1,53)=4.47$, $p=0.039$ and $F(1,53)=6.28$, $p=0.015$, respectively).

Supplementary references

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Table S1. Coordinates from frontal regions that comprised the search area for response inhibition tasks requiring suppression of a prepotent response.

Anatomical label	Hemisphere	x	y	z
Anterior insula	R	38	20	-2
	L	-42	16	-6
Inferior frontal gyrus	R	48	16	18
Pre-supplementary motor area	R	14	16	58
Middle Frontal gyrus	R	34	42	28
	L	-36	38	24
Anterior cingulate	R	6	22	36
Middle frontal gyrus	L	-38	54	18
Dorsal premotor cortex	R	30	0	44
	L	-26	-4	52

Table S2. Group differences in activations associated with stopping at whole brain $p < 0.001$ uncorrected extent threshold 10 voxels.

Hemisphere	Z-score	Peak coordinates MNI (mm)			Cluster size (voxel)	Brain Region
		x	y	z		
R	3.36	4	24	18	27	Anterior Cingulate
L	3.58	-2	26	30	42	
R	3.23	10	20	46	14	Pre-SMA
R	3.35	12	-18	34	12	Middle Cingulate
R	3.54	10	54	26	21	Superior frontal gyrus
L	3.51	-10	58	14	44	
R	3.34	16	46	24	21	Superior medial gyrus
L	3.27	-32	54	2	13	Superior middle gyrus
L	3.47	-32	-8	34	10	Precentral gyrus
R	3.44	16	-38	10	13	Hippocampus
R	3.32	34	-74	-4	11	Inferior Occipital
R	3.37	30	-60	20	20	Occipital
L	3.73	-30	-68	-4	32	Fusiform
L	3.50	-32	-50	-4	13	Fusiform

Figure S1. The anatomical region of interest volumes (right and left pre-supplementary motor area and anterior cingulate and right inferior frontal cortex comprising of the inferior frontal gyrus and anterior insula).

