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BRIEF REPORTS

Recreational Use of Cocaine Eliminates Inhibition of Return

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Chronic and recreational use of cocaine has been shown to impair inhibitory output control (response inhibition) but whether input control is also affected is an open question. For the first time, this study compared the ability to perform a cued target-discrimination task that measured inhibition of return (IOR), a reflexive inhibitory mechanism that delays attention from returning to a previously attended location, in adult recreational users and in a cocaine-free-matched sample controlled for age, race, gender distribution, and level of intelligence. Results show that the recreational use of cocaine eliminates IOR, suggesting that input control is strongly impaired.

Keywords: cocaine, inhibition, dopamine, IOR

Since 2007 cocaine is Europe's second preferred recreational drug after cannabis (European Monitoring Centre for Drugs & Drug Addiction, 2007). Taking cocaine by snorting route is not a "privileged habit" anymore, as it was in the 1980s, but now is affordable for everyone, in particular for recreational purposes. Cocaine has, thus, become a common street drug. It therefore is likely that the recreational use of cocaine will become a public health issue in the next few years (because of the addictive properties of this stimulant drug), as is already the case for ecstasy (Ramaekers, Kuypers & Samyn, 2006).

At long term, chronic (i.e., daily) use of cocaine is associated with reduced functioning of dopamine D2 (DAD2) receptors (Volkow, Fowler, & Wang, 1999) and dysfunctions in frontal brain regions (Bolla, Cadet, & London, 1998; Bolla et al., 2004; Hester & Garavan, 2004)—areas that play a key role in the regulation of human cognition and the control of goal-directed behavior (Miller, 2000). Therefore it is not surprising that cocaine dependence impairs cognitive control functions, such as the ability to inhibit overt responses (Fillmore & Rush, 2002). Consistent with this picture, Colzato, van den Wildenberg, and Hommel (2007) observed in a stop-signal task (Logan, 1994) that response inhibition, but not response execution, is impaired in recreational cocaine users. This dissociation fits in the picture because response execution is presumably driven by DAD1-dominated neural pathways targeting prefrontal cortex (Frank, Seeberger & O'Reilly, 2004), whereas response inhibition depends more on DAD2-related pathways (Frank et al., 2004). More interesting, the magnitude of the inhibitory deficit was positively correlated with the individual lifetime cocaine exposure, suggesting that the amount of cocaine consumption (and the implied degree of DAD2 receptor density loss) is proportional to the magnitude of performance impairments. This also is suggested by the observation that the magnitude of the inhibitory deficit was reliable but somewhat smaller than found in chronic users (Fillmore & Rush, 2002). Note that the causal relation between inhibitory control functions and cocaine is not straightforward because it is not possible to exclude preexistent neuro-developmental factors. Recent evidence has shown, for instance, that people who have preexisting lowered D2 receptor densities run a higher risks to use cocaine and to become addicted (Nader et al., 2006), and that chronic users may suffer preexisting problems in inhibitory control (Bechara, 2005). In any case, however, the connection between cocaine, DAD2 pathways, and difficulties in inhibiting overt responses seems strong.

Previous studies on cocaine have focused on inhibitory output control, such as the intentional suppression of overt prepotent actions. In the present study, we investigated whether input control processes (attentional selection) may also be affected. Perhaps the most reliable inhibitory phenomenon in human attention is the so-called inhibition of return (IOR) effect (Posner & Cohen, 1984). It is observed if people attend sequential displays or scan complex visual scenes (Klein, 1988), or other circumstances under which they move their attentional focus from one object to another until an interesting or searched-for object has been found. Once a given location has been inspected and attention has moved to another location, the time needed to return to that previous location is increased—presumably to enhance the efficiency of attentional scanning by biasing it away from irrelevant, old information (Klein, 1988). Considering that cocaine use is associated with impairments in the functioning of D2 receptors, there are a number of reasons suggesting that cocaine might impact IOR. IOR is enhanced after the intake of d-amphetamine, which stimulates D2 receptors (Fillmore, Rush & Abroms, 2005), and is reduced in patients with Parkinson's disease, who suffer from a loss of nigrostratial dopaminergic cells (Filoteo et al., 1997; Yamaguchi & Kobayashi, 1998). These studies fit with the proposed crucial role of dopamine as

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neurobiological mechanism underlying IOR (Poliakoff et al., 2003)—the transmitter targeted by cocaine consume.

