CONTROLLING THOUGHT AND ACTION: A PERSPECTIVE FROM KHAT USERS AND COCAINE USERS

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EL CONTROL DEL PENSAMIENTO Y LA ACCIÓN:

UNA PERSPECTIVA DE LOS CONSUMIDORES DE KHAT Y CONSUMIDORES DE COCAÍNA

Manuel Jesús Ruiz Muñoz

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CONTROLLING THOUGHT AND ACTION: A PERSPECTIVE FROM KHAT USERS AND COCAINE USERS

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Tesis doctoral presentada por Manuel Jesús Ruiz Muñoz, en el Departamento de Psicología Experimental, para aspirar al grado de Doctor Internacional en el programa de Doctorado de Psicología de la Universidad de Granada.

El doctorando, **Manuel Jesús Ruiz Muñoz**, y los directores de la tesis, **Mª Teresa Bajo Molina** y **Bernhard Hommel** garantizamos, al firmar esta tesis doctoral, que el trabajo ha sido realizado por el doctorando bajo la dirección de los directores de la tesis y hasta donde nuestro conocimiento alcanza, en la realización del trabajo, se han respetado los derechos de otros autores a ser citados, cuando se han utilizado sus resultados o publicaciones.

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PROEFSCHRIFT

ter verkrijging van
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Promotor:	Prof. Dr. B. Hommel
Co-promotor:	Prof. Dr. M.T. Bajo, Universidad de Granada
	Dr. Lorenza S. Colzato, Universiteit Leiden

A todos aquellos que alguna vez me enseñaron algo,

To everyone who has at one point taught me something,

Sapere aude

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Chapter 1

Introduction

Cognitive control

One of the most intriguing mysteries of human cognition is the capacity for judgment, reasoning, decision-making and planning. This capacity allow us to face problems that need to be solved immediately and make decisions quickly and appropriately by monitoring the information of the external world continuously. Executive functions are considered the key that allows human high-order cognitive processes. They coordinate operations of various processes to accomplish a particular goal in a flexible manner (Miyake & Shah, 1999; Roberts, Robbins, & Weiskrantz, 1998). The mechanism or system responsible for the coordination of operations is called 'cognitive control'.

Cognitive control is a construct from contemporary cognitive neuroscience that refers to processes that coordinate and combine information from different cognitive systems. This control is reached through the adaptive selection and execution of information processing strategies. These strategies may vary from moment to moment depending on current goals, avoiding a rigid and inflexible cognitive system. A number of theoretical models have been proposed for how the control of cognition is achieved (Baddeley, 1996; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Cohen, Dunbar, & McClelland, 1990; Miyake et al., 2000; Norman & Shallice, 1986) and progress has been made towards identifying its neuroanatomical substrates (Cohen & O'Reilly, 1996; Goldman-Rakic, 1996; Luria, 1973; Posner & Petersen, 1989; see Niendam et al., 2012 for a review). The widely accepted Miyake's (2000) framework of cognitive control describes it as a set of general-purpose control mechanisms, often linked to the prefrontal cortex (PFC) of the brain, that regulate the dynamics of human cognition

and action. This model proposes that cognitive control emerges from three distinct cognitive processes: switching between mental sets or task sets (mental flexibility), monitoring and updating of information in working memory (WM updating), and inhibiting automatic or prepotent responses (inhibitory control). These processes have been studied in different contexts, such as development (Jones, Rothbart, & Posner, 2003), healthy aging (see Braver & Barch, 2002 for a review), bilingualism (Bialystok, Klein, & Viswanathan, 2004), psychiatric disorders (see Millan et al., 2012 for a review), and drug abuse (see Gould, 2010 for a review), providing useful insights into the nature, organization and role of individual differences in executive functions.

In spite of a prolonged effort, the understanding of this complex cognitive control and its neural foundations continues to evolve. There has been substantial progress in the last few decades regarding the research on the neural basis and architecture of cognitive control. The majority of research efforts have focused on the PFC, which subserves a range of cognitive control processes. Namely, the organization of lateral prefrontal cortex (LPFC) (Fletcher & Henson, 2001; Fuster, 2008; Miller, 2000; Shallice & Burgess, 1996) and its influence through top-down interactions between LPFC regions and premotor or posterior associative cortices are the main brain substrates that enable our constant adaptation to changing environments (see Badre, 2008 for a review). One outstanding question in this area is the relative role of dopamine (DA) as a gating signal in the basal ganglia and PFC. Some models focus on the role of DA in training a selective gating signal in the PFC that is capable of manipulating new information into some regions of the PFC, while leaving others to actively maintain older information (O'Reilly, Herd, & Pauli, 2010). In addition, during information processing, the phenomenon of conflict is likely to occur and it needs to be overcome by selecting the relevant information and suppressing the processing of irrelevant information. DA plays an important role in the modulation of information processing (Cools & Robbins, 2004). Cognitive control results from the ability of DA (Cools & Robbins,

2004; Robbins & Arnsten, 2009) to modulate the flow of information processing and the high sensibility of PFC to neurochemical environment alterations (Arnsten & Robbins, 2002). This interaction between the dopaminergic system and the PFC may serve as a gating function that regulates and protects from interference during information processing. Several factors like severe periods of stress and fatigue may alter this particular relationship (Chaudhuri & Behan, 2000; Lorist, Boksem, & Ridderinkhof, 2005; Lorist & Tops, 2003), but central for the aim of this thesis we focused on the stimulant drugs' ability to produce a core failure between neurotransmission and adapting behaviour to changing environmental demands (Dalley, Everitt, & Robbins, 2011; Ersche et al., 2012; Garavan & Hester, 2007; Jentsch & Taylor, 1999; Volkow et al., 2010).

Cognitive processes on drug abuse

Psychoactive drugs have the ability to alter mood state or behaviour by acting directly on mechanisms of brain function. Thus, it is not surprising that these drugs act in a similar manner to natural chemicals found in the brain, like neurotransmitters or hormones that regulate mood and behavior. However, beyond the biological role that drugs play in the body, drug abuse is commonly characterized by an affective, emotional, or social phenomenon, given the psychological factors and processes that sustain this behavior, such as reward, reinforcement, craving, and stress. Research on drug abuse and addiction has yielded important insights into abusers' desire to use drugs, and the process of addiction shows that it largely depends on altered brain function (Ersche et al., 2012; Hyman & Malenka, 2001; Leshner, 1997; Rácz, 2014). Drugs of abuse are known to produce their acute psychoactive effect by a multitude of neurochemical actions on nucleus accumbens and prefrontal cortical areas (Goldstein & Volkow, 2002; Koob, Sanna, & Bloom, 1998; Koob, 1992; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). However, the continuous use of the drug leads to feelings of craving and dependence, which are the results of a dysregulation of the brain's neurochemistry and abnormal cortical structures such as striatal tissues and prefrontal

cortices (Goldstein & Volkow, 2002; Koob & Le Moal, 2001; Nader et al., 2002; Rácz, 2014; Smith, Jones, Bullmore, Robbins, & Ersche, 2013; Volkow et al., 1993; Volkow et al., 2010).

Although hedonic and pleasant feelings might be at the center of motivation for the drive to seek and take drugs, certain cognitive processes such as memory likely contribute to obeying the drive, whereas others, like inhibitory control, contribute to the individual's effort to resist it. From this point of view, cognitive processes may be of significance in understanding the resisting to take the drugs, the transition from recreational use to chronic drug abuse, and the relapse so typical of those attempting abstinence or recovery when the drug use ceases. A core deficit in drug abuse is the failure to regulate behavior in response to changing environmental demands, leading to mental inflexibility, impulsivity, and/or compulsivity, therefore making the cognitive system more vulnerable to the intrusion of distracting information (Bolla et al., 2003; Colzato, Ruiz, van den Wildenberg, Bajo, & Hommel, 2011; Colzato, Ruiz, van den Wildenberg, & Hommel, 2012; Colzato, van den Wildenberg, & Hommel, 2007; Colzato, Ruiz, van den Wildenberg, & Hommel, 2011; Crean, Crane, & Mason, 2011; Fillmore & Rush, 2002; Fishbein et al., 2005; Hester & Garavan, 2004; Kelley, Yeager, Pepper, & Beversdorf, 2005; Kenney & Gould, 2008; Lyvers & Yakimoff, 2003; Moriyama, Muramatsu, Kato, Mimura, & Kashima, 2006; Ornstein et al., 2000; Solowij et al., 2002; Verdejo-García, Perales, & Pérez-García, 2007).

Thesis Question

Khat, an amphetamine-like compound from the khat plant (*Catha Edulis*), and cocaine, an alkaloid derivative extracted from coca plant *(Erythroxylon coca)*, are two drugs that are abused for their stimulant properties. Over the past few decades, the growing number of individuals using cocaine has increased the number of studies researching impaired cognitive processes during and after cocaine abuse. However, although khat is very popular in East Africa countries, it continues being a world-wide less known drug,

and there is still a lack of studies researching the possible cognitive impairment of khat users.

Both drugs are powerful stimulants of the central nervous system, acting on catecholaminergic synapses by releasing DA in the synaptic cleft and/or blocking the re-uptake action of dopamine transporters (DAT). Cathinone and cocaine also potentiate the neurotransmission of serotonin, epinephrine, and norepinephrine. Although these neurotransmitters are not mainly responsible for the rewarding properties of the drugs, they do have an effect on the central and peripheral nervous system. In any case, the major part of this research is concerned with the rewarding, reinforcing, and addicting properties of khat and cocaine that occur through their effect on DA and its transporters (Banjaw, Mayerhofer, & Schmidt, 2003; Kalix, 1990; Kuhar, Ritz, & Boja, 1991; Ritz, Lamb, Goldberg, & Kuhar, 1987).

The chewing of khat is a cultural, world-wide phenomenon that receives less attention than other stimulant drugs of abuse. Khat consumption in East Africa has increased during the last decades and has spread to ethnic communities in the rest of the world, such as in the Netherlands, United Kingdom, Canada, and the United States. Khat leaves have been chewed on since ancient times to alleviate fatigue, enhance work capacity, stay alert, reduce hunger, and induce euphoria and enhanced self-esteem. Studies addressing the neurobiological mechanisms underlying the use of khat are still very scarce, as are studies that have systematically investigated the acute and long-term cognitive effects of khat use. With regards to this last statement, this thesis shows the first findings in the research of khat and its impact on cognitive control functions through a series of experiments assessing inhibitory control, WM monitoring, mental flexibility and resolution of response conflict. In addition, this thesis reviews what is known about the pharmacological mechanisms, effects, toxicity, and withdrawal symptoms of khat and the synthetic cathinone mephedrone (4-methcathinone).

Regarding the stimulant drug cocaine, the available studies on chronic cocaine abuse still produce inconsistent results when comparing the performance of different types of cocaine users with cocaine-free controls (Goldstein et al., 2004; Jovanovski, Erb, & Zakzanis, 2005; Rogers & Robbins, 2001). Although certain studies have found deficits in memory, attention abstraction, decision-making and visuospatial abilities, others have failed to find deficits in some of the same functions (see Spronk et al., 2013 for a review). A common executive dysfunction that researchers in this field agree upon is related to inhibitory function (Bolla, Rothman, & Cadet, 1999; Colzato & Hommel, 2009; Colzato et al., 2007; Fillmore & Rush, 2002; Rosselli & Ardila, 1996; Verdejo-García, López-Torrecillas, Aguilar de Arcos, & Pérez-García, 2005). We investigated if this dysfunction extends to the performance of inhibition in the field of memory and language production. This thesis shows a set of studies in which chronic and recreational cocaine users were tested through a blocked-cycled naming task and a directed forgetting procedure. The performance on these tasks requires inhibition of word representations in virtue of their semantic-relatedness, and inhibition of prepotent memories in episodic memory, respectively.

Outline of thesis

This thesis contains six chapters reporting empirical work on the impact of khat and cocaine abuse on cognitive control and a review about the pharmacokinetics and pharmacodynamics of khat and mephedrone.

Chapter 2 reviews the behavioral and physiological effects of the natural psychomotor stimulants khat and the cathinone-derived designer drug mephedrone. This chapter describes their diverse historical and geographical background, their variety, their mechanisms of action, and their potential for producing abuse and dependence.

Chapter 3 investigates, in an experiment, the ability to inhibit and execute behavioral responses in adult khat and khat-free

users. Response inhibition and response execution were measured in a stop-signal paradigm. The results show that users and non-users are comparable in terms of response execution, but users need significantly more time to inhibit responses than non-users.

Chapter 4 reports two experiments studying whether khat use is associated with changes in working memory (WM) and cognitive flexibility in adult khat and khat-free users. The results show that khat users perform significantly worse than controls on tasks tapping into cognitive flexibility and monitoring of information in WM. The inability to monitor information in WM, and to adjust behavior rapidly and flexibly may have repercussions on daily life activities.

Chapter 5 presents an experiment on the impact of khat on the emergence and resolution of response conflict. Khat users and khat-free controls were tested on response conflict, as measured through a Simon task. Khat users show a general slowing and less efficient resolution of response conflicts, which is likely to impair decision making in everyday life situations.

Chapter 6 investigates the possible impairment of inhibitory control in language production among recreational and chronic cocaine polydrug users. Two experiments were carried out with chronic and recreational cocaine polydrug users using a blocked-cycled naming task, an index of semantic interference. Chronic and recreational users show bigger semantic interference than cocaine-free controls, as indicated by a deficit in inhibiting interfering information. We propose that the consumption of cocaine impacts the inhibitory processes that suppress the overactive lexical representations in the semantic context.

Chapter 7 reports two experiments that test the ability of intentional forgetting in chronic and recreational cocaine users. Chronic and recreational cocaine users were matched to a control group and were compared in their performance on a directed forgetting task. Results showed that chronic and recreational cocaine users are not able to inhibit irrelevant memories. We

attribute the inability to exert memory inhibition in chronic and recreational cocaine users to cocaine consumption.

Chapters 2 to 7 are published, under revision, or submitted in international psychological journals. They have been inserted in this thesis in their original, submitted, or published form. To acknowledge the important contributions of several co-authors to each of these articles, a list of references is presented here.

Chapter 2: Ruiz, M. J. & Colzato, L. S. (2014). Pharmacokinetics and Pharmacodynamics of khat, mephedrone and MDPV. Submitted to The Handbook of Drug & Alcohol Studies Volume 2. SAGE publications.

Review of the existing literature and development of writing: Manuel J. Ruiz and Lorenza S. Colzato.

Chapter 3: Colzato, L. S., Ruiz, M. J., van den Wildenberg, W. P. M., Bajo, M. T., & Hommel, B. (2011). Long-Term Effects of Chronic Khat Use: Impaired Inhibitory Control. *Frontiers in Psychology*, *1*.

Conceived and designed the experiments: Lorenza S. Colzato. Performed the experiments: Manuel J. Ruiz. Analyzed the data: Wery Van Den Wildenberg. Contributed reagents/materials/analysis tools: Wery Van Den Wildenberg and Teresa Bajo. Wrote the paper: Lorenza S. Colzato and Bernhard Hommel.

Chapter 4: Colzato, L. S., Ruiz, M. J., van den Wildenberg, W. P. M., & Hommel, B. (2011). Khat use is associated with impaired working memory and cognitive flexibility. *PloS one*, *6*(6).

Conceived and designed the experiments: Lorenza S. Colzato. Performed the experiments: Manuel J. Ruiz. Analyzed the data: Wery Van Den Wildenberg. Contributed reagents/materials/analysis tools: Wery Van Den Wildenberg. Wrote the paper: Lorenza S. Colzato and Bernhard Hommel

Chapter 5: Colzato, L. S., Ruiz, M. J., van den Wildenberg, W. P. M., & Hommel, B. (2012). Khat use is associated with increased response conflict in humans. *Human psychopharmacology*, *27*(3), 315-321.

