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Chapter 7

Directed Forgetting of memories and cocaine use

Abstract

Memory retrieval requires an effective recruitment of inhibitory control to successfully reject unnecessary memories. The use of cocaine is associated with poor cognitive control processes, but little is known about the impact of chronic and recreational use of cocaine on inhibitory control during intentional forgetting. We studied whether chronic and recreational users of cocaine show impairments on the mechanism responsible for intentional forgetting of memories. Two experiments were carried out on chronic cocaine users in rehabilitation (experiment 1) and recreational cocaine polydrug users (experiment 2) performing a directed forgetting (DF) task, an index of memory suppression. Participants were matched for sex, age, and intelligence (Raven’s standard progressive matrices) with cocaine-free controls and compared on their performance on a DF procedure. Chronic cocaine users in rehabilitation and recreational cocaine polydrug users compared to controls were not able to intentionally suppress the required information, and they did not show a reliable DF effect. The consumption of cocaine appears to alter the control processes related to intentional suppression of non-relevant memories in episodic memory. The use of cocaine, even for recreational purposes, seems to be associated with poor performance in effectively triggering this control mechanism. The inability to suppress interference in declarative memory may have repercussion for daily activities.
Introduction

The use of cocaine is, after heroin, the second most problematic illicit drug world-wide in terms of negative health consequences (United Nations Office on Drugs & Crime, 2013). The popularity of cocaine has risen in the last years, and it is estimated that about 2.2 million young adults aged 15 to 34 used cocaine in 2013 (EMCDDA, 2014). Despite the negative consequences associated with repeated drug abuse, cocaine users continue to use the drug. In the last years the focus on cocaine-related cognitive deficits has risen and a number of studies have examined the long-term effects of cocaine on cognitive processes when comparing users to cocaine-free individuals (Bolla, Rothman, & Cadet, 1999; Goldstein et al., 2004; Jovanovski, Erb, & Zakzanis, 2005; Hulka et al. 2013a, b, c). Typically observed impairments include deficits in cognitive flexibility (Verdejo-García, Bechara, Recknor, & Pérez-García, 2006; Verdejo-García & Pérez-García, 2007), episodic memory (Manschreck et al., 1990; Mittenberg & Motta, 1993; Reske, Eidt, Delis, & Paulus, 2010; Vonmoos et al., 2013b), inhibitory control processes (Ersche et al., 2012; Fillmore & Rush, 2002; Goldstein & Volkow, 2002; Rosselli, Ardila, Lubomski, Murray, & King, 2001; Volkow et al., 2010), social and non-social decision-making (Hulka et al., 2014), prosodic and cross-modal emotion processing (Hulka, Preller, Vonmoos, Broicher, & Quednow, 2013) and recently, the control of semantic interference in language production (Ruiz et al. 2014). Thus, many processes that regulate thought and action seem to be especially impaired after long-term consumption (Block, Erwin, & Ghoneim, 2002; Jovanovski, et al., 2005; Volkow et al., 1992). Chronic users, compared to non-users, show impaired performance on a variety of tasks that measure executive control related-functions: a poorer ability to inhibit overt responses (Fillmore & Rush, 2002), compromised performance on tasks measuring flexibility (Verdejo-García, et al., 2006), dysfunctions in attention switching (Kübler, Murphy, & Garavan, 2005) and a poor performance on decision-making tasks ( Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001). Namely inhibition, the ability to stop predominant responses
or suppress irrelevant information, has been highlighted as a relevant impairment in stimulant abusers (Fillmore & Rush, 2002; Hester and Garavan, 2004; Morie et al. 2014; Morein-Zamir et al. 2013). The fronto-striatal circuitry is proposed as the neural substrate for inhibitory control (Bari & Robbins, 2013; Miller & Cohen, 2001) and dopamine, the neurotransmitter targeted by cocaine (Hershey et al., 2004) plays an important neuromodulatory role (Arnsten, Wang, & Paspalas, 2012; Previc, 1999; Robbins & Arnsten, 2009). In this regard, response-inhibition has proven a useful cognitive function to gauge the integrity of fronto-striatal systems in stimulant drugs users (Morein-Zamir and Robbins, 2014).

Recent studies show that an increasing population of recreational cocaine polydrug users, who do not meet the criteria for abuse or dependence but take cocaine on a monthly frequency (1-4 g per month), show similar cognitive impairments to chronic cocaine users. For example, in the study of Colzato, van den Wildenberg and Hommel (2007), it was shown that recreational cocaine polydrug users evidenced impairments in response inhibition, but not response execution, measured through a stop signal task. They also do not show the phenomenon of inhibition of return as compared to non-cocaine users (Colzato & Hommel, 2009). Furthermore, recent studies show that recreational use of cocaine is also associated with impairments on tasks tapping sustained attention and attentional shifting (Soar, Mason, Potton, & Dawkins, 2012; Vonmoos et al., 2013) and the emergence and resolution of response conflict (Sellaro, Hommel, & Colzato, 2013).

Many studies have consistently demonstrated difficulties in the ability to inhibit responses in cocaine users (Bolla, Cadet, & London, 1998; Colzato & Hommel, 2009; Colzato, et al., 2007; Morie at al. 2014; Fillmore et al. 2002; Hester and Garavan, 2002; Garavan and Hester, 2004). Inhibition represents a family of processes, rather than a single-unitary process, that acts at different stages of information processing. For this reason, Miyake and colleagues (2004) proposed two processes that distinguish between
the stopping of dominant responses (behavioral inhibition) and the capacity to suppress interference, i.e. the exclusion of non-relevant information in accordance with the demands of the current situation (cognitive inhibition). This cognitive inhibition permits the selection of relevant information and avoids the irrelevant information that can interfere during processing stages (Harnishfeger, 1995; Nigg, 2000). Similarly, memory retrieval requires us to suppress no-longer relevant information from our memory and replace it with new information, possibly by erasing the memory traces and associated information through an inhibitory-like mechanism (Anderson, 2003; Bjork, Bjork, & Anderson, 1998; Bjork, 1989).