The present study investigated the impact of recreational intake of cocaine, strictly controlled for confounds, on IOR. In our slightly modified (but extensively tested, see footnote 1) version of the IOR task (see Hommel & Colzato, 2004, and Figure 1), a visual cue was briefly presented in a peripheral location of a computer display. Following the cue, a visual target stimulus appeared in either the same location as the cue (cued condition) or in a different location (uncued condition). Participants performed a binary-choice response to the target's orientation (vertical vs. horizontal). IOR would be indicated by longer a reaction times in the cued than in the uncued condition. The magnitude of the IOR effect can be taken to indicate the efficiency of inhibitory input control, so that a small IOR would reflect a lower level of inhibitory efficiency. If so, our considerations suggest that recreational users of cocaine might show a smaller IOR than controls.

Method

Participants

Thirty-two young healthy adults served as participants for partial fulfillment of course credit or a financial reward and constituted the two groups: recreational users of cocaine and cocaine-free controls. The sample was drawn from adults in the Leiden and Delft metropolitan area, who volunteered to participate in studies of behavioral pharmacology. Participants were recruited via ads posted on community bulletin boards and by word of mouth. Three participants were excluded from the user group because it turned out that they did not comply with the instructions given by the experimental protocol (consuming large amount of alcohol the night before the experimental session).

Following Colzato et al. (2007) we made sure that the users met the following criteria: (a) a monthly consumption (1 to 4 g) by snorting route for a minimum of 2 years; (b) no Axis I psychiatric disorder (*Diagnostic and Statistical Manual of Mental Disorders–IV;* American Psychiatric Association, 1994), including "substance abuse"; (c) no clinically significant medical disease; (d) no use of medication; and (e) no family history of alcoholism and/or substance use disorder. Cocaine-free controls met the same criteria except that they reported no history of past or current cocaine use. Participants were selected by means of a phone interview by a research assistant with the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), a brief diagnostic tool that screens for several psychiatric disorders. The sample was obtained from a pool of approximately 35 potential volunteers who responded to the advertisement for studies conducted in our lab over the period of 6 months. Within this pool of potential volunteers, the most common reason for excluding an individual from the study was meeting psychiatric disorder (ADHD, Mania) or medication.

Participants were asked to refrain from taking drugs for 2 days and from all caffeine containing foods and beverages for 12 hr prior to the experimental sessions, not to consume alcohol on the night before the experimental session and to have a normal night rest. Participants' compliance with the instructions was encouraged by taking a (not further analyzed) saliva sample at the beginning of the session (cf. Colzato, Erasmus & Hommel, 2004; Colzato, Fagioli, Erasmus & Hommel, 2005).

In the last month 6 of the 13 recreational users also smoked marijuana, whereas 4 reported to have taken one MDMA (ecstasy) tablet. The cocaine-free controls reported to have not to have used any drug.

Participants in the two groups were matched for race (100% White), age, sex, and IQ (measured by Raven's Standard Progressive Matrices [SPM]; Raven, Court, & Raven, 1988). Demographic and drug use statistics are provided in Tables 1 and 2. Written informed consent was obtained from all participants after the nature and possible consequences of the study were explained to them; the protocol was approved by the local ethical committee.

Apparatus, Stimuli, and Procedure

All participants were tested individually. They first provided a saliva sample then completed the intelligence test and the behavioral task measuring IOR. Individual IQs were determined by means of a 30-min reasoning-based intelligence test (SPM). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely used test to measure Spearman's *g* factor and of fluid intelligence in particular (Raven et al., 1988).