Conceived and designed the experiments: Lorenza S. Colzato. Performed the experiments: Manuel J. Ruiz. Analyzed the data: Wery Van Den Wildenberg. Contributed reagents/materials/analysis tools: Wery Van Den Wildenberg. Wrote the paper: Lorenza S. Colzato and Bernhard Hommel.

Chapter 6: Ruiz, M. J., Paolieri, D., Colzato, L. S., & Bajo, M. T. (2014). Chronic and recreational use of cocaine is associated with a vulnerability to semantic interference. *Psychopharmacology,* 1-10. doi: 10.1007/s00213-014-3806-9.

Conceived and designed the experiments: Manuel J, Ruiz, Daniela Paolieri and Teresa Bajo. Performed the experiments: Manuel J. Ruiz. Analyzed the data: Manuel J. Ruiz and Daniela Paolieri. Contributed reagents/materials/analysis tools: Lorenza Colzato. Wrote the paper: Manuel J. Ruiz, Daniela Paolieri and Teresa Bajo

Chapter 7: Ruiz, M. J., Paolieri, D., Colzato, L. S., & Bajo, M. T. Directed forgetting of Memories and cocaine use. *Submitted to Psychopharmacology.*

Conceived and designed the experiments: Manuel J, Ruiz, Daniela Paolieri and Teresa Bajo. Performed the experiments: Manuel J. Ruiz. Analyzed the data: Manuel J. Ruiz and Daniela Paolieri. Contributed reagents/materials/analysis tools: Lorenza Colzato. Wrote the paper: Manuel J. Ruiz, Daniela Paolieri and Teresa Bajo.

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Chapter 2

Pharmacokinetics and pharmacodynamics of khat and mephedrone

Abstract

This chapter considers the behavioral and physiological effects of the natural psychomotor stimulants khat (*Catha Edulis*) and the cathinone-derived designer drug mephedrone. These natural and synthetic stimulants increase alertness, arousal, energy, talkativeness and motor excitement. This chapter describes their diverse historical and geographical background, their variety, their mechanisms of action, and their potential for producing abuse and dependence.

Khat

Background and History

Khat is the transliteration of an Arabic word that indicates the leaves and shoots of *Catha Edulis*. This is a plant of the *Celastraceae* family endemic in countries around the Red Sea and East Africa. Its leaves are chewed on since ancient times as part of cultural tradition. The khat chewing habit is deeply rooted in African countries, such as Sudan, Eritrea, Ethiopia, Djibouti, Kenya, and Tanzania, and in the southwestern countries of the Arabia Peninsula, such as Yemen, which is a country with a major population of chewers (United Nations and United Nations Office on Drugs and Crime, 2013). This drug is abused for its stimulant effect, and the acute consumption is associated with optimism, euphoria, excitation, talkativeness and increased energy. The effects are long-lasting and may prevent fatigue. Recently, due to air transportation improvement and the influx of immigrants from

East Africa and the Arabian Peninsula have spread the use of khat leaves around the world. Fresh khat is usually wrapped in banana leaves for transportation to preserve its moisture. The vast majority of those ingesting khat do it by chewing. Only a small number ingest it by making a "tea" from dried leaves, or, even more rarely by smoking dried leaves. The chewer fills his mouth with fresh leaves and young stalks, and chews them slowly and intermittently to release the active components in the juice, which is swallowed along with saliva. When khat leaves and stalks are chewed, cathinone is absorbed through the buccal mucosa and the stomach. In a single khat session, approximately 100-500 g of fresh khat is chewed for several hours (Feyissa and Kelly, 2008).

Mechanisms of Khat action

Since one characteristic property of khat is stimulation of the central nervous system, the pharmacodynamics aspects of khat constituents is of particular interest. The chemical similarity between cathinone and amphetamine, and the amphetamine-like effects, lead cathinone to be called a "natural amphetamine" (Kalix, 1992). Experimental studies conducted to investigate khat's central and peripheral effects have determined that cathinone and amphetamine share a common pharmacological activity. Khat alkaloids comprise two groups. The first group is the cathamines, and the second is cathaedulines. Cathamines are more abundant and widely known than cathaedulines. Khat contains more than forty compounds, such as alkaloids, glycosides, tannins, amino acids, vitamins and minerals. But three phenylalkylamine alkaloids are responsible for its psychoactive effects. These are (−)-S-cathinone α-aminopropriophenone (cathinone), (+)-norpseudoephedrine (cathine) and norephedrine (Szendrei, 1980), which are phenylpropylamines structurally related to amphetamine and noradrenaline. The major active constituent in fresh khat is (−)-S-cathinone. The plant contains the (−)-enantiomer only, the (+)-enantiomer has not been found (Kalix & Braenden, 1985), which has the same molecular configuration as S-(+)-amphetamine (Kohli and Goldberg, 1982). Given its potency and high

liposolubility (Kalix and Braenden, 1985), it facilitates access into the central nervous system (CNS) (Zelger et al., 1980). So, it can be assumed that khat-induced symptoms are mainly due to cathinone (Kalix, 1990). Cathinone, mainly increases levels of dopamine and norepinephrine in the brain by acting on catecholaminergic synapses, delaying the reuptake and/or enhancing the release of those neurotransmitters. Cathinone is relatively unstable and during maturation it is enzymatically degraded to cathine and norephedrine (Al-Obaid et al., 1998) within a few days after harvesting. These molecules are less lipophilic and act at a peripheral level, provoking the sympathomimetic effects. Thus, only fresh picked leaves have full efficacy, while cathine and norpseudoephedrine occur mainly just in older leaves and/or by degradation of cathinone (Sporkert et al., 2003). The phenylalkylamine content of khat leaves varies within wide limits. Other phenylalkylamine alkaloids found in khat leaves are the phenylpentenylamines merucathinone, pseudomerucathine and merucathine. However, they seem to contribute less to the stimulant effects of khat (Geisshüsler and Brenneisen, 1987).

In view of its peripheral action, cathinone is accompanied by sympathomimetic syndrome. Several studies have looked into the cardiac effect of khat. Cathinone provokes increases in blood pressure and heart rate, characterized by transient hypertension and tachycardia (Brenneisen et al., 1990; Halbach, 1972; Hassan et al., 2005, 2000). These effects seem to be mediated by the stimulant effect of cathinone on β-adrenoceptors in the heart (Kennedy et al., 1983). Other peripheral effects include dry mouth, hyperthermia, mydriasis and anorexia (Nencini et al., 1984). These effects are thought to result from the ability of cathinone to release noradrenaline from sympathetic nerve terminals with an effect and potency similar to those of amphetamines (Kalix, 1992; Kohli and Goldberg, 1982). The main effects of cathinone are relief of fatigue, hyperactivity, increased alertness, euphoria, loquacity, improved ability to communicate, and restlessness. Khat chewing is thought to exert its effects by increasing concentrations of stimulant neurotransmitters, such as dopamine, serotonin and/or

noradrenaline in specific regions of the brain. The animal model of psychostimulation has been widely used to observe the action of khat alkaloids on the CNS. The acute effect of khat alkaloids on neurotransmission is comparable to that induced by amphetamines: Cathinone and cathine interact with the dopaminergic pathways, increasing dopamine and serotonin, and preventing reuptake of noradrenaline and dopamine (Kalix, 1984, 1983; Pehek et al., 1990). Cathinone inhibits MAO more strongly than amphetamine (nencini, 1984) and is more selective toward the iso-enzyme MAO-B (Nencini et al., 1984; Osorio-Olivares et al., 2004), provoking a synaptic accumulation of this catecholamine due to a decrease in dopamine degradation. Cathinone is not considered a direct dopamine agonist but rather a presynaptic releaser and inhibitor of dopamine. The major metabolites of cathinone, i.e. cathine and norephedrine, have weaker effects on the CNS due to their less lipophilic properties. The pharmacology of cathinone has not been well characterized in the CNS (Kite et al., 2003), however there are enough experimental results that suggest that khat's psychostimulant effect is primarily mediated via meso-cortico-limbic dopaminergic pathways (Banjaw et al., 2003; Kalix, 1990). There is evidence from animal studies that cathinone releases 5-HT in rat striatal tissue (Kalix, 1984) and repeated administration of khat to rats led to a depletion of the 5-HT neurotransmitter and its metabolite 5-Hydroxyindoleacetic acid in anterior and posterior striatum. However the relevance of 5-HT pathways to the behavioral action of cathinone is less studied and defined than that of dopamine. Since both cathinone and amphetamine have shown to reduce the uptake of 5-HT in animal models of psychostimulation, a possible involvement of 5-HT in mediating the euphoric action of cathinone cannot be ruled out (Al-Motarreb et al., 2002).

Basic Pharmacology of Khat

Absorption

Khat alkaloids plasma concentration-time data are usually described using a two-compartment model with two segment absorption (Toennes et al., 2003). Khat is used predominantly by oral route. Cathinone and cathine are rapidly and completely absorbed by this route with nearly 100% bioavailability. There are considerable differences in cathinone content in khat leaves from different origins and type. The scientific studies consider that cathinone alkaloid is present at around 36-343 mg, cathine 86-120 mg and norephedrine 8-47 mg per 100 g of fresh leaves (Al-Motarreb et al., 2002; Geisshüsler and Brenneisen, 1987; Toennes et al., 2003; Widler et al., 1994). One of the reasons for this difference in cathinone concentration is that cathinone is unstable, and it is rapidly transformed by enzymatic reduction into cathine and norephedrine once the leaves have been harvested. The psychostimulant effects induced by khat appear after approximately half an hour of chewing, and last about 3h (Brenneisen et al., 1990; Kalix, 1996). Cathinone and cathine are isolated from the leaves of *Catha edulis* by enzymes present in saliva. The absorption of the constituents of khat is said to have two phases, the first being at the buccal mucosa, which plays an important role in the absorption of alkaloids; and a second phase is after swallowing of the extract, at the lining of the stomach or small intestine (Arunotayanun and Gibbons, 2012; Feyissa and Kelly, 2008; Toennes et al., 2003). In one study four naïve non-drug users chewed an average of 44g of khat for an hour, and they showed, on average, a maximum plasma concentration of cathinone occurring at 2.3h for cathinone, 2.5h for cathine and 2.8 h for norephedrine (Toennes et al., 2003); 8h later, amount of cathinone was reported to be 245±49 μg min ml^{-1}. In a study by Wilder et al. (1994) six subjects chewing a single amount of khat corresponding to 0.8 mg/kg body weight, showed maximum plasma concentration of cathine to be at 2h, and the total cathinone absorbed in the body after 9h was 25±13 μg min ml^{-1}. In a study by Halket et al. (1995a), maximum peak plasma

levels were on average 83 μg ml^{-1} after one hour of chewing 60 grams of fresh khat leaves.

Distribution

The active ingredients are not extracted rapidly by chewing and thus do not have a fast onset of action. Little is known about the distribution of khat psychoactive alkaloids in the human body, and a consistent pharmacokinetic model of action has not been developed. Plasma concentration curves vary between studies due to differences in the alkaloids doses, however these studies show a good agreement in results (Halket, Karasu, & Murray-Lyon, 1995; Widler et al, 1994; Toennes, Harder, Schramm, Niess, & Kauert, 2003). In the study by Toennes et al. (2003) the plasma concentration-time was described using a two-compartment model with two segment absorption. The time until the compound appeared in the central compartment (tlag 1) was between 0.1-0.2 h for the three alkaloids, whereas the lag time for the second segment (tlag 2) was more than 1.2 h. Maximum plasma concentrations were reached, on average, after 2.3h for cathinone (58±18.8 μg L^{-1}), after 2.6h for cathine (58±18.8 μg L^{-1}), and after 2.8 h for norephedrine (72±12.2 μg L^{-1}). Cathinone in the central compartment had an average half-life of 1.50±0.8 h. The apparent volume of distribution from central compartment was 2.7±1.6 L kg^{-1} for cathinone and 0.7±0.4 L kg^{-1} for cathine. Cathinone is a more lipophilic alkaloid than cathine, and its more rapid and intense action is explained by its higher lipid solubility, which facilitates access into the CNS (Zelger et al., 1980).

Metabolism and Excretion

The psychostimulant effects appear 15-30 min after one starts chewing, and they last for three hours. During this time, nearly 90% of alkaloids are released. There is a rapid biotransformation due to the steroselective metabolism of (-)-S-cathinone to cathine and norephedrine. First-pass metabolism of cathinone by liver microsomal enzymes reduces the β-keto group to an alcohol, resulting in cathine and norephedrine (Brenneisen et al.,

1986; Guantai and Maitai, 1983). The principal stereoisomer S-(−)-cathinone is metabolized to norephedrine and cathine. Both metabolites remain active in plasma concentrations for no less than 9h, when cathinone is no longer found in plasma. Cathine is excreted unaltered for nearly 24 hours (Maitai and Mugera, 1975; Widler et al., 1994). Since both norephedrine and cathine are pharmacologically active compounds, they may contribute to the general effects of khat chewing (Graziani et al., 2008). Less than 7% of cathinone is excreted unchanged in the urine (Brenneisen et al., 1986; Toennes and Kauert, 2002). Since norephedrine is both a khat alkaloid and a cathinone metabolite, it is difficult to determine its metabolism and excretion. There is evidence of higher amounts of norephedrine being excreted in urine than is ingested due to a combination of absorbed norephedrine and the product of cathinone metabolism (Mathys and Brenneisen, 1992; Toennes and Kauert, 2002). Brenneisen et al. (1986) found that 21-50% of cathinone was recovered mainly as aminoalcohol metabolites in 24 hour urine samples. The elimination half-life of cathinone is 1.5±0.8 hours, and that of cathine is 5.2 ± 3.4 hours. In the study of Toennes et al. (2002) the maximum concentrations of cathinone, cathine and norephedrine in urine samples were 2.5, 20 and 30 mg L^{-1}, respectively. The metabolite cathine has been found in both urine and breast-milk of lactating women who habitually chewed khat. As a result, breast-fed infants will ingest a sympathomimetic and anorectic compound, such as cathine (Kristiansson et al., 1987).

Behavioral and Neural Effects of Khat: Abuse and Dependence

Chronic khat use is commonly associated with cardiac, psychological, neurological and gastrointestinal complications. Increased blood pressure and heart rate have been associated with a higher risk of ischemic and myocardial infarction (Al-Motarreb et al., 2005; Kalix, 1981). Also, tannins from khat plant produce esophagitis, gastritis, oral keratosis, periodontal diseases and grastroduodenal ulcers. Tannins and norpseudoephedrine contribute to constipation, the most common complaint of khat

users. Khat use also affects nutrition and absorption of nutrients, which leads to malnutrition. (Al-Habori, 2005). There is evidence for a strong association between the development of buccal cancer and cirrhosis and khat use (Chapman et al., 2010; Fasanmade et al., 2007; Kassie et al., 2001), especially when combined with alcohol and tobacco. Habitual use of khat is known to seriously impair male sexual functions leading to a high incidence of spermathorrea and a permanent impotence (el-Shoura et al., 1995; Halbach, 1972; Mwenda et al., 2003).

Khat is known to produce paranoid psychosis, auditory hallucinations and hypomanic illness with grandiose delusions, fear and anxiety (Kalix, 1988). These effects are exceptional and associated with chewing high amounts of khat, moreover these effects disappear spontaneously within 1-2 days of cessation of khat use. Depression often appears during withdrawal, but in nearly all cases that report this symptom, it disappears after khat cessation as well (Hassan et al., 2002; Kalix and Braenden, 1985; Pantelis et al., 1989). The administration of benzodiazepine and antipsychotic medication is often necessary. To date there are no sufficient scientific reports and large-scale studies, excepting clinical cases, that associate the effects of khat use and psychiatric disorders (Warfa et al., 2007). However, literature suggests that the adverse psychiatric sequelae may relate to traumatic experiences such as war or combat, and the lack of social support of immigrants, which favors the experience of negative effects of the drug in vulnerable subjects.