To date, much research has sought to clarify the relationship between drug abuse and inhibitory control using selective attention and action control tasks (see Bardo, Fishbein & Milich, 2011), however few studies have studied specifically the plausible impairment of intentional memory suppression in drug abuse (Noël et al., 2009; Zou, Zhang, Huang, & Weng, 2011).

The aim of this paper is to observe whether cocaine abuse may contribute to impairments in intentional suppression in episodic memory. In order to examine this possibility, we used a directed forgetting (DF) task using the list method (Bjork, 1970, 1989; MacLeod, 1999), in which participants are overtly instructed to forget recently encoded items, inducing memory impairment for those items. In the list version of DF, participants are presented with a list of items to be studied for later recall. After presentation of the first list, participants in the forget condition are instructed to forget the items they have just learned. Following these instructions, a second list is presented, and participants are required to learn these new items. For the recall test, they are asked to remember the items from both lists. As a control, there is a remember condition where participants are presented two lists of items, and they are instructed to remember both. That is, participants in the remember condition also learn two lists, but they are not instructed to forget the first one before presentation of the
second list. Although the procedure usually involves comparison of two groups, remember and forget, directed forgetting effects are also observed in within-participant designs, where all participants performed the remember task in the first session and the forget task in the second session (e.g., Soriano et al. 2009). Two findings are observed consistently: First, cost effects triggered by the instruction to forget, where people’s recall is impaired for List 1 items in the forget condition as compared to List 1 recall in the remember condition and as compared to List 2 recall in the forget condition. Second, when participants believe that they can forget the first list, they often recall more List 2 items on the final test when compared to the remember condition, providing a clear benefit effect from the instruction to forget. The so-called directed forgetting effects (lower recall of List 1 items as compared to List 2 items in the forget instructions and List 1 items in the recall condition) are taken as measures of memory suppression (Bjork, et al., 1998; Johnson, 1994; MacLeod, 1999).

Although there are alternative accounts of the DF effects and there might be more than one possible factor underlying them, current theories favor an account in terms of inhibition (Anderson & Hanslmayr, 2014; Bjork, et al., 1998; Bjork, 1989; see Sahakyan & Kelley, 2002 for a contextual-based account). This account assumes that instructions to forget convert List 1 items to potential competitors that may suffer a transitory state of inhibition, which is regulated by a control mechanism that reduces the accessibility of List1 items (Anderson, 2001; Anderson & Green, 2001; Bjork, et al., 1998; Bjork, 1989). Several studies found reduced DF effects in populations thought to suffer executive control deficit, such as the elderly (Aguirre, Gomez-Ariza, Bajo, Andres, & Mazzoni, 2014; Zacks & Hasher, 1994), young children (Harnishfeger & Pope, 1996), frontal-lobe damaged patients (Conway & Fthenaki, 2003), and patients with schizophrenia (Soriano, Jimenez, Roman, & Bajo, 2009). More relevant for our work is that DF seems to be impaired in abstinent heroin addicts (Zou, et al., 2011) and abstinent individuals with alcoholism (Noël, et al., 2009), who show greater susceptibility to proactive interference.
In this paper, we investigated whether cocaine use may impair the mechanism responsible for intentional forgetting of memories in chronic cocaine users in rehabilitation (experiment 1) and recreational cocaine polydrug users (experiment 2), by using a DF procedure (Bjork, Laberge, & Legrand, 1968) in which participants were overtly instructed to self-initiate the forgetting of recent acquired information. Based on recent research showing deficits in inhibitory control in cocaine users, we expected reduced DF effects for both chronic users (experiment 1) and recreational users (experiment 2)¹ relative to matched cocaine-free control participants.

General methods

Apparatus, stimuli and procedure

All participants were tested individually. They first completed a drug use questionnaire, then they performed the screening and the intelligence task, and finally the DF task using the list method. In this task participants were told that they would be presented with two lists of words to learn that they would have to recall later. The DF procedure’s stimuli consisted of two lists of ten words each that were matched on frequency and word length (stimuli were drawn from Soriano & Bajo, 2007). For the remember condition and the forget condition, two lists of ten words each were randomly taken from a pool of twenty words: ten words served as stimuli for List 1 and the remaining words constituted the List 2 stimuli. The two lists were randomly assigned to the condition of forget or remember instructions. The assignment of items to each list was constant for all participants. Item order

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¹ Chronic cocaine users in rehabilitation were screened for other drug use. We found that they only used cocaine except for one participant, who had also used MDMA. Recreational cocaine users, on the other hand, sporadically used other drugs such as MDMA or cannabis, but they mainly and preferably used cocaine. As the recreational users were not “pure” cocaine users, this group of users was called “recreational cocaine polydrug users”.


within the lists was randomized for each participant and each list was equally often used in the condition of remember and forget, and equally often served as the first or second presented list. The experiment had a 2 x 2 x 2 mixed design, with instructions (remember or forget) and list output (List 1 and List 2) as within participants factors and group (chronic cocaine users in abstinence or recreational cocaine polydrug users and controls) as the between-groups factor.