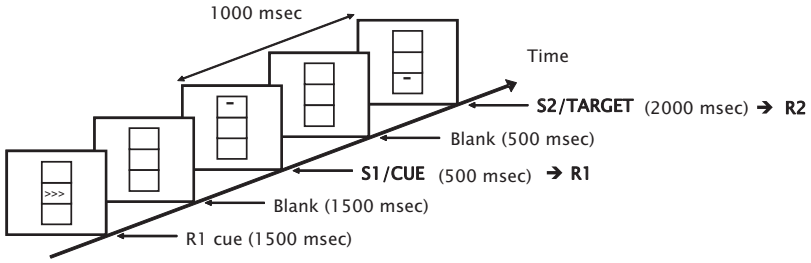

Figure 1. Sequence of events in the present experiments (cf., Hommel & Colzato, 2004). A response cue signaled a *left* or *right key* press (R1) that was to be delayed until presentation of S1, a red or green, vertical or horizontal line in a top or bottom box. S2 appeared 1 s later—another red or green, vertical or horizontal line in the top or bottom box. S2 orientation signaled R2, also a speeded *left* or *right key* press. R2 speed and accuracy were analyzed as function of the repetition versus alternation of stimulus orientation, color, and location, and of the response.

The behavioral task measuring IOR was adopted from Hommel and Colzato (2004)[1], see Figure 1, which took 45 min to complete.

Participants faced three gray square outlines in the middle of a monitor, vertically arranged, as illustrated in Figure 1. From viewing distance of about 60 cm, each of these frames measured 2.6° × 3.1°. A vertical line (0.1° × 0.6°) and a horizontal line (0.3° × 0.1°) served as S1 and S2 alternatives, which were presented in red or green in the top or bottom frame. Participants carried out two responses per trial. R1 was a delayed simple reaction with the *left* or *right key*, as indicated by a 100%-valid response cue (left- or right-pointing arrow in the middle box) that preceded the trigger stimulus *S1* by 3,000 ms. S1 varied randomly in orientation (a thin vertical or horizontal line), color (red or green), and location (top or bottom box). R1 was to be carried out as soon as S1 appeared according to the direction of the response cue, independent of its orientation, color, or location; that is, if the response cue was pointing to the right, participants were encouraged to respond with the *right key* to the mere onset of S1. R2 was a binary-choice reaction to the orientation of S2 (vertical or horizontal), which also appeared in red or green, and in the top or bottom box, 1,000 ms after S1 onset. Responses to S1 and to S2 were made by pressing the *left* or *right shift-key* of the computer keyboard with the corresponding index finger. The experiment was composed of a factorial combination of the two possible orientations, colors, and locations of S2, the repetition versus alternation of orientation, color, location, and the response, and three replications per condition ($2 \times 2 \times 2 \times 2 \times 2 \times 2 \times 2 \times 3 = 384$).

Results

After excluding trials (1.4%) with missing (>1500 ms) or anticipatory responses (<200 ms), mean reaction times (RTs) and proportions of errors for R2 were analyzed. RTs and percentages of errors (PEs) were analyzed by means of analyses of variances (ANOVAs) with cueing (cued vs. uncued) as within-participant factors, and group (recreational cocaine users vs. cocaine free-controls) as a between-participants factor (see Table 3 for means). The RT analysis yielded two reliable effects: a main effect of cueing, $F(1, 27) = 17.81$, $p = .0002$, $\eta^2 = .40$, and an interaction between group and cueing, $F(1, 27) = 8.56$, $p = .007$, $\eta^2 = .25$. As expected, the cuing effect, calculated as the difference between the uncued and cued condition, was negative (−11 ms), confirming that we obtained IOR. However, cuing affected the two groups differently: Whereas the cocaine-free controls showed a normal, significant IOR (−18 ms, $SD = 15$), $F(1, 15) = 22.65$, $p = .0002$, $\eta^2 = .60$, recreational users of cocaine did not (−3 ms, $SD = 11$), $F(1, 12) = 1.12$, $p = .31$, $\eta^2 = .08$. PEs did not reveal any significant effect.

Table 1
Demographic Characteristics

Sample	Controls	Recreational users	Significance
N (Men:Women)	16 (14:2)	13 (11:2)	*ns*
Age (years)	29.0 (6.4)	26.2 (4.6)	*ns*
Raven IQ	119.8 (4.2)	114.5 (4.7)	*ns*
Monthly drinks	44.3 (55.3)	84.3 (78.3)	*ns*
Monthly cigarettes	76.2 (232.0)	380.0 (194.1)	*

Note. IQ measured by means of the Raven Progressive Matrices. Standard error is presented in parentheses.
* $p < .01$.