Cathinone is a reinforcing drug and it maintains very high rates of responding in animal experiments (Kalix, 1984), but there are conflicting opinions regarding the existence of a withdrawal syndrome. Accumulating evidence demonstrates withdrawal symptoms and low tolerance in humans. Withdrawal symptoms after long-term use of khat have been described as and include lethargy, mild depression, trembling and nightmares (Corkery et al., 2011). The development of tolerance is still a debated issue due to the variable conclusion of clinical trials and research. Development

of tolerance should be similar to amphetamine tolerance, however, it is improbable that khat users ingest enough cathinone to develop dependence, because the bulk volume of khat self-limits consumption (Nencini and Ahmed, 1989). Nevertheless, khat-induced changes appear to be less pronounced in chronic users, which would indicate that tolerance may develop for the acute sympathomimetic and neuroendocrine effects of khat, such as increased levels in blood pressure, heart rate, respiratory rate and body temperature (Kalix and Braenden, 1985). The reinforcing properties of khat are weaker than amphetamines or cocaine; thus development of dependence is unlikely to be similar in extent and severity to amphetamines. In fact, there are very few cases of khat dependence and khat users do not have serious problems when they stop using it.

Cognitive Effects of Khat Exposure

Long-term cognitive deficit

Several studies have systematically looked into the detrimental effect of chronic use of khat on cognition. First, Colzato, Ruiz, van den Wildenberg, Bajo, and Hommel (2011a) reported that chronic khat users compared to khat-free controls, in a stop-signal paradigm, exhibit impairments in the inhibition of behavioral responses when they had to refrain from responding to a red arrow (stop-signal). Second, Colzato, Ruiz, van den Wildenberg, and Hommel (2011b) showed that chronic khat users performed significantly worse than controls in a task-switching paradigm (an index of cognitive flexibility) and on the N-back task (an index of working memory updating). In the task-switching paradigm participants were supposed to switch between two different tasks: responding to the global or to the local target dimension of hierarchical geometrical figures. Chronic khat users showed more pronounced switching costs (i.e., a greater difference in reaction times between when the task was alternated compared when it was repeated) than khat-free controls, an indication of decreased cognitive flexibility. In the N-back task, participants were confronted with a stream of letters and had to indicate whether the

present letter matched the one that was presented directly before (1-back) or in the second-to-last trial (2-back). Chronic khat users made significantly more errors in both the 1-back and 2-back conditions, an indication of more deficient WM updating.

Third, Colzato, Ruiz, van den Wildenberg, and Hommel (2012) showed that chronic khat users displayed less efficient resolution of response conflicts in the Simon task in which participants had to respond, by pressing left and right response buttons, to the color of visual stimuli while disregarding their irrelevant location. Moreover, the amount of hours chewing khat positively correlated with the size of the Simon effect, indicating that longer chewing was associated with increased response conflict.

Acute Cognitive Effects

So far, only one study has investigated the acute effect of khat on cognition. Colzato and colleagues (2013) explored how acute khat use affects the emergence and resolution of response conflict as measured by the Simon task. In one single session, participants worked through two task blocks: the khat group chewed exclusively khat whereas the khat-free group chewed solely a gum. Results showed that in the second block, which reflects the acute impact of khat, the khat group was better than controls in resolving stimulus-induced response conflict. These results suggest that the acute intake of khat may improve participants' ability to handle response conflict.

Mephedrone (4-methcathinone)

Background and History

In recent years, a new class of designer drugs has appeared on the drug of abuse market in many countries. It has risen in popularity in European countries, especially in the UK, as well in

the South–East Asia, Australia and North America. These are the so-called beta-keto designer drugs. They come from synthetic ring-substituted phenylethylamines with substitution of a ketone group at the β-carbon position (Gibbons and Zloh, 2010; Gibbons, 2012). Various R-group substitutions give rise to approximately 30 known synthetic cathinones, many of them identical except for the β-carbon ketone group (European Monitoring Centre for Drugs and Drug Addiction, 2012).The most widely abused synthetic cathinones are 4-methcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV). Mephedrone is the most abused synthetic drug in Europe, while methylone and MDPV are the most frequently abused synthetic cathinones within the US. The first most popular synthetic cathinone in EU countries was mephedrone (4-methcathinone, 4-MMC), and it was seen as an alternative to MDMA (3,4-methylenedioxymethylamphetamine).

It is a derivative from the psychoactive alkaloid cathinone occurring naturally in the plant khat (*Catha Edulis).* Mephedrone is abused for its stimulant effect, which is similar to the psychoactive and sympathomimetic effects exerted by cocaine and MDMA. It appeared for the first time on the internet in 2007 (Walsh, 2011), and it has several street names, such as "meaow-meaow", "drone", "meph", "bubles" or "Ronzio". This substance was synthesized by Roger Adams for the first time in the late 1920's (Hyde et al., 1928), was then used as a neuroleptic ("Methylaminopropiophenone compounds and methods for producing the same," 1957), and was examined as a locomotor stimulant by van der Schoot et al. (1962). Prior to the banning, it was sold under its name, then after becoming a controlled substance it was marketed as "bath salt" in Europe or "plant food" in the US, commonly labeled "not for human consumption" to circumvent the legislation of drug of abuse (EMCDDA, 2011; Kelly, 2011; National Drug Intelligence Center [U.S.], 2011; Schifano et al., 2010a). In the 2000's, mephedrone had received a renewed popularity as a synthetic drug, particularly in young people. The synthesis of synthetic cathinones is relatively simple and can be carried out with similar equipment

and knowledge as amphetamines (Camilleri et al., 2010). Synthetic cathinones are usually produced in countries such as China, India or Pakistan by rogue chemists, and it is then shipped directly to distributors. Mephedrone was controlled as a Class B substance under Misuse of Drug acts, 1971 in the UK. The substance is available from a number of different sources, including drug-dealers, headshops, and most importantly via the internet. Before the UK legislation in 2010, there were more than 50 websites that sold mephedrone and other cathinones. Since the banning, the number of websites decreased, and people started to sell replacements called "legal highs". In May 2010 the Council of the European Union decided that mephedrone should be controlled in all EU countries based on a risk assessment by a scientific committee (EMCDDA, 2011). There are little data about the prevalence of use of mephedrone. The available data are from self-reported surveys of particular demographics, showing that it was a very popular "party drug" frequently used in nightclubs, discos and dance parties (Dick and Torrance, 2010; Schifano et al., 2010a; Winstock, 2011). However, the use of mephedrone has declined, primarily due to the banning of the substance, the increasing difficulty in gaining access to it, and the increased price of the drug. In the absence of epidemiological data on prevalence, an internet-based cross-sectional survey in 2012 of over 22,000 world-wide clubbers showed that 13.9% of the UK subgroup reported to have used mephedrone in the last 12 months (MixMag's Global Drug Survey, 2013).

Mephedrone is typically sold to users in powder form, and it is generally described as being a white crystalline powder with a light yellow color (EMCDDA, 2011; Newcombe, 2009; Schifano et al., 2010a). The most common routes of use are insufflation (snorting), oral ingestion, diluted in drinks or wrapped in smoking paper (known as "bombing"); and intramuscular or intravenous injections. Smoked and rectal insertions are rare methods of administration, but they are commonly used as well (Measham, Moore, Newcombe, & Smith, 2010; Winstock et al., 2011; Wood et al., 2010). Mephedrone and other synthetic cathinones have been

regularly used in conjunction with other drug of abuse including GHB, alcohol, cannabis, opiates, cocaine, MDMA, ketamine and amphetamine (Dargan et al., 2011).

Basic Pharmacology and Mechanisms of Mephedrone action

Very little information is available about the pharmacokinetic processes of the synthetic drug mephedrone. Recent studies used animal models to figure out the pharmacokinetic parameters (Martínez-Clemente et al., 2013). Most mephedrone data come from the internet, population surveys and case reports, and the amount of used mephedrone widely varies from 5-125 mg via nasal route to 15-250 mg by oral route ("Erowid 4-Methylmethcathinone Vault : Dose/Dosage"). Users commonly report re-dosing to maintain the desired effects for an average of six hours, showing that mephedrone usage often does not comprise a single dose, using an amount of 300-700 mg per session (James et al., 2011; Regan et al., 2010; Winstock et al., 2011; Wood et al., 2010a, 2010b). The effects have a rapid onset, appearing within minutes and lasting at least for an hour when the substance is insufflated; or having an onset time of nearly 45 min and lasting for 2-4 hours by oral route. Given the affiliation of mephedrone to beta-ketoamphetamines, it is expected to act on the central nervous system by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake (Feyissa and Kelly, 2008; Kalix, 1990). In vitro studies showed that mephedrone's main mechanism of action is very similar to that of amphetamines (Cozzi et al., 1999). The cathinone derivatives often have an amphetamine analogue; cathinone and methylone are structurally comparable to amphetamine and MDMA, respectively. However, there is no common amphetamine analogue of mephedrone. Particularly in mephedrone, the presence of the ring substituent on the phenethylamine core modifies its pharmacological properties, giving the compound some MDMA-like effects. Mephedrone has a chiral center, so it exists in two forms, the S(−) and R(−) mephedrone. Like the alkaloid cathinone, mephedrone's S(−)

stereoisomer is thought to be more potent than (R). Mephedrone is less lipophilic than amphetamines, therefore it shows a reduced ability to cross the blood-brain barrier due to the presence of the beta group (Gygi et al., 1996; Nagai et al., 2007). At present, the pharmacokinetics of synthetic cathinones in humans is poorly documented and it is compared to traditional amphetamines pharmacokinetics. However, animal studies and the action of natural cathinones show insights in the action of these drugs.

Absorption and distribution

There are no studies examining mephedrone absorption in humans. The results are drawn from users that reported the consumption of the substance, user surveys or clinical reports. The absorption of mephedrone depends on the route of use, with the onset of desired effects occurring a few minutes after nasal insufflation or intravenous injection, and between 15-45 min after oral ingestion ("Erowid 4-Methylmethcathinone Vault : Dose/Dosage", "Erowid 4-Methylmethcathinone Vault : Effects"). In a typical session a low dose of mephedrone is used (15-150 mg orally and 5-125 mg for insufflation), and usually no more than 1 g is used ("Erowid 4-Methylmethcathinone Vault : Dose/Dosage"; Newcombe, 2009). The majority of users prefer to combine different administration routes, (e.g insufflation and ingestion) and repeated doses, rather than a single use, to maintain the desired effects (DeLuca, 2009). A study investigating plasma parameters was carried by Wright et al. (2012) in Wistar and Sprague-Dawley rats. In this study a subcutaneous injection of 5.6 mg/kg of mephedrone was administered, resulting in a peak plasma concentration of 868 $\mu g \cdot ml^{-1}$ and 1206 $\mu g \cdot ml^{-1}$ for the Wistar and Sprague-Dawley rats respectively; peak plasma concentrations were reached after 15 minutes. A rapid reduction of plasma concentration, probably due to the rapid clearing of mephedrone, was found in both animal models, with an area under the curve (AUC) of 870 $\mu g\ ml^{-1}$ and 1170 $\mu g\ ml^{-1}$ in Wistar and Sprague-Dawley rats, respectively. In a study of forensic traffic cases, blood concentrations ranged from 1 to 51 $\mu g/kg$ in mephedrone users. In

a more recent study carried out by Martínez-Clemente and colleagues (2013) mephedrone was administered intravenously (10 mg/kg) and orally (30 and 60 mg/kg) to Sprague-Dawley rats. Results fitted a two compartment model, showing that after oral administration mephedrone achieved a peak concentration between 0.5-1 hours and declined to undetectable levels after 9 hours. The bioavailability of mephedrone was about 10% and the percentage of mephedrone protein binding was 21.59±3.67%.

The effects of cathinone when taken by insufflation start within 10-20 min and last 1-2 hours, with oral effects taking longer to peak, at around 20-40 min and lasting 2-4 hours. This may vary in association with the amount of food present in the stomach (Wright et al., 2012).

Metabolism and excretion

Synthetic cathinones metabolites have been detected using gas/liquid chromatography-mass spectrometry. All cathinone derivatives have been shown to pass phase I metabolism. The first study that looked into mephedrone metabolism was conducted by Meyer et al. (2010b). They administered a single dose of 20 mg/kg of mephedrone by gastric intubation to rats, and urine samples were collected during 24 hours after the drug administration. They showed that synthetic cathinone undergoes three overlapping phase I metabolism pathways in rat and human urine samples, with seven metabolites being identified in human samples and six in rat urine. Mephedrone can be N-demethylated to a primary amine, responsible for the metabolites nor-mephedrone, nor-dihydro mephedrone and nor-hydroxytolyl mephedrone; subsequently, ketone moieties can be reduced to alcohols, producing nor-dihydro mephedrone and 4-carboxy-dihydro mephedrone; or finally, tolyl groups are oxidized to the corresponding alcohol and carboxylic acid, giving as metabolites hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone. Further phase II metabolites can be found, resulting from glucuronidation and/or sulfation reactions (Khreit et al., 2013; Meyer et al., 2010c). A recent in vitro study conducted by Khreit et al. (2013) used rat liver hepatocytes, and

they found 17 metabolites from Phase I and Phase II, and a half-life of 61.9 min for the active substance mephedrone.

In an in vitro study by Pedersen et al. (2013) using cDNA-expressed CYP enzymes and human liver microsomal preparations, it was demonstrated that the cytochrome P450 (CYP) 2D6 is the main responsible enzyme for the phase I metabolism of mephedrone, with some minor contribution from other NAPDH-dependent enzymes. The majority of cathinone derivatives are eliminated by metabolites via urine, which can be detected with appropriate urine testing technology (Meyer and Maurer, 2010). However, there is still a lack of studies that look into the time course detection and/or the major metabolites in blood.

Behavioral and Neural Effects of Mephedrone: Abuse, Dependence and Toxicity

There are very few data about the human pharmacodynamics processes of mephedrone and few studies on the pharmacological targets have been published (Hadlock et al., 2011; Kehr et al., 2011; Martínez-Clemente et al., 2012; Motbey et al., 2012a). The desired effects looked for by the users are those similar to cocaine-like stimulant effects or MDMA-like hallucinogenic effects: increased alertness, increased energy and motivation, euphoria, excitement, improved mood, empathogenic effects, sociability, enhanced appreciation for music, reduced appetite, mild-sexual stimulation and insomnia (Kapitány-Fövény et al., 2013; Schifano et al., 2010a; Winstock et al., 2011; Zawilska and Wojcieszak, 2013). Many of these effects can be ascribed to general sympathomimetic activation, with several effects on the peripheral and central nervous systems being similar to those described in khat users, but greatly enhanced due to the higher consumed amount of the psychoactive compound. Few studies have evaluated the effect of mephedrone on the PNS, but they agree on profound changes in peripheral organs systems, such as the cardiovascular and digestive system (Baumann et al., 2013a, 2012; Meng et al., 2012; Varner et al., 2013). Different animal models show the effects of mephedrone on monoamine neurotransmission in the CNS, and one may

postulate that the stimulant and empathogenic effect may be exerted by increasing concentrations of catecholamines such as dopamine (DA), serotonin (5-HT) and norepinephrine (NE), with similar releasing potencies in each neurotransmitter (Baumann et al., 2012; Cameron et al., 2013; Cozzi et al., 1999; Kehr et al., 2011; Martínez-Clemente et al., 2012; Motbey et al., 2012b; Ramoz et al., 2012). An animal model study conducted by Hadlock (2011) revealed that mephedrone has a DA-releasing capability in striatal tissue resembling methamphetamines, but this does not cause dopaminergic deficits. Repeated administrations rapidly decreased DA and 5HT transporter functions by 20% in rat striatal and hippocampal synaptosomes, causing serotonergic, but not dopaminergic deficits. Hadlock also observed reduced DAT and SERT function by approximately 20% in the striatal and hippocampal synaptosomes, respectively. In addition, in vivo mycrodialisys studies in rats demonstrated that mephedrone produces increased extracellular DA levels in the nucleus accumbens (Baumann et al., 2013a, 2012; Kehr et al., 2011).