In the remember condition, participants were instructed to study two list of items. First, a List 1 was presented in the center of a computer screen in intervals of two seconds. Second, after a pause, List 2 items were also presented for studying. Once List 1 and List 2 were presented, participants were required to count backwards from a three-digit number in steps of three for 30 seconds as a distractor task to control for recency effects. After this, participants were given a sheet of paper and were asked to freely recall as many of the words as they could from both lists.

The forget condition was similar to the remember condition with the exception of the forget instructions provided after studying List 1. Participants were told that List 1 was just a practice list to familiarize them with the procedure; and they were asked to forget the just presented items and to remember only the next list, which was the real experimental list that they would have to recall later. At recall, they were asked to recall all of the words they were presented, even the words they had been told to forget (see figure 1). The experiment was conducted in two sessions. The order of the conditions remained fixed for all participants, since results by Zellner and Bauml (2006) and Soriano and Bajo (2007) have shown that the order of conditions does not affect the DF effect. Also, presenting the remember condition first avoided confronting the participants with the surprise test after the first session, and having to give them further instructions to ensure that they would not be deceived again (see Soriano et al., 2009 for a similar procedure). To avoid that participants noticed that both
tasks were related, care was taken that a period between 1 and 3 months elapsed between the two sessions.

**Figure 1.** Sketch of the directed forgetting procedure used in experiment 1 and experiment 2.

In both experiments, participants were matched for race, age and IQ [measured by Raven’s standard progressive matrices (Raven et al. 1988)]. Furthermore, to ensure intact verbal and memory functions, the participants preformed a Boston naming test (Kaplan et al. 1983), a modified version of the verbal fluency test (VFT) for native Spanish speakers from SCIP [Screen for cognitive impairment in psychiatric patients] (Pino et al. 2006) and the memory span test (Daneman and Carpenter 1980). Participants filled in a self-report questionnaire on recent use, amounts, and patterns of alcohol and drug consumption during the last six months (cf. Colzato and Hommel, 2009, Colzato et al., 2007). To encourage participants’ compliance with the instructions, saliva samples were obtained (not further analyzed) at the beginning of the experiment (cf. Colzato, Erasmus and Hommel, 2004). We obtained written informed consent from all participants after providing them with an explanation of the nature of the experiment. The local ethics committee approved the protocol and the compensation of 20 euro for participation in the study.

**Statistical analysis**

Analyses were performed using IBM SPSS statistics® 20. In both experiments we adopted a significance level of $p < 0.05$. 
Independent samples $t$-tests were used to analyze binary comparisons and analyses of variance (ANOVAs) otherwise. We performed $t$-test for analysis of age, IQ, and alcohol consumption and neuropsychological screening task differences between the chronic cocaine users in rehabilitation group or the recreational cocaine users groups, and cocaine-free controls. Differences between groups in the DF effects were analyzed using repeated measures ANOVA, with group (chronic cocaine users in abstinence or recreational cocaine polydrug users vs cocaine-free controls) as between-subject factor. We also performed interquartile analyses for outliers detection. The results of these analyses indicated that two participants from Experiment 1 (one in the control group and one chronic cocaine user) were classified as outliers and they were excluded from the analyses. Newman-Keuls post hoc analyses were carried out on the critical comparisons to assess DF effects. Partial correlation coefficients were computed between relevant cocaine use variables (e.g., lifetime amount, times per week of cocaine use, maximum peak in 12 hours, and monthly consumed cocaine in grams) and cognitive performance on the DF task in order to test whether the magnitude of cognitive impairments is proportional to the amount of cocaine consumed and to control for the consumption of those drugs (alcohol, tobacco, and cannabis) that varied significantly between the cocaine groups and controls. Effect magnitudes were assessed by calculating partial Eta squared ($\eta^2_p$).

Experiment 1

Participants

Thirty-eight adults (33 men and 5 women) participated in the experiments. They formed the two experimental groups of 19 chronic users in rehabilitation and 19 cocaine-free control. Chronic cocaine users in rehabilitation were recruited from Proyecto Hombre Granada rehabilitation center. Before their participation in the rehabilitation program, chronic users were taking cocaine on a daily basis for several years ($M=8.92$, $SD=4.67$), administrated by
snorting route. Cocaine abstinence is a requirement to attend the rehabilitation program, and at the moment of experimental testing, they were cocaine abstinent for several months ($M=4.71$, $SD=4.03$). The inclusion criteria were 1) meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for cocaine dependence as assessed by the Structured Clinical Interview for DSM-IV disorders (American Psychological Association, 2000) – Clinician version (SCID, First et al. 1997); 2) a minimum abstinence interval of 30 days for all abuse substances except tobacco, checked by periodic urine toxicology tests, therapists or self-reports. The exclusion criteria were 1) the presence of any Axis I or Axis II disorders except substance abuse, determined by the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997), a brief diagnostic tool that screens for several psychiatric disorders; 2) a history of brain injury or central nervous system diseases; 3) an excessive intake of alcohol (>280 g/week for men and >168 g/week for women) (Foster and Marriott 2006). At the time of the assessment, individuals in the rehabilitation program were free of psychiatric prescription medication. Nineteen adults comprised the control group. We recruited the control participants via notes posted on community bulletin boards and by word of mouth. Control group individuals did not meet any Axis I or Axis II psychiatric disorders, including substance abuse (except for tobacco) and no clinically significant medical disease (e.g. multiple sclerosis). Participants in the two groups were matched on race, age and IQ [measured by Raven’s standard progressive matrices (Raven, Court, & Raven, 1988)].