Table 2
Self-Reported Use of Cocaine for the Recreational Cocaine Users

Sample	*M* (*SD*)
Highest regular frequency (times per month)	3.1 (2.6)
Highest amount in a 12-hr period (peak; grams)	1.19 (0.75)
Monthly grams	2.19 (1.13)
Lifetime exposure grams	239 (172)
Monthly money cocaine (Euro)	109.5 (56.5)

Second, we further tested whether alcohol and cigarettes consumption contributed to the effect on IOR measure. However, an ANOVA on the IOR difference scores with group as independent variable and monthly drinks and cigarettes as covariates did not point out such contribution: the effects of the covariates was far from significant, for drinks, $F(1, 25) = 0.02$, $p = .892$, $\eta^2 = .001$, and cigarettes, $F(1, 25) = 0.06$, $p = .810$, $\eta^2 = .002$, and the group effect remained reliable, $F(1, 25) = 6.80$, $p = .015$, $\eta^2 = .214$.

Third, to test whether the magnitude of cognitive impairments is proportional to the amount of cocaine consume, as in the case of inhibitory output control (Colzato et al., 2007), we computed Pearson correlation coefficients between the individual lifetime cocaine exposure (in gram), peak in a 12-hr period (in milligram) and monthly cocaine dose (in milligram) and IOR measure. The correlations between lifetime cocaine exposure, $r(13) = -.131$, $p = .670$ and monthly cocaine dose, $r(13) = -.273$, $p = .366$; between peak, $r(13) = -.374$, $p = .207$ and between monthly drinks, $r(13) = -.081$, $p = .793$ and cigarettes, $r(13) = -.100$, $p = .745$ did not reach significance, probably due to the limited power in this study (a small sample of 13 users).

Conclusions

This study investigated, for the first time, whether the recreational use of cocaine leads to a detectable deficiency in inhibitory input control—as indicated in IOR. The outcome confirms our hypothesis: In contrast to cocaine-free controls, recreational users do not show a reliable IOR. As IOR is assumed to assist the extraction of visual information from complex scenes (Klein, 1988), this implies that even small doses of cocaine (1 to 4 g monthly) can lead to a considerable impairment of the acquisition and attentional selection of perceptual information. This is likely to have nontrivial consequences for numerous real-life situations, like monitoring tasks or traffic behavior, which call for efficient input control.

[1] The task used is comprised of two sequential reactions (one to the cue and one to the target stimulus), and is longer than other IOR tasks—but we extensively tested this task and demonstrated in numerous studies that it produces reliable IOR effects (e.g., Colzato et al., 2008; Colzato, Warrens & Hommel, 2006; Hommel & Colzato, 2004). The reason we prefer this version is that it provides additional measures of priming and feature integration processes, which we investigate in a broader project. Given that neither the group effects nor IOR interacted with any other variable in the present study, we limited our focus to the relationship between cocaine use and IOR.

Table 3
Means of Mean Reaction Times for Responses to the Target and Percentages of Errors On R2, as a Function of Group

Recreational cocaine users				Cocaine free-controls			
Cued		Uncued		Cued		Uncued	
RT	PE	RT	PE	RT	PE	RT	PE
473 (18)	11.8 (2.6)	470 (18)	11.2 (2.4)	483 (16)	8.4 (1.4)	465 (16)	7.1 (0.9)

Note. RT = reaction times; PE = percentages of errors. Standard error is presented in parentheses.

The magnitude of impairments for inhibitory input control is not proportional to the amount of cocaine consume, as in the case of inhibitory output control (Colzato et al., 2007). This result is in line with other studies (Bolla et al., 2004; Franken, Van Strien, Franzek, & van de Wetering, 2007; Hester & Garavan, 2004) that did not report significant correlation between the amount of cocaine consume and impairments in cognitive flexibility and conflict monitoring. Given that cocaine impairs D2 receptors in particular in the striatum (Volkow et al., 1999)—the area involved in inhibitory output control (Frank, Samanta, Moustafa & Sherman, 2007)—whereas the areas responsible for IOR are located in the frontal eye fields (Klein, 2000; Ro, Farnè & Chang, 2003), it makes sense that response inhibition is particular sensitive to the proportional use of cocaine.