Acute and long-term exposure to amphetamines has been associated with a loss of transporter function in the DA and 5-HT systems (Fleckenstein et al., 1999), so it seem plausible that synthetics cathinones follow the same pattern of DA and 5-HT neurotoxicity, and DAT and SERT activity. However, there are a number of other studies that report no loss of DA and 5-HT, or transporter alterations following several mephedrone doses at different administrations (Angoa-Perez et al., 2012; Baumann et al., 2012; den Hollander et al., 2013; Motbey et al., 2012b). All synthetic cathinones also inhibit NE transporters (NET; Eshleman et al., 2013; Iversen et al., 2013). Increased NE levels in the brain are not known to correlate with the intoxicating effects of the drug, but this feature is likely to contribute importantly to peripheral sympathomimetic effects (Iversen et al., 2014).

Recently, several studies of animal models have displayed the behavioral effects and neurotoxicity of mephedrone and other synthetic cathinones, especially highlighting impacts on locomotor

activity, learning and memory, thermoregulation and abuse liability (Shawn M Aarde et al., 2013; Angoa-Perez et al., 2012; Baumann et al., 2012; den Hollander et al., 2013; Gregg and Rawls, 2014; Lisek et al., 2012; López-Arnau et al., 2012; Marusich et al., 2012; Motbey et al., 2012b; Wright et al., 2012; Shortall et al., 2013; Dargan and Wood, 2013).

There is a variety of sources of information about the acute effects of mephedrone, which include self-reported toxicity on internet discussion fora, data from sub-population user surveys, data from regional and national poisons information services and published case reports and case series of mephedrone intoxication. Despite the different origin of intoxication information, a general acute toxic effect pattern can be observed (Wood and Dargan, 2012), and the clinical presentations of intoxicated humans coincide with the monoamine dysfunctions observed in animal studies. Most of the effects seem to be similar to those already documented for amphetamine, methamphetamine and MDMA (Schifano et al., 2010a).

The most common adverse symptoms following the use of mephedrone are those related to the CNS (seizures hyperthermia, insomnia, agitation, hallucination/delusion, confusion) and peripheral (tachycardia, hypertension, hyperthermia, hyponatremia, nausea, vomiting and chest pain) (Dargan et al., 2010; Winstock et al., 2011; Wood et al., 2010b). Psychotic disturbances may appear after high and multiple doses during one session, or in users with an underlying psychobiological vulnerability (Winstock et al., 2011). Synthetic cathinone hallucinations are frequently auditory and long lasting, they may appear after cessation and persist for several days thereafter while receiving treatment. The anxiolytic and antipsychotic drugs lorazepam, haloperidol, diazepam and risperidone have been used alone or in combination to successfully treat synthetic cathinone induced psychiatric disorders (Kasick et al., 2012; Lusthof et al., 2011; Stoica and Felthous, 2013). Synthetic cathinones produced serious physical problems that requiresubstantial and prolonged medical treatment, including liver

failure, kidney failure, rhabdomyolysis, and the developments of compartment syndrome (Adebamiro and Perazella, 2012; Borek and Holstege, 2012; Levine et al., 2013; Stoica and Felthous, 2013). There have been numerous, well-documented deaths associated with mephedrone and other synthetic cathinones, some linked to self-reported use, others with post-mortem toxicological analysis (Aromatario et al., 2012; Cosbey et al., 2013; Dickson et al., 2010; European Monitoring Centre for Drugs and Drug Addiction, 2011, 2012; Ghodse et al., 2010; Marinetti and Antonides, 2013; Maskell et al., 2011; Schifano et al., 2012; Torrance and Cooper, 2010; Wood et al., 2010a). However, the data must be interpreted with caution due to the concomitant consumption of synthetic cathinones and other recreational drugs such as alcohol, cannabis, cocaine, amphetamine or opioids (Dargan et al., 2011).

The potential abuse liability of mephedrone has received limited investigation in comparison with others stimulants. However, the studies on animal models using drug-discrimination, place preference or self-administrations indicate a significant abuse liability for synthetic cathinones (Aarde et al., 2013; Hadlock et al., 2011; Lisek et al., 2012). These models are thought to reflect the positive reinforcing, or rewarding, effects of drugs and subjective effects in human users, and these may be comparable to mephedrone users who report significantly increased desire and craving for the drug, paired with the development of withdrawal effects and tolerance (Freeman et al., 2012; Winstock et al., 2011). Effects during withdrawal period have been observed to include nasal congestion, tiredness, insomnia, irritability and an inability to concentrate (Winstock et al., 2011). There is not a described withdrawal treatment, so primarily supportive treatment is comprised of low benzodiazepine doses and antipsychotics for agitation and paranoia. Mephedrone seems to have the potential to induce tolerance, therefore a quick progression to regular drug use is possible (Schifano et al., 2010a). Users may feel a strong urge to use and keep using despite problems, prompting a potential abuse liability. Of particular interest is mephedrone related dependence. Mephedrone users reported addictive potential of several synthetic

cathinones, which is likely related to the increase in extracellular dopamine in the nucleus accumbens that has been demonstrated in animals models (Kehr et al., 2011). There is strong evidence for craving responses elicited in mephedrone users that reveal an intense compulsion to self-administer the drug on repeated occasions (Bajaj et al., 2010; Dargan et al., 2011; EMCDDA, 2011; Newcombe, 2009).

Cognitive Effects of Mephedrone Exposure

Only few studies have investigated cognitive deficits associated with mephedrone exposure in humans. Freeman and colleagues (2012) have assessed working memory (WM), phonological and semantic fluency, psychomotor speed and executive control in mephedrone users. Compared to controls, they showed only a significant deficit in working memory performance, but not in the other domains. Herzig and colleagues (2013) speculated that "mephedrone consumption does not necessarily exert a negative impact on cognitive functioning by itself. Instead, mephedrone users are likely to be those individuals who are prone to consuming other psychoactive drugs in conjunction with mephedrone".

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Chapter 3

Long-term effects of chronic khat use: impaired inhibitory control

Abstract

So far no studies have systematically looked into cognitive impairments in khat users. This study compared the ability to inhibit and execute behavioral responses in adult khat users and in khat-free-matched sample controlled for age, race, gender distribution, level of intelligence, and alcohol and cannabis consumption. Response inhibition and response execution were measured by a stop-signal paradigm. Results show that users and non-users are comparable in terms of response execution but users need significantly more time to inhibit responses to stop-signals than non-users. The inability to stop on time may have repercussions for daily life activities as driving a car.

Introduction

Leaves from the flowering evergreen khat tree have been chewed in East-Africa since ancient times to alleviate fatigue, stay alert, reduce hunger and induce euphoria. Khat consumption has increased during the last decades in Eastern Africa and has become a global phenomenon spreading to ethnic communities in the rest of the world, such as in The Netherlands, United Kingdom, Canada or United States (United Nations Office on Drugs and Crime, 2010). The airport of Amsterdam and London, where arrived weekly a big amount of khat, have become the European distribution points (Beckerleg, 2008; Pennings, Opperhuizen, & van Amsterdam, 2008). In particular, in The Netherlands, it is legal to buy and sell khat bundles compared to other countries as Canada,

U.S.A., France, Norway, Poland where the use, sell and possess of khat is considered illegal.

The acute consumption of khat is associated with optimism, mild euphoria, excitation, talkativeness, increased energy and enhanced self-esteem (Brenneisen, Fisch, Koelbing, Geisshusler, & Kalix, 1990; Kalix, 1996). The half-life is about 4 hours, depending on the amount of chewed khat. When the acute effects vanish, users experience feeling of depletion, insomnia, numbness, depression, lack of energy and mental fatigue. At a long term, chronic (i.e. daily) use of khat is associated with increased blood pressure, development of gastrointestinal tract problems, cytotoxic effects on liver and kidneys and keratotic lesions at the side of chewing).

Cathine (Norpseudoephedrine) and cathinone (Benzoylethanamine), the active ingredients of khat, are similar in structure and pharmacological activity to amphetamines (Wagner et al., 1982). The two alkaloids act by increasing dopamine (DA), serotonin and noradrenalin (Kalix & Braenden, 1985). For this reason khat is also called "natural amphetamines". Cathinone increases levels of DA in the brain by acting on the cathecholaminergic synapses, retarding DA reuptake inactivation and/or enhancing DA release (Patel, 2000; Wagner et al., 1982), in particular in the striatum (Zelger & Carlini, 1981).

Studies addressing the neurobiological mechanism underlying the use of khat are still lacking as well as studies that have systematically looked into the long-term cognitive effects of chronic khat use. Nevertheless, given the similarity of khat and amphetamine in structure and pharmacological activity, it makes sense to assume that the long-term use of khat affects the same neurotransmitter and brain structures as the chronic use of amphetamine (see Berman et al., 2008). At a structural level, one may thus expect white matter abnormalities, lower cortical gray matter volume, and higher striatal volume. In particular, higher striatal volumes might reflect a compensation for toxicity in the

dopamine-rich basal ganglia. At a functional level, in turn, chronic khat use is likely to be associated with reduced functioning of dopamine D2 (DAD2) receptors in the striatum and dysfunctions in prefrontal cortex (PFC) and orbitofrontal cortex (OFC) – areas that have been shown to play major roles in the control of goal-directed action (Miller, 2000).

Interestingly, DA has a key role in inhibitory action control (Colzato et al., 2010; Colzato et al., 2009). Behavioral inhibitory efficiency is commonly assessed by means of the stop-signal task (Logan & Cowan, 1984). In this task, participants are first presented with a stimulus (i.e., a go signal) prompting them to execute a particular manual response, and this stimulus may or may not be followed by a stop signal calling for the immediate abortion of that response. Based on the mathematical considerations formulated by Logan and Cowan (1984), the stop-signal paradigm provides a direct behavioral assessment of the individual ability to stop a planned or ongoing motor response in a voluntary fashion and a quantitative estimate of the duration of the covert response-inhibition process (i.e., stop-signal reaction time or SSRT; see Figure 1). Parkinson's patients, who suffer from loss of dopaminergic neurons in the basal ganglia, showed longer SSRTs (Gauggel, Rieger, & Feghoff, 2004) and impaired suppression of conflicting responses (Wylie et al., 2009; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010) compared to matched controls. Consistent with this picture, spontaneous eyeblink rate (EBR), a marker of dopaminergic functioning, reliably predicts the efficiency in inhibiting unwanted action tendencies in a stop-signal task (Colzato et al., 2009; see Logan, 1994, for a review). Along the same lines Colzato and colleagues observed that recreational users of cocaine, who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow, Fowler, & Wang, 1999), need significantly more time to inhibit responses to stop-signals than non-users. Very recently, Colzato et al. (2010) found that DA D2 receptor (DRD2) C957T T/T homozygotes were also less efficient in inhibiting prepotent responses.

So far, surprisingly, no studies have systematically looked into cognitive impairments in khat users. In the present study we tested, by means of the stop-signal task (Logan & Cowan, 1984), whether khat use produces deficiencies of inhibitory control. Given the above mentioned links between DA and inhibitory action control on the one hand and between DA and khat on the other hand, we expected impairments of inhibitory control among khat users.

Material and Method

Participants

Forty young healthy adults (36 men and 4 women) were compensated for their collaboration. They constituted the two groups of khat users and khat-free controls. The sample was drawn from 50 adults in the Leiden and The Hague 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. We made sure that the users met the following criteria: (1) last month consumption by chewing route for a minimum 1 year; (2) no clinically significant medical disease and (3) no use of medication criteria. All khat users met more than four of the seven criteria that according to the American psychiatric Association DSM-IV and the World Health Organization (ICD-10) define addiction: tolerance, withdrawal, difficulty controlling the use, negative consequences for job, family and health, significant time or emotional energy spent in searching/consuming the drug, put off or neglected activities because of the use, and desire to cut down the use. Khat-free controls met the same criteria except that no one reported any history of past or current khat use.

Participants were asked to refrain from taking all psychoactive drugs for at least 24 hours before the test, not to consume alcohol on the night before the experimental session, and

to have a normal night rest. Participant's compliance with the instruction was encouraged by taking a (no further analyzed) saliva sample test at the beginning of the session. In psychopharmacological research this deceptive method is often used and considered effective in studies addressing acute effects (Colzato, Erasmus, & Hommel, 2004; Ridderinkhof et al., 2002) and long-term effects of drugs (Alting von Geusau, Stalenhoef, Huizinga, Snel, & Ridderinkhof, 2004; Colzato et al., 2009).

Participants in two groups were matched for ethnicity (100% African), age, sex, IQ, (measured by Raven's Standard progressive matrices (SPM); Raven, 1988) and alcohol and cannabis consumption. Even if khat was the preferred drug of use for the participants, some of them drunk alcohol (7) on a weekly base and used cannabis (3) monthly base. All khat users (and non-users) reported to have never used LSD, MDMA, cocaine, amphetamine, barbiturates, ketamine, GHB or speed. Demographic and drug use statistics are provided in Table 1. Written informed consent was obtained from all participants after the nature of the study was explained to them. The protocol and the remuneration arrangements of 25 Euro were approved by institutional review board (Leiden University, Institute for Psychological Research).

Sample	Khat users	Khat-free controls
N (M:F)[ns]	20 (18:2)	20 (18:2)
Age (years) [ns]	31.3 (6.5)	30.7 (5.8)
IQ [ns]	110 (3.3)	112 (3.0)
Khat exposure (years) **	10.5 (6.5)	0
Khat times in a week **	3.1 (1.8)	0
Bundles used (khat shrubs) **	3.0 (1.2)	0
Bundles used in one session	1.0 (1.9)	0
Hours chewing khat **	5.8 (1.7)	0
Monthly exposure (joints) [ns]	2.0 (0.4)	2.1 (0.3)
Monthly drinks (units) [ns]	8.4 (0.5)	6.4 (0.6)
Lifetime cocaine (grams) [ns]	0	0
Lifetime amphetamines (grams) [ns]	0	0
Lifetime ketamine (grams) [ns]	0	0
Lifetime Speed (grams) [ns]	0	0

Table 1. Demographic characteristics and self-reported use of khat and other psychoactive drugs. Standard deviations are presented within parentheses.

Notes. IQ: measured by means of the Raven's Standard Progressive Matrices,

Bundles used: number of khat bundles consumed in a typical day/session

Hours chewing khat: amount of time the users spend chewing khat in a typical day/session

Monthly drinks: monthly number of standard alcoholic drinks

[ns] Nonsignificant group difference

* Significant group difference, $p<0.05$

** Significant group difference, $p<0.01$

Apparatus and stimuli

The experiment was controlled by a ACPI uniprocessor PC running on an Intel Celeron 2.8 gHz processor, attached to a Philips 109B6 17 inch monitor (LightFrame 3, 96 dpi with a refresh rate of 120 Hz). Responses were made by pressing the "Z" or "?" of the QWERTY computer keyboard with the left and right index finger, respectively. Participants were required to react quickly and accurately by pressing the left and right key in response to the direction of a left- or right-pointing green arrow (go trials) of about 3.5 X 2.0 cm with the corresponding index finger.

Procedure

All participants were tested individually. Participants completed the SPM (Raven et al., 1988) and performed the stop-signal task for about 30-min. Participants were allowed to take a short break (up to 5 minutes) between task blocks.

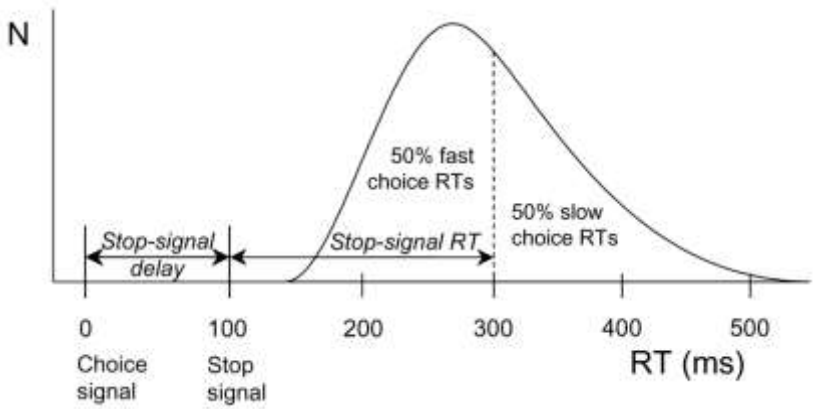
IQ

Individual IQs were determined by means of a 30-min reasoning-based intelligence test (Raven Standard Progressive Matrices: 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 as well as fluid intelligence (Raven et al., 1988). Participants completed the SPM and subsequently performed on the behavioral task measuring inhibitory control.