In the last six months, prior to participation, five chronic cocaine users in rehabilitation and three cocaine-free user also smoked marijuana, while one chronic cocaine user in rehabilitation reported having used MDMA (ecstasy). All participants reported never using ketamine, LSD, steroids, GHB, barbiturates or opioids. Although chronic cocaine users in rehabilitation group were engaged in the detoxification program, they were periodically (every 30 days) screened for drug use through urine analysis, and we asked them to refrain from taking all types of psychoactive drugs for at
least two days before the experiment. In addition, all participants were asked not to consume alcohol the night before the experimental session and to have a normal night of rest.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Chronic cocaine users in rehabilitation</th>
<th>Cocaine-free controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M:F) ns</td>
<td>19 (16:3)</td>
<td>19 (17:2)</td>
</tr>
<tr>
<td>Age (years) ns</td>
<td>31.9 (4.7)</td>
<td>29.6 (5.9)</td>
</tr>
<tr>
<td>Raven IQ ns</td>
<td>104.7 (7.7)</td>
<td>101.6 (5)</td>
</tr>
<tr>
<td>Cigarettes (unit/day) *</td>
<td>12.6 (7.1)</td>
<td>1.9 (3.7)</td>
</tr>
<tr>
<td>Alcohol (units/weeks) **</td>
<td>26.9 (22.81)</td>
<td>4.2 (4.9)</td>
</tr>
<tr>
<td>Monthly cannabis (joints) ns</td>
<td>3.6 (7.3)</td>
<td>0.6 (1.5)</td>
</tr>
<tr>
<td>Years using cocaine</td>
<td>8.9 (4.68)</td>
<td>0</td>
</tr>
<tr>
<td>Monthly exposure (grams)</td>
<td>14.9 (15.9)</td>
<td>0</td>
</tr>
<tr>
<td>Maximum amount in a 12-h period (grams)</td>
<td>2.7 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Mean months in abstinence</td>
<td>4.01 (4.73)</td>
<td>0</td>
</tr>
<tr>
<td>Monthly spent money (EUR)</td>
<td>896 (956.9)</td>
<td>0</td>
</tr>
<tr>
<td>MDMA (grams/last 6 months)</td>
<td>0.3 (1.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Demographic characteristics and self-reported use of cocaine and other psychoactive drugs in experiment 1.

Notes. Raven IQ: IQ measured by means of the Raven’s standard progressive matrices, MST: Memory span test
nsNon-significant difference
*Significant group difference; p< 0.05; ** p < 0.01
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Results

Demographics and drug use statistics are provided in Table 1. As mentioned, we assessed the alcohol habits of the participants through a self-reported questionnaire enquiring about their weekly intake of alcoholic drinks. Since the strengths of different types of alcoholic beverages vary significantly, we adopted the definitions of standard "drinks" or "units," equal to a 10 ml or 8 grams of pure ethanol (International Center for Alcohol Policies, 2005; Spanish Ministry of Health, 2007). As can be observed in Table 1, chronic cocaine users differed from controls in the amount of tobacco, alcohol and cannabis consumed before they entered into the rehabilitation program, although all of them were not consuming alcohol or cannabis once they entered into the program.

<table>
<thead>
<tr>
<th>Test</th>
<th>Chronic cocaine users in rehabilitation</th>
<th>Cocaine-free controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>51.8 (4.9)</td>
<td>49.6 (5.4)</td>
</tr>
<tr>
<td>VFT</td>
<td>44.4 (8.3)</td>
<td>47 (10.8)</td>
</tr>
<tr>
<td>MST</td>
<td>3.2 (0.7)</td>
<td>2.78 (1.03)</td>
</tr>
</tbody>
</table>

Table 2. Mean scores of neuropsychological test performance in Experiment 1.

Notes. BNT: Boston naming test; VF: Verbal fluency test; MST: Memory span test.

ns=Non-significant difference.

Figure 2. Mean number of recalled words as a function of group, instruction, and list in experiment 1. Error bars represent standard error of mean.
To ensure intact verbal and memory functions, the participants performed several screening tasks: a Boston naming test (Kaplan, Goodglass, & Weintraub, 1983), a modified version of test of verbal fluency (VFT) for native Spanish speakers from SCIP [Screen for cognitive impairment in psychiatric patients] (Pino et al., 2006) and the memory span test (Daneman & Carpenter, 1980). No significant group differences were obtained for intelligence, \( t(36) = -1.49, p = 0.14 \); memory span test, \( t(36) = -1.63, p = 0.11 \); Boston naming task, \( t(36) = -1.31, p = 0.19 \) or verbal fluency, \( t(36) = 0.82, p = 0.41 \). Table 2 shows performance on intelligence and neuropsychological test.

Figure 2 shows the mean number of words recalled for each condition of the DF experiment. The results of the ANOVA on correct recall with group (chronic cocaine users and cocaine-free controls) as a between subject factor, and instructions (forget and remember) and List (List 1 and List 2) as a within-subject factor showed a significant main effect of group \( F(1, 36) = 32.63, p < 0.001, \eta^2_p = 0.37 \]. This indicated that the cocaine-free control group remembered more items \( (M=4.66, SD=1.93) \) relative to the chronic cocaine users in rehabilitation group \( (M=2.75, SD=1.34) \). Moreover, the main effect of List was significant \( F(1, 36) = 21.35, p < 0.001, \eta^2_p = 0.27 \] showing that more items were recalled for List 2 \( (M=4.16, SD=2.03) \) than for List 1 \( (M=3.25, SD=1.67) \). The interaction List x group was significant \( F(1, 36) = 11.64, p < 0.01, \eta^2_p = 0.27 \].
\( \eta^2_p = 0.24 \). Post hoc Newman-Keuls analyses showed that the control group remembered fewer List 1 items \((M=3.87, SD=1.76)\) relative to List 2 items \((M=5.45, SD=1.78)\) \(p < 0.001\), whereas this difference between List 1 \((M=2.63, SD=1.34)\) and List 2 \((M=2.87, SD=1.34)\) was not present for the chronic cocaine users in rehabilitation \(p = 0.39\). Importantly, the interaction List x instructions was significant \([F (1, 36) = 21.35, p < 0.001, \eta^2_p = 0.37]\). Post hoc Newman-Keuls analyses showed the typical DF effect with less List 1 items recalled in the forgetting condition \((M=2.71, SD=1.56)\) than List 2 items in the remember condition \((M=4.55, SD=2.13)\) \(p < 0.01\). The three way interaction instructions x List x group was significant \([F (1, 36) = 4.61, p = 0.039, \eta^2_p = 0.11]\). To further analyze this interaction, we performed post hoc Newman-Keuls procedure for the cocaine-free controls and chronic cocaine users groups to explore cost and benefit effects.