In view of evidence suggesting that cocaine is associated with hypoactivity in the frontal region (Bolla et al., 1998, 2004; Hester & Garavan, 2004), our findings are consistent with the hypothesis that IOR depends on the proper functioning of the frontal eye fields (Klein 2000; Ro et al., 2003). Moreover, given the selective effect of cocaine on DAD2 (Volkow et al., 1999), our findings support the hypothesis that dopamine modulates response IOR (Poliakoff et al., 2003). In contrast to numerous previous studies of chronic cocaine users (see Jovanoski, Erb, & Zakzanis, 2005), the design of our study allowed us to reject a number of alternative accounts of our observations. Participants were screened for several psychiatric disorders and matched for age, race, IQ, and sex, which ruleed out accounts in terms of preexisting psychiatric disorders (as schizophrenia, ADHD, and obsessive–compulsive disorder) that are known to affect inhibition (Rosenberg, Dick, O'Hearn, & Sweeney, 1997; Schachar & Logan, 1990; Thoma, Wiebel, & Daum, 2007). Particularly important was the matching of the age range: From studies on output control, it is known that inhibitory control is unrelated to general intelligence (Logan, 1994), whereas inhibitory efficiency declines with increasing age (Logan, 1994). Indeed, age affects the initiation and resolution of IOR in aging (Castel, Chasteen, Scialfa, & Pratt, 2003; Langley, Fuentes, Vivas, & Saville, 2007). Given that MDMA is associated with impairments in working memory processes and cannabis is related to dysfunctions in cognitive flexibility, and that both drugs seem to be unrelated to malfunction in inhibitory control function (Verdejo-Garcia, Lopez-Torrecillas, Aguilar de Arcos, & Perez-Garcia, 2005), we doubt that our results can be attributed to the use of marijuana and MDMA. In fact, using the same behavioral task measuring IOR in recreational users of MDMA and cannabis adequately matched with controls, we did not find that any effect of these drug on IOR measures (Colzato & Hommel, 2007; Colzato & Hommel, 2008). An open question is whether recreational cocaine users also show impairments in conflict control, a process that is known to interact with IOR (Vivas & Fuentes, 2001).

Of particular theoretical interest is the parallel between our present finding and that of Colzato et al. (2007). Even though the mechanism underlying IOR is unlikely to be identical to that permitting one to inhibit prepotent manual responses, the observation that both mechanisms are sensitive to cocaine use suggests that they both depend on DAD2 pathways. For one, this fits Frank's (2005) suggestion that striatal DAD1-driven signals may be responsible for the priming of intentional action, whereas DAD2-driven signals may serve to suppress activated but unwanted responses. For another, the parallel between IOR and response inhibition supports approaches that attribute the IOR phenomenon to the inhibition of responses to repeated stimuli rather than to the inhibition of the stimuli (or their representations) themselves (Fuentes, Vivas, & Humphreys, 1999; Ivanoff & Klein, 2004; Vivas & Fuentes, 2001). That is, some sort of action-prevention operation may be involved in both cases, and it may be this operation that is fueled by DAD2 pathways and that is sensitive to longer-term use of cocaine.

Although in the current study there was not any evidence of IOR in the recreational cocaine user group, it is possible that cocaine use only impairs inhibitory input control without eliminating it altogether. Future research is needed to investigate exactly how and to which degree cocaine impacts the timing and/or strength of inhibitory processes.

To conclude, the findings obtained in this study are important because they suggest a selective behavioral deficit resulting from, or at least connected with, the consumption of rather small doses of cocaine. However, the status of cocaine use as cause versus effect in the context of this and other disorders of impulse control, such as ADHD and pathological gambling, is still uncertain, and more research is needed to determine the relative contributions of cocaine consumption and other preexisting constellations in impairing inhibitory control.

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