Stop-Signal Task

The experimental session consisted of a 30-min session in which participants completed a version of the stop-signal task adopted from Colzato et al., (2007); see also Colzato et al., 2009; Colzato et al., 2010). Each trial began with the presentation of an arrow (pseudo-randomly) pointing to the left of right (with a probability of 50% each). Arrows were presented pseudo-randomly for maximal 1500 ms, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response-terminated. Intervals between subsequent go signals varied randomly but equiprobably, from 1250 to 1750 ms in steps of 125 ms. During these interstimulus intervals, a white fixation point (3 mm in diameter) was presented. The green arrow changed to red on 30 % of the trials, upon which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal to control inhibition probability(Levitt, 1971). After a successfully inhibited stop trial, stop-signal delay in the next stop trial increased by 50 ms, whereas the stop-signal delay decreased by 50 ms in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yielded accurate estimates of SSRT and compensates for differences in choice RT between participants (Band, van der Molen, & Logan, 2003; see Figure 1). The stop task consisted of five blocks of 104 trials each, the first of which served as a practice block to obtain stable performance.

Figure 1. Calculation of stop-signal RT (SSRT) according to a race model. The curve depicts the distribution of RTs on go trials (trials without a stop signal) representing the finishing times of the response processes. Assuming independence of go and stop processes, the finishing time of the stop process bisects the go RT distribution. Given that the button-press response could be withheld in 50% of all stop trials, stop-signal RT (200 ms) is calculated by subtracting the mean stop-signal delay (100 ms) from the median go RT (300 ms).



Statistical analysis

First, independent samples t-tests were performed for analyses of age, sex, IQ differences between genotype groups. Second, individual SSRTs for stop-signal trials were calculated to index response inhibition for all participants. SSRTs were analyzed separately by means of univariate ANOVAs with Group (Khat users vs. Khat-free controls) as between-subject factor. Third, to test whether the magnitude of inhibitory efficiency is proportional to the degree of exposure to khat, we computed Pearson correlation coefficients between the amount of cocaine consumed and SSRT. A significance level of $p<.05$ was adopted for all statistical tests.

Results

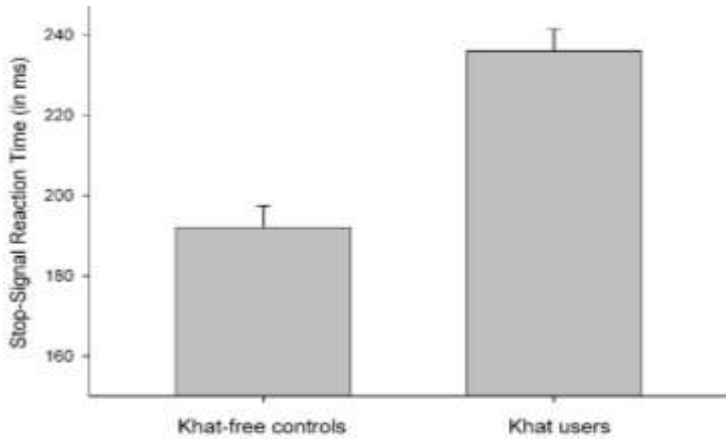
Participants

No significant group differences were obtained for age, $t(38)= 0.306$, $p=0.761$, intelligence, $t(38)= -0.973$, $p=0.337$, alcohol consumption, $t(38)= 0.478$, $p=0.521$, or cannabis consumption, $t(38)= 0.169$, $p=1.00$. Table 1 shows drug-use profiles for the two groups.

Stop-Signal Task

Analyses of mean RT to go-signals showed that khat users (530 ms) did not react significantly faster than khat-free controls (480 ms). SSRTs were computed for each participant and for each group separately. All participants were able to stop their responses on stop-signal trials successfully in about half of the time a stop signal instructed them to do so (51.9 % in Khat users and 49.7 % in Khat-free controls), indicating that the dynamic tracking algorithm worked well in both groups. The percentage of choice errors to go-signals was low and did not discriminate between Khat users (1.8 %) and Khat-free users (1.0%). Most importantly, SSRTs were significantly longer for users (236 ms) than for non-users (192 ms), $F(1,38) = 33.21$, $p< 0.001$, $MSE = 584.624$, $\eta^2p = 0.47$, see Figure 1. To test whether the magnitude of cognitive impairments is proportional to the amount of Khat consumed, we computed Pearson correlation coefficients between the individual lifetime khat exposure, hours chewing and number of bundles used in a khat session and SSRT. No significant correlations were obtained, probably due to the limited distribution of the data.

Figure 2. Calculation of stop-signal RT (SSRT) according to a race model. The curve depicts the distribution of RTs on go trials (trials without a stop signal) representing the finishing times of the response processes. Assuming independence of go and stop processes, the finishing time of the stop process bisects the go RT distribution. Given that the button-press response could be withheld in 50% of all stop trials, stop-signal RT (200 ms) is calculated by subtracting the mean stop-signal delay (100 ms) from the median go RT (300 ms).



Discussion

This study tested, for the first time, whether the use of khat is associated with a detectable selective impairment in the ability to inhibit responses. As expected, we found that khat users were roughly comparable to khat free controls in Go RT but khat users showed significantly elevated SSRTs. In other words, chronic khat use is associated with impaired inhibitory control. We attribute this deficit to the possibility that, at long-term use, cathinone, the active ingredient of khat, is associated to dysfuctions in PFC and a reduced DA level in the striatum – the neurotransmitter that plays a crucial role in response inhibition (Colzato et al., 2010; Colzato & Hommel, 2009; Colzato et al., 2007; Gauggel et al., 2004).

It may be important to note that the group difference in response execution was unreliable but approached the statistical significance level, suggesting that a larger sample might have rendered this effect reliable. On the one hand, this means that it would be premature to exclude a general performance deficit in chronic khat users until converging evidence is available. On the other hand, however, the staircase method that we used allowed separating SSRT from the general RT level, which ensures that the former cannot be explained on the basis of the latter. That is, the SSRT effect does indicate a specific impairment in inhibitory processes in khat users over and beyond a possible general performance deficit.

Even though the empirical connection between inhibitory control functions and khat use is considerable, the causal relation between the two may not be straightforward. Indeed, we cannot exclude that preexisting neuro-developmental factors may play a mediating role and that khat users may suffer preexisting problems in inhibitory control and impulsivity, as it is already the case for cocaine users(Bechara, 2005; Verdejo-García, Lawrence, & Clark, 2008). Notwithstanding this caveat, the connection between inhibitory efficiency and khat use seems rather strong – the more so as a number of possible confounds were controlled for in this study: the khat users that participated in the current study were barely exposed to other drugs and the two groups were well matched in terms of age, IQ, sex, race, and alcohol and cannabis consumption. Especially the matching of age was essential: while inhibitory control seems not to be related to general intelligence, there is evidence that cognitive inhibitory processes decline in efficacy throughout the life span (Williams, Ponesse, Schachar, Logan, & Tannock, 1999).

The present findings raise the question whether recreational khat users also show impairments in other cognitive control functions, such as the shifting between tasks and mental sets, and the updating and monitoring of working memory (Miyake et al., 2000). The direct effects of khat use on the brain need to be

explored as well. It remains to be demonstrated, for instance, that the use of khat produces changes at neuromodulatory level (DA), cortical functioning (decreased neural activity in the striatum and prefrontal cortex), genetic vulnerability and changes in expression of genes. For instance, it would be informative to investigate whether, among khat users, there is also a genetic association with the Taq A1 of the DRD2 polymorphism as in the case of alcohol dependence(Blum et al., 1990)and cocaine addiction(Noble et al., 1993). This association would be useful as marker for a genetic vulnerability.

Of particular interest would be to look into the acute effects of khat. Previous research addressing the acute effect of other psychostimulant drugs – as cocaine – has shown a drug-induced *facilitation* of inhibitory control (Fillmore, Rush, & Hays, 2006). Interestingly, in this study, stop-signal performance revealed a quadratic dose–response function suggesting that the improvement of inhibitory control is limited to a range of intermediate doses, while with lower and higher doses performance deficits are more likely. It also remains to be seen whether the long-term use of khat has similar effects and after-effects (after periods of abstinence) on receptor characteristics, DA sensitivity, etc., as have been observed with the long-term use of other psychostimulant drugs like cocaine (Kreek, Nielsen, Butelman, & LaForge, 2005).

The findings of this study are rather worrying because, first, many real-life situations require the active inhibition of pre-potent actions, as in the case of traffic lights turning red or of criminal actions. Consistent with this idea, the increasing number of traffic accidents in the Eastern Africa countries has been related to the chewing khat habit(Toennes & Kauert, 2004). Chronic khat use may indeed lead to a marked deterioration of psychophysical functions (as inhibitory control) implicated in driving behaviour.

Second, this impairment of inhibitory control has serious implications for personal or societal functioning. This reduced level

of inhibitory control may even be involved in the emergence of addiction: the more a drug is used, the less able users are to prevent themselves from using it. In fact, socioeconomic and familiar problems are common among khat consumers. Many men secure their daily portion of khat at the expense of vital needs, indicating dependence. Family life is harmed because of neglect, dissipation of family income and inappropriate behaviour and in countries like Ethiopia or Kenya, khat addicts are the main group among persons treated for drug problems (UNODC: World Drug Report, 2010).

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Chapter 4

Khat use is associated with impaired Working Memory and Cognitive Flexibility

Abstract

Khat consumption has increased during the last decades in Eastern Africa and has become a global phenomenon spreading to ethnic communities in the rest of the world, such as in The Netherlands, United Kingdom, Canada, and the United States. Very little is known, however, about the relation between khat use and cognitive control functions in khat users.We studied whether khat use is associated with changes in working memory (WM) and cognitive flexibility, two central cognitive control functions.Khat users and khat-free controls were matched in terms of sex, ethnicity, age, alcohol and cannabis consumption, and IQ (Raven's progressive matrices). Groups were tested on cognitive flexibility, as measured by a Global-Local task, and on WM using an N-back task. Khat users performed significantly worse than controls on tasks tapping into cognitive flexibilityas well as monitoring of information in WM.The present findings suggest that khat use impairs both cognitive flexibility and the updating of information in WM. The inability to monitor information in WM and to adjust behavior rapidly and flexibly may have repercussions on daily life activities.

Introduction

The khat plant (Catha Edulis) is a flowering evergreen tree that grows at high altitudes. It is cultivated especially in East-Africa and the south west of the Arabian Peninsula, in countries such as Somalia, Kenya, Djibuti, Yemen, or Ethiopia. In those countries

the chewing of khat is also very common; it is consumed as qat and kat in Yemen; eschat in Ethiopia; miraa, kijiti, gomba, mbachu or veve in Kenya; and as mairungi in Uganda.

Historically, khat leaves have been chewed since ancient times to alleviate fatigue, enhance work capacity, stay alert, reduce hunger, and to induce euphoria and enhanced self-esteem (Brenneisen, Fisch, Koelbing, Geisshusler, & Kalix, 1990; Kalix, 1996). Khat has been appreciated for medical purposes too (Carrier, 2008), and even for its aphrodisiac effects, but it is also used for recreational purposes (Krikorian, 1984). It is habitually used in informal meetings (khat sessions) in which the participants are engaged in discussions and maintain social contact. During khat sessions, the leaves and the tender younger stalks of the plant are chewed slowly over several hours and they are kept in the side of the cheek until the mouth is filled with fresh leaves. The users then chew intermittently to release the active components and then spit out the residues (Al-Habori, 2005).

The half-life of khat is about 4 hours, depending on the amount of chewed khat. When the acute effects disappear, consumers experience feelings of depletion, insomnia, numbness, depression, lack of energy, and mental fatigue. Long-term, chronic (i.e. daily) use of khat is associated with increased blood pressure, development of gastrointestinal tract problems, cytotoxic effects on liver and kidneys, and keratotic lesions at the side of chewing (Al-Habori, 2005).

Many authors have argued about the causal role of khat in exacerbating psychotic reactions. In psychotic patients, khat may aggravate thought disturbances (hallucinations and delusions), induce aggressive behavior, and create difficulties in treating these patients (Hassan, Gunaid, & Murray-Lyon, 2007; Kalix & Braenden, 1985). Regular users with a predisposition to psychotic symptoms, including schizotypal or schizoid traits and family disorders, also have an increased risk of khat-induced psychosis. The psychotic symptoms are abated rapidly when khat is withdrawn

(Hoffman & al' Absi, 2010; Pantelis, Hindler, & Taylor, 1989). However, recently, Odenwald, (2007) challenged this assumption concluding that the causal relationship between general psychopathology and khat use remains unclear and that people with preexisting vulnerability should avoid using khat. Socio-economic and familiar problems may also arise in khat consumers (Balint, Falkay, & Balint, 2009; Cox, 2003; Pennings, Opperhuizen, & van Amsterdam, 2008). Many men secure their daily portion of khat at the expense of vital needs, indicating dependence. Family life is harmed because of neglect, dissipation of family income, and inappropriate behaviour. In countries like Ethiopia or Kenya, khat-dependent individuals are the main group among those treated for drug problems (UNODC, 2010).

The active ingredients of Catha Edulis are cathine (norpseudoephedrine) and cathinone (Benzoylethanamine). These alkaloids are similar in structure and pharmacological activity to amphetamines (Wagner, Preston, Ricaurte, Schuster, & Seiden, 1982). The acute effects of cathinone and cathine on neurotransmitters are basically comparable to amphetamines effects: both stimulate the CNS and suppress appetite. However, cathinone has a more rapid onset and a shorter half life than amphetamine. The two alkaloids act by increasing dopamine (DA), serotonin and noradrenaline (Kalix & Braenden, 1985). For this reason khat is called a "natural amphetamine". Even though the literature on the effect of Catha Edulis compounds on humans is scarce, khat is considered to increase blood pressure and heart rate, and is associated with euphoregenic and psychoestimulants effects (Brenneisen et al., 1990).

Cathinone is probably the main contributor to the stimulant effect of khat. Cathinone is an unstable molecule that rapidly transformes into cathine. Cathine is a less powerful stimulant and the pharmacological conversion from cathinone to cathine causes the decrease of stimulating properties of khat leaves over time. Fresh leaves have a greater ratio of cathinone to cathine than dried ones (Chappell & Lee, 2010). Therefore, the fresh leaves

have more psychoactive effects and a number of techniques are in use to slow down the degradation process (e.g., wrapping the khat in banana leaves). To provide consumers with fresh leaves, khat is delivered by air around the world, commonly no later than five days after been harvested. When the leaves are chewed, cathinone is absorbed through the buccal mucosa and the stomach. After absorption it is metabolically transformed into norephedrine (Feyissa & Kelly, 2008). The effects of oral administration of cathinone occur more rapidly than the effects of amphetamine; roughly 15 minutes as compared to 30 minutes in amphetamine. Cathinone increases levels of DA in the brain by acting on the cathecholaminergic synapses, delaying DA reuptake inactivation and/or enhancing DA release (Patel, 2000; Zelger & Carlini, 1981), in particular in the striatum (Zelger & Carlini, 1981). However, it is important to note that the consumption of cathinone in pure form is not entirely comparable with chewing khat leaves.