First, we analyzed the costs of instructions to forget on List 1. These comparisons indicated, first, that cocaine-free controls’ recall for the List 1 items of the forget condition \((M=3.16, SD=1.8)\) was significantly lower than the recall of List 1 items in the remember condition \((M=4.58, SD=1.43)\) \(p < 0.01\), whereas chronic cocaine users in rehabilitation did not forget significantly more List 1 items in the forget task \((M=2.26, SD=1.15)\) than in the remember task \((M=3, SD=1.45)\) \(p = 0.27\) (see figure 2). Similarly, comparisons of recall from List 1 items in the forget condition relative to List 2 items in the forget condition was significant for the control group \(p < 0.01\), whereas the chronic cocaine users in rehabilitation did not show this difference \(p = 0.17\). Finally, we analyzed the benefits of forgetting. This comparison showed that cocaine-free controls recalled more List 2 items in the forget condition \((M=6.11, SD=1.63)\) than in the remember condition \((M=4.79, SD=1.72)\) \(p < 0.01\). However, for the chronic cocaine users in rehabilitation the recall of list 2 items in the forget condition \((M=3, SD=1.25)\) as compared to the remember condition \((M=2.74, SD=1.45)\) was not significantly different \(p = 0.51\).
Discussion

Experiment 1 aimed to test the hypothesis that chronic cocaine users in rehabilitation might not be able to intentionally forget no-longer relevant information when instructed to do so, even when instructions stressed that this information might interfere with recall of relevant information. Results show that while cocaine-free controls show the typical memory suppression effects associated with the directed forgetting procedure, the chronic cocaine users in rehabilitation do not show these effects. That is, they did not show the usual impairment of List 1 items relative List 2 when instructed to forget or the diminished recall of List 1 items in the forget condition relative to List 1 in the remember condition. In addition, chronic cocaine users in rehabilitation did not show the benefit of forgetting. They were not able to benefit from forgetting of List 1. Thus, recall of List 2 in forget and recall conditions was similar for the users, whereas the cocaine-free controls showed better recall of list 2 in the forget than in the remember condition. Presumably, chronic cocaine users were not able to suppress information from List 1 as instructed, and they were not able to benefit from it, possibly because List 1 forgetting might not have been strong enough to produce this benefit so that chronic users still suffer from proactive interference.

In order to assess whether other cocaine users that do not qualify as chronic cocaine users, but often consume cocaine for recreational purposes, would more clearly show intentional forgetting deficits, we conducted a new experiment with the same materials and procedure as experiment 1, but testing recreational cocaine polydrug users’ ability to forget non-relevant memories.

Experiment 2

Participants

Forty-four healthy adults (21 men and 23 women) served as participants for partial fulfillment of course credits or a financial
compensation. These constituted both the recreational cocaine polydrug users and cocaine-free controls. We recruited the participants via notes posted on community bulletin boards and by word of mouth. Recreational cocaine polydrug users met the following criteria: 1) a monthly consumption (1 to 4 grams) by snorting for a minimum of two years; 2) no axis I or Axis II psychiatric disorders [DSM-IV; (American Psychological Association 2000)], including substance abuse other than cocaine and tobacco; 3) no clinically significant medical diseases; 4) no use of prescription medication. Cocaine-free controls met the same criteria except they reported no history of past or current cocaine use. Participants were selected by means of a phone interview using the MINI (Lecrubier et al. 1997), a brief diagnostic tool that screens for several psychiatric disorders. The sample was obtained from a pool of approximately 50 potential volunteers who responded to the advertisements for studies conducted in our lab over a period of six months. Within this pool of potential participants, the most common reason for excluding an individual from the study was meeting criteria for psychiatric disorders (psychotic symptoms, anxiety and depression), alcohol abuse or medication. Furthermore, to ensure intact verbal and memory functioning the participants performed a Boston naming test (Kaplan et al. 1983), a modified version of VFT for native Spanish speakers from SCIP (Pino et al. 2006) and the memory span test (Daneman & Carpenter, 1980).

Participants were asked to refrain from taking all psychoactive drugs for at least two days, not to consume alcohol on the night before the experimental session and to have a normal night rest. To encourage participants’ compliance with the instructions, saliva samples were obtained (not further analyzed) at the beginning of the experiment (cf. Colzato, Erasmus and Hommel 2004).