Studies addressing the neurobiological mechanism underlying the use of khat are still missing as well as studies that have systematically investigated the long-term cognitive effects of chronic khat use. Nevertheless, given the similarity of khat and amphetamine in structure and pharmacological activity, it makes sense to assume that the long-term use of khat affects the same neurotransmitter and brain structures as the chronic use of amphetamine (see Berman, O'Neill, Fears, Bartzokis, & London, 2008). At a structural level, one may thus expect white matter abnormalities, lower cortical gray matter volume, and higher striatal volume. In particular, higher striatal volumes might reflect a compensation for toxicity in the dopamine-rich basal ganglia. At a functional level, in turn, chronic khat use is likely to be associated with reduced functioning of Dopamine D2 (DAD2) receptors in the striatum and dysfunctions in prefrontal cortex (PFC) and orbitofrontal cortex (OFC)—areas that have been shown to play major roles in cognitive control (Miller, 2000).

Interestingly, DA has a key role in WM processes (Braver & Cohen, 2000; Sawaguchi & Goldman-Rakic, 1991) and in the

ability to flexibly alter cognitive representations (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). According to Moustafa et al.(2008), the striatum serves as a gate to modulate when and when not to update information into PFC. Consistent with this idea, Siessmeier et al.(2006) found that administering DA agents to healthy subjects leads to a correlation between DA uptake in the striatum and dorso-lateral PFC (DLPFC) BOLD activity, suggesting that the striatum might drive activity in the PFC. Moreover, a PET study showed that working memory capacity predicts dopamine synthesis capacity in the striatum (Cools et al., 2008). Consistent with these findings, previous studies on chronic amphetamine users and mice provided evidence for impairment on WM due to amphetamine use (Baicy & London, 2007; Berman et al., 2008; Daumann, Fischermann, Heekeren, Thron, & Gouzoulismayfrank, 2004; Daumann et al., 2003). Similarly, studies investigating patients with Parkinson's disease (PD), a neurodegenerative disorder characterized by severe DA depletion in the striatum, showed decrements for the flexible alteration of cognitive representations (Roshan Cools & Robbins, 2004). Along the same lines, there is evidence of decreasing mental flexibility due to amphetamine use (van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2009).

Khat consumption in Eastern Africa has increased during the last decades and has become a global phenomenon spreading to ethnic communities in the rest of the world, such as in the Netherlands, United Kingdom, Canada, and the United States UNODC, 2010). Amsterdam airport, where a large amount of khat arrives weekly, has become a European distribution point (Beckerleg, 2008; Pennings et al., 2008). In the Netherlands, khat bundles are commonly sold in restaurants, grocery stores and smartshops, which makes this country a suitable platform to investigate the effects of the drug.

Surprisingly, only one study has systematically looked into cognitive impairments in khat users so far. Colzato et al.(2011) reported that khat users exhibit impairments in the inhibition of

overt manual responses assumed to rely on proper dopaminergic functioning (Colzato, van den Wildenberg, Van der Does, & Hommel, 2010). The ability to inhibit unwanted thoughts and actions is commonly considered an important part of executive control, but it represents just one of a larger set of cognitive control functions. In an attempt to categorize the available concepts and measures in a coherent fashion, Miyake and colleagues have investigated the psychometric relationships between the tests and tasks that are commonly used to assess cognitive control (Friedman & Miyake, 2004; Friedman et al., 2006; Miyake et al., 2000). Their findings suggest the existence of three major, separable control functions: the "inhibition" of unwanted responses, the "shifting" between tasks and mental sets (also called "flexibility"), and the "updating" (and monitoring of) working memory (WM) representations. Miyake et al. 's model has been previously used to investigate cognitive impairments among recreational users of cocaine and MDMA (Alting von Geusau, Stalenhoef, Huizinga, Snel, & Ridderinkhof, 2004; Colzato, Huizinga, & Hommel, 2009).

Given the link between khat use and impaired inhibitory control, the current study focused on the two remaining cognitive control functions; flexibility and updating. Importantly for the current study, the above mentioned links between DA and "updating" (and monitoring of) WM representations and mental flexibility on the one hand, and between DA and khat on the other, suggest that WM monitoring and mental flexibility are impaired in khat users. We tested both hypotheses by comparing khat users and matched khat-free controls in a task assessing the efficiency of monitoring information in WM and a task that taps into cognitive flexibility.

Material and Method

Participants

Forty young healthy adults (36 men and 4 women) were compensated for their participation. They constituted the two groups of 20 khat users and 20 khat-free controls. The sample was drawn from 50 adults in the Leiden and The Hague 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. Participants were selected via a phone interview. Based on the interview, we excluded 10 of the 50 potential participants because of current medication use.

We made sure that the users met the following criteria: (1) khat consumption by chewing route for a minimum of 1 year; (2) no clinically significant medical disease and (3) no use of medication. All khat users met more than four of the seven criteria that according to the American psychiatric Association DSM-IV and the World Health Organization (ICD-10) define addiction: tolerance, withdrawal, difficulty controlling the use, negative consequences for job, family and health, significant time or emotional energy spent in searching/consuming the drug, put off or neglected activities because of the use, and desire to cut down the use. None of the khat-free controls reported any history of past or current khat use.

Participants were asked to refrain from taking any psychoactive drugs for at least 24 hours before the test, not to consume alcohol on the night before the experimental session, and to have a normal night rest. Participant's compliance with the instruction was encouraged by taking a (not further analyzed) saliva sample test at the beginning of the session (cf. Colzato et al., 2009; Colzato, Erasmus, & Hommel, 2004).

The two groups were matched for ethnicity (100% African), age, sex, IQ, (measured by Raven's Standard progressive matrices (SPM); Raven, Court, & Raven, 1988) and alcohol and cannabis consumption. Even though khat was the preferred drug for users, some of them drink alcohol (7) on a weekly base and used cannabis (3) on a monthly base. Khat users and non-users reported to have never used LSD, MDMA, cocaine, amphetamine, barbiturates, ketamine, GHB or speed. Demographic and drug use information are provided in Table 1. Written informed consent was obtained from all participants after the nature of the study was explained to them. The protocol and the remuneration arrangements of 25 Euro were approved by the institutional review board (Leiden University, Institute for Psychological Research).

Sample	Khat users	Khat-free controls
N (M:F) [ns]	20 (18:2)	20 (18:2)
Age (years) [ns]	31.3 (6.5)	30.7 (5.8)
Raven IQ [ns]	110 (3.3)	112 (3.0)
Khat exposure (years) **	10.5 (6.5)	0
Khat times in a week **	3.1 (1.8)	0
Bundles used (khat shrubs) **	3.0 (1.2)	0
Bundles used in one session	1.0 (1.9)	0
Hours chewing khat **	5.8 (1.7)	0
Monthly exposure (joints) [ns]	2.0 (0.4)	2.1 (0.3)
Monthly drinks (units) [ns]	8.4 (0.5)	6.4 (0.6)
Lifetime cocaine (grams) [ns]	0	0
Lifetime amphetamines (grams) [ns]	0	0
Lifetime ketamine (grams) [ns]	0	0
Lifetime Speed (grams) [ns]	0	0

Table 1. Demographic characteristics and self-reported use of khat and other psychoactive drugs. Standard deviations are presented within parentheses.

Notes. Raven IQ: IQ measured by means of the Raven's Standard Progressive Matrices,
Bundles used: number of khat bundles consumed in a typical day/session
Hours chewing khat: amount of time the users spend chewing khat in a typical day/session
Monthly drinks: monthly number of standard alcoholic drinks
[ns] Nonsignificant group difference
* Significant group difference, $p<0.05$
** Significant group difference, $p<0.01$

Computerized task

The tasks used in this study have been previously employed to systematically investigate the neurotoxic effects of recreational MDMA use (Alting von Geusau et al., 2004; Daumann et al., 2004) and recreational use of cocaine (Colzato et al., 2009; Colzato, van den Wildenberg, & Hommel, 2007). Similar to these studies and following Miyake et al., we defined cognitive flexibility as the ability to adapt and restructure cognitive representations in response to changing situational demands (cf., Monsell, 1996). We used the N-back task (see, Kane, Conway, Miura, & Colflesh, (2007), for a recent review) to assess the operational component of WM and a task-switching design (Colzato, van Leeuwen, van den Wildenberg, & Hommel, 2010) to assess flexibility.

All participants were tested individually. 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). Participants provided a saliva sample, completed the SPM, and subsequently performed the behavioral tasks measuring cognitive flexibility and WM capacity. Participants were allowed to take a short break (maximal 10 minutes) between task blocks. The experiment was controlled by a PC attached to a 17-inch monitor with a refresh rate of 120 Hz. Participants were seated approximately 0.5 m from the screen.

N-Back task (WM monitoring)

Participants performed two N-back tasks consisting of the sequential visual presentation (stimulus onset asynchrony 2000 ms; duration of presentation 1000 ms) of single letters (B, C, D, G, P, T, F, N, L). Participants had to press the left or right shift-key of the computer-keyboard when the target or the non-target appeared, respectively. Target definition differed with respect to the experimental condition. In the 1-back condition, targets were

defined as stimuli within the sequence that were identical to the immediately preceding one. In the 2-back condition, participants had to respond if the presented letter matched the one that was presented two trials before. The 1-back, and 2-back tasks differ in their amount of memory load and demands on executive control for the processing of information within working memory. Each block consisted of four cycles of the same task.

Task switching (flexibility)

Participants responded to randomly presented rectangles or squares by pressing a left or right response button, respectively. The target stimuli contained a global dimension (i.e., the overal shape was either a rectangle or a square) and a local dimension (the overall shape consisted either of small squares or small rectangles). Three blocks of trials were administered, two training blocks in which the instruction (global or local) was constant across all trials, followed by the experimental block in which participants switched between the global and the local task. In one of the two training blocks, participants responded to the local figure, in the other block they responded to the global figure. The order of the training blocks was randomized across participants and each block consisted of 50 trials. In the third block consisting of 160 trials, participants alternated between predictable sequences of four "local" and four "global" trials). A cue indicated to which dimension (global or local) the participants should respond. Cues that related to the global (local) dimension consisted of a big (small) square, presented at one side of the target stimulus, and a big (small) rectangle, presented at the other side of the target stimulus. The color of cues and target was red. Both remained on the screen until a response was given or 2500 ms had passed. The time interval between presentation of the cue and of the target stimulus varied between 400 ms and 500 ms and the interval between responses and the next presentation of the cue varied between 900 ms and 1100 ms.

Statistical Analysis

We adopted a significance level of $p<.05$ for all statistical tests. Independent samples t-tests were used to analyze binary comparisons and ANOVAs otherwise.

T-tests were performed for Group analysis of age, sex, IQ and alcohol, and cannabis consumption and in the N-back task to assess differences between khat users and khat-free controls. For switching performance mean RTs and proportions of errors (PE) were analyzed by means of ANOVAs using Target level (global vs. local), the Congruency between the stimuli on the two levels (congruent vs. incongruent), and Task switch (i.e., same vs. different target level as in previous trial: task repetition vs. alternation) as within-participants factor and Group (khat users vs. khat-free controls) as between-participants factor. Spearman correlation coefficients were computed between the degree of exposure to khat and cognitive performance in order to test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed. Effect magnitudes were assessed by calculating partial Eta squared (η^2p) for repeated measures ANOVAs.

Results

Participants

No significant group differences were obtained for age, $t(38) = 0.306$, $p = 0.761$, intelligence, $t(38) = -0.973$, $p = 0.337$, alcohol consumption, $t(38) = 0.478$, $p = 0.521$, or cannabis consumption, $t(38) = 0.169$, $p = 1.00$. Table 1 shows drug-use profiles for the two groups.

Task

The results per cognitive task are summarized below and in Table 2. The data of two male khat-users were excluded in both tasks because of their excessive error rates in the task-switching paradigm (PE>45%).

Task Switching

Analyses of Mean RT showed three reliable main effects (see Table 2). First, the effect of Task switch, $F(1,36) = 38.30$, $p<.0001$, $MSE = 7916.15$, $\eta^2p = 0.52$, was due to that repeating the task allowed for faster responding than switching between target levels (475 vs. 537 ms). Second, the effect of Target level, $F(1,36) = 23.52$, $p<.0001$, $MSE = 8728.09$, $\eta^2p = 0.39$, reflected the well-known global preference (Navon, 1977), that is, faster responses to globally than locally defined targets (480 vs. 532 ms). Third, the Congruency effect, $F(1,36) = 7.46$, $p<.01$, $MSE = 10881.70$, $\eta^2p = 0.17$, indicated interference from the non-target level, that is, faster responses if the stimulus at the currently irrelevant level was congruent (e.g., a global square shape consisting of local squares) with the present target than if that stimulus was incongruent (e.g., a global square consisting of local rectangles; 489 vs. 522 ms, respectively).

More important for present purposes, the size of the Switch effect varied by Group, $F(1,36) = 5.68$, $p<.05$, $MSE = 8073.45$, $\eta^2p = 0.14$: khat users showed more pronounced switching costs (i.e., a greater difference in RT between alternation trials and repetition trials) than khat-free controls. No other interaction was reliable.

Analyses of error rates revealed three reliable main effects. First, an effect of Group, $F(1,36) = 73.91$, $p<.0001$, $MSE = 3065.69$, $\eta^2p = 0.67$: khat users committed significantly more errors than khat-free controls (21.3% vs. 4.0%). Second, the effect of Congruency, $F(1,36) = 83.49$, $p<.0001$, $MSE = 322.34$, $\eta^2p = 0.70$, reflecting the interference of the irrelevant target level, as indicated by a smaller proportion of errors on congruent as compared to incongruent trials (3.3% vs. 22.1%). Third, the effect of Target level, $F(1,36) = 5.17$, $p<.05$, $MSE = 686.91$, $\eta^2p = 0.13$, suggesting less errors to globally than locally defined targets (10.1% vs. 15.2%). No other effect was significant.

N-Back Task

Mean RTs and accuracy—with the latter commonly being the more reliable measure in this task—were submitted to independent *t*-tests, see Table 2 for means. As expected, khat users committed significantly more errors in both the 1-back, $t(36) = 4.72$, $p = 0.001$, and 2-back conditions, $t(36) = .75$, $p = 0.001$, see Table 2. RTs revealed no significant group differences in the 1-back, $t(36) = 0.53$, $p = 0.59$, and 2-back conditions, $t(36) = 1.37$, $p = 0.18$.

Task	**Khat users**	**Khat-free**
N-BACK (WM monitoring)		
1-back		
Reaction Times (ms)	494 (55)	504 (62)
Accuracy (%)	70 (17.5)*	91 (7.9)*
2-back		
Reaction Times (ms)	497 (68)	523 (50)
Accuracy (%)	62 (12.9)*	81 (11.4)*
TASK SWITCHING (flexibility)		
Repetition		
Reaction Times (ms)	494 (25)	455 (24)
Error Rates (%)	20.7 (1.6)	3.8 (1.5)
Alternation		
Reaction Times (ms)	581 (27)	492 (25)
Error Rates (%)	21.8 (1.7)	4.2 (1.6)
Switch Costs		
Reaction Times (ms)	**87***	**37***
Error Rates (%)	0.1	0.1

Table 2. Means responses latencies (in ms), error rates (in percent), and standard deviations of measures for the N-back task and task switching.
Switch Costs Reaction Times: difference in RT between alternation trials and repetition trials
Switch Costs Error Rates: difference in error rates between alternation trials and repetition trials
* Significant group difference, $p<0.05$ (referring to the interaction effect reported in the text)

Correlations

To test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed, we computed Pearson correlation coefficients between the individual life time khat exposure, hours chewing and number of bundles used in a khat session and switching costs, as well as accuracy in the n-back task. No significant correlations were obtained, probably due to the limited variability across users.

Discussion

This study tested, for the first time, whether khat use is associated with a detectable selective impairment in cognitive flexibility and WM. As expected, khat users showed increased switching costs, suggesting that recreational use is associated with impaired cognitive flexibility. Performance in khat users differed from performance in non-users also with respect to WM updating (the executive component of WM). We attribute these deficits to the possibility that long-term use of cathinone, the active ingredient of khat, is associated with dysfunctions in PFC and a reduced DA level in the striatum—the neurotransmitter that plays a crucial role in cognitive flexibility and updating of WM (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010; Cools, 2006; Moustafa et al., 2008). Bearing in mind the similarity between cathinone and amphetamine, our results are also consistent with previous studies in humans showing impairments in WM (Baicy & London, 2007; Daumann et al., 2004; Daumann et al., 2003; Nordahl, Salo, & Leamon, 2003) and cognitive flexibility (van der Plas et al., 2009) as consequences of long-term amphetamine and methamphetamine use.

Given that khat users committed significantly more errors also in the 1-back task, a condition that requires hardly any active maintenance of information, we suggest that khat use may be associated with impairment of the updating rather than the maintenance component of WM. Khat users may thus not

necessarily process or store fewer items than khat-free controls but, rather, are less selective with regard to what they store (Vogel, McCollough, & Machizawa, 2005). In an N-back task, this would imply that khat users are less efficient in discriminating targets from non-targets, which means that non-targets are more likely to enter WM and interfere with target information.

Bearing in mind the similarity between cathinone and amphetamine, our results are also consistent with previous studies in humans showing impairments in WM (Baicy & London, 2007; Daumann et al., 2004; Daumann et al., 2003; Nordahl et al., 2003) and cognitive flexibility (van der Plas et al., 2009) as consequences of long-term amphetamine and methamphetamine use. Together with our previous observation of impaired inhibitory control in khat users (Colzato et al., 2011), this suggests that khat use may be associated with a general decrement in cognitive control. Another, not necessarily exclusive possibility is that the impairments on tasks measuring mental flexibility and WM were the result of transitory khat-induced withdrawal symptoms. Indeed, chronic khat users experience withdrawal symptoms during the first days, especially sleeping problems, depressive states, attentional problems, and intense cravings (Al-Habori, 2005). Moreover, given that cathine stays longer than 24 hours in the body, it cannot be excluded that our pattern of results is due to possible acute effects potentially masking or potentiating longer-term effects (Al-Habori, 2005).

It is important to emphasize that the causal relation between cognitive impairment and the regular use of khat is not necessarily straightforward. For instance, we cannot exclude that pre-existing genetic or neurodevelopmental factors may play a mediating role. What we can exclude are contributions from other drugs, to which our khat users were barely exposed, and from individual characteristics as age or intelligence, which do impact performance on working-memory tasks (Ackerman, Beier, & Boyle, 2005; Colzato, van Wouwe, Lavender, & Hommel, 2006; Hartman & Warren, 2005; Kray, Li, & Lindenberger, 2002) but were controlled in this study.

Although data on the density of DA receptors in khat users are not yet available, one may speculate that khat users suffer from the impaired functioning of dopaminergic receptors in the frontostriatal circuit. Indeed, the striatum is assumed to underlie the ability to flexibly alter cognitive representations (Roshan Cools, 2006) and to serve as a gate to modulate when to update information in the PFC structures subserving WM (Moustafa et al., 2008).

The present findings raise the question whether khat users also show impairments in other cognitive control functions, such as strategic planning and decision making (Hoffman & al' Absi, 2010). The acute effect of khat on cognitive functions needs to be investigated as well. Moreover, it would very useful to explore the direct effect of khat use on the brain. It remains to be demonstrated, for instance, that khat use produces changes at the neuromodulatory (reduced functioning of DAD2 receptors) and functional level (dysfunction in PFC and striatum) that may be proportional to the degree of behavioural performance deficits. Of particular interest would be to investigate whether khat users suffer from impulsive behaviour—given that cathinone has been found to enhance aggressive behavior in isolated rats (Banjaw & Schmidt, 2005) and that dysfunctional impulsivity has been associated with genetic markers of striatal dopamine (Colzato et al., 2010).

As pointed out, the observations that khat use is apparently associated with all three major functions of cognitive control (WM monitoring/updating, flexibility, and inhibition: (Miyake et al., 2000) suggest a broad and general impact of khat use on human cognition. Accordingly, using khat can be expected to affect a broad range of everyday behavior, ranging from car driving to work performance and social behavior.

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Chapter *5*

Khat use is associated with increased response conflict in humans

Abstract

Khat consumption has become a worldwide phenomenon broadening from Eastern Africa and the south west of the Arabian Peninsula to ethnic communities in the rest of the world. Only few studies have systematically looked into cognitive impairments in khat users. We studied whether khat use is associated with changes in the emergence and resolution of response conflict, a central cognitive control function. Khat users (n = 16) and khat-free controls (n = 16) were matched in terms of sex, ethnicity, socio-economic situation, age, alcohol and cannabis consumption, and IQ (Raven's Progressive Matrices). Groups were tested on response conflict, as measured by the Simon task. Khat users performed significantly slower than controls and were more strongly affected by stimulus-induced response conflict. Khat use is associated with specific impairments in behavioral control: general slowing and less efficient resolution of response conflicts, which is likely to impair decision making in everyday life.

Introduction

The khat plant (*Catha edulis*) is a flowering evergreen. Its leaves have been chewed in East-Africa and the south west of the Arabian Peninsula since ancient times to ease exhaustion, increase alertness and self-esteem, decrease hunger, and induce euphoria and feelings of well-being (Brenneisen, Fisch, Koelbing, Geisshusler, & Kalix, 1990; Kalix, 1996). Khat has been used for medical purposes as an appetite suppressant and an anti-ulcer agent (Carrier, 2008) and even for its aphrodisiac effects and to treat

premature ejaculation. It is also used for recreational purposes (Krikorian, 1984) during casual meetings (so called khat sessions) in which individuals actively engage in discussions and develop and/or preserve social contact. During those sessions, the leaves and the tender younger stalks of khat are chewed slowly, but intermittently to release the active components, over several hours (Al-Habori, 2005).

However, once the positive acute effects vanish, users undergo feelings of exhaustion, sleeplessness, apathy, depression, lethargy, mental fatigue, and concentration difficulties. In humans, chronic (i.e., daily) long-term use of khat is associated with several adverse effects, such as blood vessel constriction, prolonged malnutrition, increased blood pressure, development of gastrointestinal tract problems, cytotoxic effects on liver and kidneys, and keratotic lesions at the side of chewing (Al-Habori, 2005).

The active ingredients of *Catha edulis* are cathine (norpseudoephedrine) and cathinone (benzoylethanamine), the latter is the main contributor of the stimulant effect of khat. These alkaloids are similar in structure and pharmacological activity to amphetamines (Wagner, Preston, Ricaurte, Schuster, & Seiden, 1982): both stimulate the central nervous system and suppress appetite. For this reason, khat is also called a "natural amphetamine." However, cathinone has a more rapid onset (roughly 15 min) and a shorter half-life (about 4 h) than amphetamine. Cathinone increases levels of dopamine (DA) and norepinerphrine in the brain by acting on the cathecholaminergic synapses, delaying the reuptake and/or enhancing the release of those neurotransmitters (Patel, 2000; Wagner et al., 1982). Nevertheless, it is important to note that the consumption of cathinone in pure form is not entirely comparable with chewing khat leaves. Interestingly, synthetic cathinones, in particular mephedrone, has replaced MDMA (3,4-methylenedioxymethamphetamine or "ecstasy") as one of the favorite recreational drugs among individuals who go clubbing, at

least in the UK (Wood, Greene, & Dargan, 2011). However, the use of mephedrone has been associated with unpleasant side effects, such as sweating, headache, palpitations, nausea, and vomiting.

The neurobiological underpinnings underlying the acute effect of khat and the long-term cognitive effects of chronic khat use are still unclear and understudied (Hoffman & al' Absi, 2010). However, given the chemical similarity of khat and amphetamine in structure and pharmacological activity, long-term use of khat likely affects the same neurotransmitter and brain structures as the chronic use of amphetamine (Berman, O'Neill, Fears, Bartzokis, & London, 2008; Salo, Nordahl, Galloway, et al., 2009a). At an anatomical level, one may suspect a lower level of structural connectivity as indication of decreased myelination of the fibers and a lower cortical gray matter volume that might underlie the possible cognitive impairments associated with chronic khat use. At a neuromodular level, instead, chronic khat use is likely to be associated with dopaminergic dysfunctions in prefrontal cortex (PFC) and dorsal anterior cingulate cortex (ACC)—circuits innervated by DA and that have been shown to play major roles in the way we control our thoughts and goal-directed behavior (Miller, 2000).

Khat use in Eastern Africa and in the south west of the Arabian Peninsula has gained popularity during the last 10 years and—mainly because of the Somali diaspora caused by the Somali civil war—has become a worldwide phenomenon broadening to ethnic communities in the rest of the world, such as in North America, Great Britain, and the Netherlands (UNODC, World Drug Report, 2010). The airports of Amsterdam and London have become the main European distribution points (Beckerleg, 2008; Pennings, Opperhuizen, & van Amsterdam, 2008). In the Netherlands, the use of the unprocessed plant is legal and unrestricted, which makes this country a suitable platform to investigate the effects of the drug.

Surprisingly, only few studies have systematically looked into cognitive impairments in khat users so far. First, Colzatoet al. (2011a) reported that khat users exhibit impairments in the inhibition of behavioral responses. Participants were asked to press a left or right button as soon as a green left-pointing or right-pointing arrow appeared (go trials). However, if the color of the arrow suddenly changed to red, the participants were supposed to refrain from responding (stop trials). On go trials, khat users performed just as well as non-users in terms of both accuracy and response speed. However, khat users found it much more difficult than do non-users to inhibit responding on stop trials.

Second, Colzato et. al (2011b) showed that khat users performed significantly worse than controls on tasks tapping into cognitive flexibility (the ability to adapt and restructure cognitive representations in response to changing situational demands; cf., (Monsell, 1996) as well as monitoring information in working memory.

The current study focused on another key cognitive control function: the ability to deal with and resolve response conflict, that is, the ability to select a correct response in the face of other, competing response tendencies. The arguably purest assessment of response conflict is provided by the Simon task (cf., Hommel, 2011). In this task, participants respond to a non-spatial feature of commonly visual stimuli (e.g., color) by pressing left and right response buttons. Importantly, the location of the stimulus varies randomly so that it can spatially correspond or not correspond with the correct response. As one might expect, performance is better with stimulus–response correspondence than with noncorrespondence—the Simon effect (Simon & Small, 1969). The effect reflects the difficulty of selecting a response in the face of competing response tendencies and can thus be taken as a rather pure measure of (the efficiency of resolving) response conflict (Hommel, 2011; Kornblum, Hasbroucq, & Osman, 1990).

Interestingly, the ACC has been considered responsible for the detection of response conflict, and DA has been suggested to play a key role in coding such a conflict (Botvinick, 2007). Holroyd and Coles, (2002) argued that response errors or negative feedback induce a dip in DA cell firing, which is transmitted to the ACC, where the drop in DA levels disinhibits the apical dendrites of motor neurons. Indeed, the stimulation of the ACC can transiently inhibit DA release (Jackson, Frost, & Moghaddam, 2001).

To sum up, in the present study, we used the Simon task (Simon & Small, 1969) to test whether khat use produces deficiencies in the resolution of response conflict. Given the aforementioned relation between DA and response conflict and ACC on the one hand, and between DA and khat on the other, we expected increased response conflict (as indicated by a larger Simon effect) in khat users than in khat-free controls.

Material and Method

Participants

Thirty-two young healthy African adults (28 men and 4 women) were compensated for their participation. They constituted the two groups of 16 khat users and 16 khat-free controls. The sample was drawn from 40 adults in the Leiden and The Hague metropolitan area, who volunteered to participate in studies of behavioral pharmacology and did not participate in previous studies of Leiden University. Participants were recruited via ads posted on community bulletin boards and by word of mouth. Participants were selected via an interview using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) (Sheehan *etal.*,1998). The Mini International Neuropsychiatric Interview is a well-established brief diagnostic tool in clinical, stress, and psychopharmacology research (Colzato, Huizinga, & Hommel, 2009; Elzinga et al., 2008; Sheehan et al., 1998) that screens for several psychiatric disorders including post-traumatic stress

disorder, schizophrenia, depression, mania, attention deficit/hyperactivity disorder, and obsessive–compulsive disorder. On the basis of the interview, we excluded 8 of the 40 potential participants because of current medication use or hints to a possible psychiatric disorder (post-traumatic stress disorder) and/or current medication.

Following Colzato et al (2011b), we made sure that the users met the following criteria: (i) khat consumption by chewing route for a minimum of 1 year; (ii) no clinically significant medical disease; and (iii) no use of medication. All khat users met more than four of the seven criteria that according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the World Health Organization (International Classification of Diseases-10) define addiction: tolerance, withdrawal, difficulty controlling the use, negative consequences for job, family and health, significant time or emotional energy spent in searching/consuming the drug, put off or neglected activities because of the use, and desire to cut down the use. None of the khat-free controls reported any history of past or current khat use.

Participants were asked to refrain from taking any psychoactive drugs for at least 24 h before the test, not to consume alcohol on the night before the experimental session, and to have a normal night rest. Participant's compliance with the instruction was encouraged by taking a (not further analyzed) saliva sample test at the beginning of the session (cf. Colzato et al., 2009; Colzato, Erasmus, & Hommel, 2004).

The two groups were matched in terms of ethnicity (100% African), age, sex, IQ, (measured by Raven's Standard Progressive Matrices (SPM); Raven, Court, & Raven, 1988), socio-economic situation, and alcohol and cannabis consumption. In the Netherlands, the use of khat is confined to East-African immigrants and is predominantly used by male individuals (Pennings et al., 2008). All participants were rated middle socioeconomic status according to the Hollingshead Occupational

Status Scale (Hollingshead, 1975). Even though khat was the preferred drug for users, some of them drank alcohol (five) on a weekly base and used cannabis (two) on a monthly base. Khat users and non-users reported to have never used LSD, MDMA, cocaine, amphetamine, barbiturates, ketamine, GHB, or speed. Demographic and drug use information is provided in Table 1. Written informed consent was obtained from all participants after the nature of the study was explained to them. The protocol and the remuneration arrangement of €12 were approved by the institutional review board (Leiden University, Institute for Psychological Research).

Sample	Khat users	Khat-free controls
N (M:F) [ns]	16 (14:2)	16 (14:2)
Age (years) [ns]	32.4 (7.2)	32.4 (7.2)
Raven IQ [ns]	108 (3.0)	108 (3.0)
Khat exposure (years) **	9.6 (6.0)	9.6 (6.0)
Khat times in a week **	3.1 (1.8)	3.1 (1.8)
Bundles used (khat shrubs) **	2.9 (1.2)	2.9 (1.2)
Bundles used in one session**	1.0 (1.9)	1.0 (1.9)
Hours chewing khat **	5.9 (1.9)	5.9 (1.9)
Monthly exposure (joints) [ns]	0.4 (1.2)	0.4 (1.2)
Monthly drinks (units) [ns]	1.5 (2.4)	1.5 (2.4)
Lifetime cocaine (grams) [ns]	0	0
Lifetime amphetamines (grams) [ns]	0	0
Lifetime ketamine (grams) [ns]	0	0
Lifetime Speed (grams) [ns]	0	0

Table 1. Demographic characteristics and self-reported use of khat and other psychoactive drugs. Standard deviations are presented within parentheses.

Notes. Raven IQ: IQ measured by means of the Raven's Standard Progressive Matrices,
Bundles used: number of khat bundles consumed in a typical day/session
Hours chewing khat: amount of time the users spend chewing khat in a typical day/session
Monthly drinks: monthly number of standard alcoholic drinks
[ns] Nonsignificant group difference
* Significant group difference, $p<0.05$
** Significant group difference, $p<0.01$

Apparatus, stimuli, and task

The Simon task has been previously used to systematically investigate the neurotoxic effects of methylphenidate (Rubia et al., 2011). The experiment consisted of a 25-min session in which participants made speeded discriminative button-press responses to

the color of a circle. Participants responded left to a green circle and right to a blue circle. Circles were equiprobably presented to the right or to the left of a central fixation point until the response was given or 1500 ms has passed. Intervals between subsequent stimuli varied randomly but equiprobably, from 1750 to 2250 ms in steps of 100 ms. Participants were to ignore the location of the stimulus and to base their response exclusively on its color. Responses were to be given as fast as possible while keeping error rates below 15% on average; feedback was provided at the end of a trial block. The task consisted of six blocks of 60 trials (with all conditions being equiprobable), the first of which served as a practice block.