In the six months prior to participation, thirteen recreational cocaine polydrug users smoked cannabis while seventeen recreational users reported having used MDMA (ecstasy) and eleven reported using ketamine. Participants in the two groups
were matched on race, age and IQ (Raven, et al., 1988)]. All participants reported never using LSD, steroids, GHB, barbiturates or opioids.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Recreational cocaine polydrug users</th>
<th>Cocaine-free controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (M:F) ns</td>
<td>22 (10:12)</td>
<td>22 (11:11)</td>
</tr>
<tr>
<td>Age (years) ns</td>
<td>25.1 (3.3)</td>
<td>23.7 (2.7)</td>
</tr>
<tr>
<td>Raven IQ ns</td>
<td>102.7 (7.0)</td>
<td>103.2 (8.8)</td>
</tr>
<tr>
<td>Cigarettes (unit/day) *</td>
<td>9 (7.3)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Alcohol (units /weeks) **</td>
<td>15.2 (10.0)</td>
<td>4.7 (3.7)</td>
</tr>
<tr>
<td>Monthly cannabis (joints) **</td>
<td>8.5 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Years using cocaine</td>
<td>4.4 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>Monthly exposure (grams)</td>
<td>3.8 (3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Maximum amount in a 12-h period (grams)</td>
<td>1.1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Mean days in abstinence</td>
<td>15.8 (18.3)</td>
<td>0</td>
</tr>
<tr>
<td>Monthly spent money (EUR)</td>
<td>94.5 (61.2)</td>
<td>0</td>
</tr>
<tr>
<td>MDMA (grams/last 6 months)</td>
<td>1.75 (2.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3.** Demographical characteristics and self-reported use of cocaine and other psychoactive drugs in experiment 2.

*Notes. Raven IQ: IQ measured by means of the Raven’s standard progressive matrices, MST: Memory span test

ns=Non-significant difference

*Significant group difference; p< 0.05; ** p < 0.01
Table 4. Mean neuropsychological test performance scores in Experiment 2.

<table>
<thead>
<tr>
<th>Test</th>
<th>Recreational cocaine polydrug users</th>
<th>Cocaine-free controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>50.6 (4.2)</td>
<td>50 (5.51)</td>
</tr>
<tr>
<td>VFT</td>
<td>43.5 (10.0)</td>
<td>41.3 (10.0)</td>
</tr>
<tr>
<td>MST</td>
<td>2.9 (0.7)</td>
<td>3.2 (0.7)</td>
</tr>
</tbody>
</table>

Notes. BNT: Boston naming Test; VF: Verbal fluency test; MST: Memory span test.
nsNon-significant difference.

Results

Demographics and drug use statistics are provided in Table 3. No significant group differences were obtained for intelligence, \( t(42) = 0.18, p = 0.85 \); memory span test, \( t(42) = 1.40, p = 0.47 \); Boston naming task, \( t(42) = -0.36, p = 0.71 \) or verbal fluency, \( t(42) = -0.72, p = 0.47 \). Table 4 shows performance on the intelligence and neuropsychological tests. We performed an overall ANOVA with group (recreational cocaine polydrug users and controls) as a between-participant factor, and instructions (forget and remember) and List (List 1 and List 2) as a within-participants factors (see Figure 3). A significant main effect of group \( [F(1, 42) = 6.44, p < 0.01, \eta^2_p = 0.13] \) indicated that the control group remembered more items \((M=5.17, SD=2.64)\) than the group of recreational cocaine polydrug users \((M=3.93, SD=1.94)\). The main effect of List was significant \( [F(1, 42) = 5.74, p < 0.05, \eta^2_p = 0.12] \) showing that List 2 recall was better \((M=4.88, SD=2.42)\) than List 1 recall \((M=4.21, SD=2.31)\). The main effect of instructions was not significant \((F<1)\), but the interaction between List and group reached significance \( [F(1, 42) = 4.29, p < 0.05, \eta^2_p = 0.09] \). Post hoc Newman-Keuls analyses showed that the control group
remembered fewer List 1 items ($M=4.54$, $SD=2.52$) relative to List 2 items ($M=5.79$, $SD=2.62$) [$p < 0.01$], whereas this difference between List 1 ($M=3.88$, $SD=2.00$) and List 2 ($M=3.97$, $SD=1.87$) was not present for the recreational cocaine polydrug users ($p = 0.81$). The interaction between List and instructions was significant [$F(1, 42) = 27.42$, $p < 0.001$, $\eta^2_p = 0.39$]. Post hoc Newman-Keuls analyses showed the typical DF effect, with fewer List 1 items being recalled in the forgetting condition ($M=3.65$, $SD=2.29$) than in the remember condition ($M=4.77$, $SD=2.17$) [$p < 0.01$]. The interaction between instructions, List and group was significant [$F(1, 42) = 13.02$, $p < 0.001$, $\eta^2_p = 0.23$]. To further analyze this interaction, we performed additional post hoc Newman-Keuls analyses for the cocaine-free controls and recreational cocaine polydrug users groups to explore cost and benefit effects.

First, we analyzed the costs of the instruction to forget List 1. These comparisons indicated, first, that cocaine-free controls’ recall for the List 1 items of the forget condition ($M=3.68$, $SD=2.47$) was significantly less than the recall of List 1 items on the remember task ($M=5.40$, $SD=2.32$) [$p < 0.01$], whereas recreational cocaine polydrug users did not forget significantly more List 1 items on the forget task ($M=3.63$, $SD=2.15$) than on the remember task ($M=4.13$, $SD=1.85$) [$p = 0.24$]. Similarly, comparisons of recall from List 1 items in the forget condition relative to List 2 items in the forget condition was significant for the control group [$p < 0.01$], whereas the recreational cocaine polydrug users did not show this difference [$p = 0.86$]. Finally, we analyzed the benefits of forgetting. This comparison showed that cocaine-free controls recalled more List 2 items at the forget condition ($M=6.90$, $SD=2.22$) than in the remember condition ($M=4.68$, $SD=2.57$) [$p < 0.001$]. However, for the recreational cocaine polydrug users the recall of list 2 items in the forget condition ($M=4.1$, $SD=1.94$) compared to the remember condition ($M=3.86$, $SD=1.83$) was not different [$p = 0.61$].
Finally, no significant Pearson’s correlations were found between the individual lifetime cocaine exposure, alcohol consumption, speed, cannabis and ketamine and the DF effect.

**Figure 3.** Mean number of recalled words as a function of group, instructions, and list in Experiment 2. Error bars represent standards error of mean.

### Discussion

Experiment 2 aimed to investigate whether recreational cocaine polydrug users showed impaired intentional inhibitory processes during episodic memory retrieval. Results clearly indicate that recreational cocaine polydrug users do not show the usual memory suppression effect associated with the directed forgetting procedure. Thus they did not show the usual impairment of List 1 items relative to List 2 when instructed to forget List 1 items in the forget condition relative to List 1 in the remember condition. Similarly, they did not show the benefit of forgetting so that recall of List 2 items in the forget condition was similar to the recall of List 2 items in the remember condition. As the DF effect is usually interpreted as the result of intentional forgetting mechanisms
(Anderson & Hanslmayr, 2014; Bjork, 1989), this pattern of results suggests that recreational cocaine polydrug users are not able to intentionally suppress List 1 items to prevent interference from List 2 items. The results show that although recreational cocaine polydrug users do not use the drug on a daily basis, their monthly continuous small amounts of cocaine ($M=3.80, SD=3.90$) seems to impact inhibitory processes engaged in the suppression of irrelevant information in episodic memory.

**General Discussion**

This study investigated for the first time the dynamics of intentional forgetting in chronic users in rehabilitation and recreational polydrug users of cocaine, who were carefully screened and matched to cocaine-free control participants performing a directed forgetting task. Different methods have been used to elicit the DF effect (see Basden & Basden, 1998; MacLeod, 1999). In the present research we used the list method to elicit the inhibitory processes engaged during remembering. Several lines of research have proposed inhibition as the mechanism underlying this effect (Bjork et al., 1998; Bjork, 1989; but see Sahakyan & Kelley, 2002 for a non-inhibitory account). In addition, there is evidence supporting the impairment of inhibitory processes in chronic and recreational cocaine users (Ersche et al., 2012; Fillmore & Rush, 2002; Goldstein & Volkow, 2002; Rosselli, Ardila, Lubomski, Murray, & King, 2001; Volkow et al., 2010; Colzato & Hommel, 2009; Colzato et al., 2007). Given the recruitment of inhibitory mechanisms in intentional forgetting and the impairment of these mechanism due to cocaine use, it creates a perfect scenario to test the relationship between them by focusing on the performance of chronic in rehabilitation and recreational cocaine polydrug users and a cocaine-free control group on their ability to actively inhibit irrelevant information in their episodic memory.

The control group in both experiment 1 and 2 replicated the typical directed forgetting effect observed in seminal studies
(Bjork et al., 1998; Bjork, 1989), showing a decrease in the recall of List 1 items under the forget instructions and the typical cost and benefit effects. In experiment 1, we found that chronic cocaine users attending a rehabilitation program do not show a reliable directed forgetting effect, indicating that they were not able to intentionally suppress information from memory. Similarly, in experiment 2 recreational cocaine polydrug users were not able to intentionally suppress information and they did not show reliable directed forgetting effects. These results suggest that cocaine consumption is related to a deficit in intentional forgetting. In addition, the results of the reduced directed forgetting effect in recreational cocaine polydrug users, compared to the control group, allow us to speculate that even the use of small amounts of cocaine results in poor performance in effectively triggering the inhibitory mechanism.

Given the relationship between cocaine abuse and reduced functioning of prefrontal cortex (Herster and Garavan, 2004; Morein-Zamir at al., 2013; see Goldstein and Volkow, 2011 for a review) and dopamine D2 (DAD2) receptors (Volkow, Fowler, & Wang, 1999), its neuromodulatory effect (Previc, 1999; Robbins & Roberts, 2007), the role of inhibitory processes in lateral prefrontal cortex (LPFC), anterior cingulate (ACC) and orbitofrontal cortex (Posner & Raichle, 1994) and the role of dLPFC and ACC in memory suppression (Anderson et al., 2004), the presence of the aforementioned memory suppression deficit was expected. And, therefore, the results are in line with those investigations that suggest that even small amounts of cocaine used regularly are connected to deficits in executive control processes (Colzato, Huizinga, & Hommel, 2009; Colzato & Hommel, 2009; Colzato, et al., 2007). In addition, the results of the reduced directed forgetting effect in recreational cocaine polydrug users, compared to the control group, allow us to speculate that the continuous and ongoing use of cocaine results in poor performance in effectively triggering the inhibitory mechanism.
The apparent link between cocaine abuse and this deficit in memory suppression highlights the variety of inhibitory processes that may be altered by the abuse of stimulant drugs that act on the catecholaminergic synapses in brain areas that regulate and control executive processes. Our results cannot be explained by several potentially confounding factors, since our participants were screened for several psychiatric disorders (schizophrenia, ADHD or obsessive-compulsive disorder) that have been associated with dopaminergic alterations (Davis, Kahn, Ko, & Davidson, 1991; Pooley, Fineberg, & Harrison, 2007; Tripp & Wickens, 2008). Given that MDMA is associated with impairments in working memory processes, and cannabis leads to dysfunction in cognitive flexibility (Verdejo-García, López-Torrecillas, Aguilar de Arcos, & Pérez-García, 2005), both drugs are unrelated to the production of impairments in inhibitory control. Hence, we doubt that our results can be attributed to the consumption of cannabis or MDMA. In addition, since our groups were matched on age, it cannot explain our results even though the directed forgetting phenomenon appears to diminish in populations thought to suffer deficits in executive control, such as in the elderly (Aguirre et al., 2014, Zacks & Hasher, 1994) or due to the decline of inhibitory efficiency associated with aging (Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Particularly important was the screening of alcohol consumption in both experiments due to the impairing effect of acute alcohol on inhibitory control (Fillmore & Vogel-Sprott, 2000; Fillmore, 2007; Noël, et al., 2009). A possible impairment of non-chronic alcohol users is undetermined. Notwithstanding, given that impaired inhibitory control could promote excessive drinking, it is reasonable that individuals who experience a greater malfunction of inhibitory control should be likely to drink alcoholic drinks more excessively (Weafer & Fillmore, 2008).

It is interesting to note that both chronic in rehabilitation and recreational cocaine users showed an overall memory deficit, and this deficit does not seem to recover after a short period of abstinence since it is still present in the chronic in rehabilitation group. This is consistent with prior research with both recreational
and abstinent chronic in rehabilitation users that shows persistent impairments in verbal learning efficiency, which results in deficits in memory storage and recall (Ardila, et al., 1991; Beatty, et al., 1995; Manschreck, et al., 1990; Mittenberg & Motta, 1993; O’Malley & Gawin, 1990; Reske, et al., 2010; Rosselli & Ardila, 1996; Vonmoos, Hulka, Preller, Jenni, Baumgartner, et al., 2013). Some studies reported improvement of cognitive processes in cocaine users after cessation of the drug consumption (De Oliveira et al., 2009; Di Sclafani, 2002; Vonmoos et al., 2014; but see Bauer, 1996; van Gorp et al., 1999 for persistent neuropsychological impairment). These studies showed that while cocaine clearly has a significant effect on cognitive functions, cocaine users can eventually return to a normal brain functioning and avoid any permanent damage to their cognitive abilities. Because chronic cocaine use produces neuroadaptations in dopamine systems (Letchworth, Nader, Smith, Friedman, & Porrino, 2001; Nader et al., 2002), the reversibility of cognitive deficits after sustained abstinence suggests that neuroplastic adaptations might occur if the repeated pharmacological stimulus is discontinued. However, the chronic cocaine users in rehabilitation in experiment 1 did not show a recovery of cognitive functions after cocaine cessation suggesting that neuroadaptations may be a slow process that needs time to show its effects.

Finally, this study has certain methodological limitations that are common to many neuropsychological studies in the area of substance abuse. First, particularly important was the screening of alcohol consumption in both groups so that participants selected for the study reported an average long-term consumption below the criteria for high alcohol use (280 g/week for men and 168g/week for women). In addition, although participants in experiment 1 were undergoing regular urine toxicology screens as part of the treatment, some participants in experiment 2 may have actively used either alcohol or cocaine within 24 to 48 hours prior to the experimental session, potentially affecting the performance in the directed forgetting task. Although with caution, the fact that the impairment appeared in both recreational and chronic users
(urine tested) suggests that this might not have been the case. Second, the design of our study allows us to reject alternative accounts of our observations in terms of age, IQ, and sex since the two user groups were matched with the controls in these variables. Similarly, the present results cannot be explained by factors regarding pre-existing psychiatric disorders which are known to affect response inhibition (Rosenberg et al. 1997; Schachar and Logan 1990; Thoma et al. 2007) since we performed a wide screening using the MINI to exclude preexisting psychiatric disorders (e.g. ADHD). Nevertheless, the results of this study for both groups do not allow us to completely rule out an account of their deficit in terms of preexistent underlying neurocognitive endophenotypes for stimulant drug addiction that may contribute to task performance (Ersche et al. 2012 a, b; Verdejo-Garcia et al. 2008). Furthermore, although we interpret the unreliable DF effects for both groups as a deficit in memory suppression due to cocaine consumption, this conclusion must be interpreted with care due to the cross-sectional design of this study and should be replicated through longitudinal studies focusing on this issue.

Another possible shortcoming of our study is that given the abuse rate of other drugs when consuming cocaine among recreational users (Grof et al. 2009; Kelly and Parsons 2008), it is difficult to separate the cognitive deficit produced by cocaine use from the effect of the use of other drugs. We tried to minimize this fact by selecting a predominant cocaine users’ sample and avoiding as much as possible selecting people that also abuse other stimulant drugs. We based our selection on self-report measures since previous studies have shown that self-reports of drug abuse are quite reliable and strongly correlated with objective measures of drug abuse (Glintborg et al. 2008; Zaldivar Basurto et al. 2009). Since our participants reported very low consumption of cannabis and MDMA, we doubt that our results may be attributed to the use of any of these two drugs. Moreover, studies that have examined the effect of MDMA and cannabis on executive functions have provided conflicting results. Whereas deficits in working memory appear to be likely consequences of chronic MDMA and
impairments in cognitive flexibility due to cannabis use (Verdejo-García et al. 2005), less consistent results were found in studies investigating inhibitory control in the abuse of both substances (Crean et al. 2011; Kalechstein et al. 2007). Despite these limitations and suggestions for further research, our study clearly suggests that impairments in memory suppression may be associated with cocaine consumption. Cocaine use seems to be associated with a low performance in inhibiting the ability to suppress irrelevant information. In summary, the results found in chronic in rehabilitation and recreational cocaine users are worrying, given that a dysfunctional adaptive mechanism of forgetting may be responsible for a variety of memory distortions in terms of updating information, which affects learning and recall in everyday behavior. This distortion can be translated to poor efficacy in forgetting information, causing a misconception of the acquirement of learning or affecting the ability to forget negative autobiographical memories.
References


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