Procedure and design

All participants were tested individually. 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). Participants provided a saliva sample, completed the SPM, and subsequently performed the behavioral tasks measuring response conflict. Participants were allowed to take a short break (maximum of 5 min) between task blocks. The experiment was controlled by a PC attached to a 17-inch monitor with a refresh rate of 120 Hz.

Statistical Analysis

Independent *t*-tests were performed to test age, IQ, alcohol, and cannabis consumption differences between the groups. In the Simon task, mean reaction times (RTs) and (square-rooted) error percentages1 were analyzed by means of analyses of variance (ANOVAs) using spatial stimulus–response correspondence (versus noncorrespondence) as a within-participant factor and group as a between-participant factor. Moreover, Pearson correlation coefficients were computed between the degree of

exposure to khat and cognitive performance to test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed. Effect magnitudes were assessed by calculating partial eta squared (η^2_p) for repeated-measures ANOVAs. A significance level of $p < 0.05$ was adopted for all tests.

Results

Participants

No significant group differences were obtained for age, $t(30) = 1.51$, $p = 0.13$, intelligence, $t(30) = 0.71$, $p = 0.48$, alcohol consumption, $t(30) = 0.15$, $p = 0.88$, or cannabis consumption, $t(30) = 0.56$, $p = 0.80$. Table 1 shows drug-use profiles for the two groups.

Simon Task

The RT analysis showed evidence of a group effect, $F(1, 30) = 7.02$, $p < 0.05$, mean squared error (MSE) = 8637.81, $\eta^2_p = 0.19$: khat users were in general slower than khat-free controls. The RT and error rates analyses showed a main effect of correspondence, $F(1, 30) = 158.81$, $p < 0.0001$, $MSE = 159.58$, $\eta^2_p = 0.84$ (RTs) and $F(1, 30) = 51.90$, $p < 0.0001$, $MSE = 11.63$, $\eta^2_p = 0.63$ (errors), which was modified by group in RTs but not in errors, $F(1, 30) = 7.27$, $p < 0.05$, $MSE = 159.58$, $\eta^2_p = 0.19$ (RTs) and $F < 1$ (errors). To verify whether the overall RT increase in khat users may have confounded this outcome, we ran another ANOVA with overall RT level as covariate; however, the crucial 3-way interaction remained significant: $F(1, 29) = 5.71$, $p < 0.05$, $MSE = 165.08$, $\eta^2_p = 0.16$.

Both groups showed a significant main effect of correspondence, $F(1, 15) = 140.87$, $p < 0.0001$, $MSE = 55.57$, $\eta^2_p = 0.90$ (RTs) and $F(1, 15) = 24.71$, $p < 0.0001$, $MSE = 8.70$, $\eta^2_p = 0.62$ (errors); $F(1, 15) = 70.85$, $p < 0.0001$, $MSE = 263.60$,

$\eta^2_p = 0.82$ (RTs) and $F(1, 15) = 27.71$, $p < 0.0001$, $MSE = 14.57$, $\eta^2_p = 0.65$ (errors), for khat-free controls and khat users, respectively. These main effects indicated that responses were faster and more accurate with stimulus–response correspondence (431 ms and 2.9%) than with non-correspondence (471 ms and 9.0%, respectively). As expected, however, the RT correspondence effect was reliably increased in khat users as compared with khat-free controls, and the error rates followed the same pattern (Table 2).

Variables	**Khat users**	**Khat-free controls**
Simon task		
Correspondence		
Reaction Times (ms)	458 (16.5)	405 (16.5)
Error Rates (%)	2.6 (0.8)	3.1 (0.8)
Noncorrespondence		
Reaction Times (ms)	506 (16.6)	436 (16.6)
Error Rates (%)	9.7 (1.6)	8.3 (1.6)
Simon effect		
Reaction Times (ms)*	**48**	**31**
Error Rates (%)	7.1	5.2

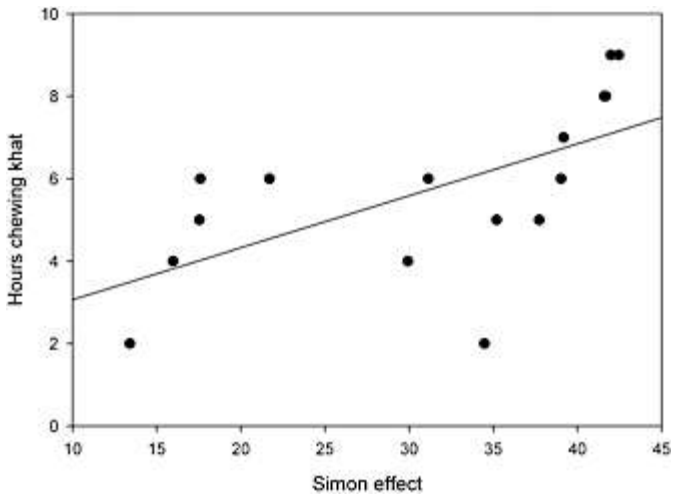
Table 2. Performance on the Simon task as a function of correspondence (correspondent vs. noncorrespondent) and group (khat users vs. khat-free controls). Standard errors of reaction times and error rates are presented in parentheses. Significant group difference; * $p < 0.05$.

Correlations

To test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed, we computed Pearson correlation coefficients between the individual lifetime

khat exposure, hours chewing, and number of bundles used in a khat session and Simon effects in RT and accuracy. Hours chewing positively correlated with Simon effect, $r(16) = 0.62$, $p = 0.01$, whereas khat exposure, peak and number of bundles used in a khat session did not, even though the direction of the associations was similar. Hence, longer chewing is associated with increased response conflict (Figure 1).

Figure 1. Scatter diagram of individual hours chewing khat against Simon effect (in ms).



Discussion

This study tested, for the first time, whether long-term khat use is associated with a detectable selective impairment in cognitive control to resolve response conflict. As expected, khat users were slower than khat-free controls in selecting the correct response when an alternative response was simultaneously activated. Moreover, the size of this deficit corresponds to the hours spent in chewing khat. Hence, the longer the chewing, the more active compounds are released, the greater the magnitude of the loss in selecting the correct response. We suggest that this

impairment may be due to the long-term use of cathinone, the active ingredient of khat, which is associated with dysfunctions in PFC and a reduced DA level—the neurotransmitter that plays a key role in resolving response conflict (Botvinick, 2007; Cools, 2006). Taking into account the chemical resemblance between cathinone and amphetamine, our results are also in line with those of previous studies in humans showing impairments in response conflict as consequences of long-term amphetamine and methamphetamine use (Rubia et al., 2011; Salo, Ursu, Buonocore, Leamon, & Carter, 2009; Salo, Nordahl, Buonocore, et al., 2009a; Salo, Nordahl, Galloway, et al., 2009b). Alongside all those studies, we found no group differences in accuracy, presumably reflecting the fact that error rates are not normally distributed and therefore less sensitive.

As our participants were screened for several psychiatric disorders, we can rule out an alternative account in terms of pre-existing psychiatric disorders (such as posttraumatic stress disorder and psychosis) that have been associated with khat-consuming populations such as Somali refugees (Kroll, Yusuf, & Fujiwara, 2011). Particularly important was the matching of the age range: the ability to resolve response conflict is known to decline with increasing age (Mager et al., 2007).

However, it is important to bear in mind that the causal relation between chronic use of khat and cognitive impairments is not necessarily clear-cut. We cannot rule out that pre-existing genetic or neurodevelopmental factors may play a modulating role. For instance, individuals with a genetic predisposition that hampers response conflict functions might be drawn to chewing khat more strongly so that what looks like an effect of drug use might actually represent a form of self-selection.

It is also important to note that we cannot exclude that pesticides as DDT, which are still used in khat-growing countries, may have partially contributed to the adverse cognitive effects of chewing khat (Daba, Hymete, Bekhit, Mohamed, & Bekhit, 2011). Moreover, two other factors may be associated with our results of

increased response conflict: First, long-term khat users are known to undergo withdrawal symptoms during the first days of abstinence, such as mental fatigue, sleeplessness, and apathy. Second, since cathine lasts longer than one day in the system, it cannot be ruled out that our findings may be due to possible acute effects potentially masking or potentiating longer term effects (Al-Habori, 2005).

Even though positron emission tomography studies on DA receptors availability still need to be carried out, we may speculate that in khat users, the inputs from midbrain dopaminergic nuclei are drastically reduced. Such nuclei are fundamental in driving the ACC, which is assumed to bias response-selection mechanisms toward the correct response (Botvinick, 2007).

The current findings raise the issue whether long-term khat use, as in the case of methamphetamine (Salo et al., 2009a), decreases the plasticity of the white matter (the structural connections between regions based on known axonal projections) underlying the cognitive control system in PFC and ACC. Of particular interest would be to investigate the acute effect of khat on cognitive functions. Given that the acute administration of amphetamine enhances inhibitory mechanisms involved in visual search (Fillmore, Rush, & Abroms, 2005) it is possible that the acute administration of khat improves rather than impairs the ability to inhibit irrelevant information and to select correct responses in the face of conflict.

Moreover, given the chemical similarity of khat and synthetic cathinones in structure and pharmacological activity, the long-term use of these so called designer drugs, such as mephedrone, is likely to be associated with similar cognitive deficits such as in the case of the chronic use of khat. Given that the use of mephedrone has increased in recent years, because of the fall in the use of MDMA, it seems of societal relevance to devote more research on the functional significance of possible deficits associated with the use of designer drugs.

Conclusion

Together with previous demonstrations of khat-related impairments in working memory updating, flexibility, and inhibitory control (Colzato et al., 2011a, 2011b), the present finding that long-term khat use is associated with general slowing and a more specific decrement in the ability to resolve response conflict suggests an extensive and wide-ranging impact of khat use on human cognition. Therefore, using khat can be expected to have a negative effect on a broad range of everyday behavior. For instance, impairments in the selection of correct actions in the presence of less appropriate alternatives is fundamental in driving behavior, which is likely to account for the increasing number of traffic accidents in Eastern Africa and the south west of the Arabian Peninsula countries linked to khat-chewing habits (Toennes & Kauert, 2004). Moreover, even though general slowing by 62 ms and a specific conflict-induced delay of 17 ms seems negligible at first sight, these numbers correspond to a 12.8% and 35.4% slowing of general response speed and decision-making time, respectively. Moreover, the task we used to assess response conflict was incredibly simple in using minimalistic stimulus and response sets related by only two stimulus–response rules. Considering the much greater complexity of many everyday life decisions, together with the fact that decision-making time increases with the number of stimuli and responses involved (Hick, 1952), it is easy to imagine that even a small-looking impairment can have considerable consequences on real-life decision making.

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Chapter 6

Chronic and recreational use of cocaine is associated with a vulnerability to semantic interference

Abstract

Language production requires that speakers effectively recruit inhibitory control to successfully produce speech. The use of cocaine is associated with impairments in cognitive control processes in the nonverbal domain, but the impact of chronic and recreational use of cocaine on these processes during language production remains undetermined. This study aims to observe the possible impairment of inhibitory control in language production among recreational and chronic cocaine polydrug users. Two experiments were carried out on chronic (experiment 1) and recreational (experiment 2) cocaine polydrug users performing a blocked-cycled naming task, yielding an index of semantic interference. Participants were matched for sex, age, and intelligence (Raven's progressive matrices) with cocaine free-controls, and their performance was compared on the blocked-cycled naming task. Chronic and recreational users showed significantly larger semantic interference effects than cocaine-free controls, thereby indicating a deficit in the ability to inhibit interfering information. Evidence indicates a relationship between the consumption of cocaine, even at recreational levels, and the inhibitory processes that suppress the overactive lexical representations in the semantic context. This deficit may be critical in adapting and responding to many real-life situations where an efficient self-monitoring system is necessary for the prevention of errors.

Introduction

Taking cocaine by the snorting route is Europe's second preferred recreational drug habit after smoking cannabis (European Centre for Drugs and Drug Addiction, 2012). The popularity of cocaine has risen in recent years, and nowadays it is no longer considered to be an "elite drug" instead being one of the most commonly used drugs and, as with the USA, its use has now been identified as a public health issue in Europe as it is in the USA (EMCDDA, 2012; United Nations Office on Drugs & Crime, 2013).

Chronic and recreational cocaine users, as well as abstinent cocaine users, are characterized by showing significant decrements in neuropsychological performance when compared to cocaine-free controls (Bolla et al. 2004; Goldstein et al. 2004; Hulka et al. 2013a, 2013b, 2013c; Jovanovski et al. 2005). Several studies have examined the long-term effects of chronic cocaine use on cognitive processes. Commonly observed impairments include deficiencies in cognitive flexibility (Verdejo-García et al. 2006; Verdejo-García and Pérez-García 2007), episodic memory (Manschreck et al. 1990; Mittenberg and Motta 1993; Reske et al. 2010; Vonmoos et al. 2013), social and non-social decision-making (Hulka et al. 2013a), prosodic and cross-modal emotion processing (Hulka et al. 2013b) and inhibitory control processes (Ersche et al. 2012; Fillmore and Rush 2002; Goldstein and Volkow 2002; Rosselli et al. 2001; Volkow et al. 2010). Inhibitory control refers to the processes responsible for suppressing irrelevant and competing information to facilitate the selection of the correct representation according to the task goal (Anderson 2003; Brainerd and Dempster 1995; Miyake et al. 2000). The frontal regions are proposed as the neural substrate for inhibitory control (Bari and Robbins 2013; Miller and Cohen 2001) and dopamine, the neurotransmitter targeted by cocaine (Hershey et al. 2004), plays an important neuromodulatory role (Arnsten et al. 2012; Previc 1999; Robbins and Arnsten 2009). It is well known that in the long term, chronic (i.e. daily) use of cocaine is associated with a reduced functioning of dopamine D2

(DAD2) receptors in the orbitofrontal cortex, cingulate gyrus and striatum (Martinez et al. 2009; Tomasi et al. 2010; Volkow et al. 1999) along with dysfunctions in the lateral prefrontal cortex, orbitofrontal cortex and anterior cingulate gyrus (Bolla et al. 2004; Bolla et al. 2003), as well the cerebellum (Hester and Garavan 2004).

Recent studies have showed that recreational cocaine polydrug users, who do not meet the criteria for abuse or dependence, but preferentially take cocaine on a monthly basis (1-4 g monthly), as well as other substances of abuse (e.g. MDMA, alcohol, cannabis) also show cognitive impairments that resemble those of chronic cocaine users. Thus, Colzato et al. (2007) provided evidence that recreational cocaine polydrug users showed impaired response inhibition, measured through a stop signal task and inhibition of return, relative to non-cocaine users (Colzato and Hommel 2009). Furthermore, recreational use of cocaine is associated with impairments on tasks tapping into sustained attention, attentional shifting (Soar et al. 2012; Vonmoos et al. 2013), and resolution of response conflict (Sellaro et al. 2013). Taken together, the available studies suggest that chronic and recreational use of small doses of cocaine may be involved in alterations in inhibitory control functions in the nonverbal domain. Nevertheless, no studies have directly investigated these executive control impairments in the language domain. Although there are some reports of worsened performance on the Stroop task (Rosselli et al. 2001; Verdejo-Garcia et al. 2004), deficits in naming ability (Ardila et al. 1991; Manschreck et al. 1990; Mittenberg and Motta 1993; Rosselli et al. 2001) and in verbal memory and abstraction (Beatty et al. 1995; O'Malley and Gawin 1990; Rosselli and Ardila 1996) observed in chronic and dependent cocaine users compared to non-users, the relationship between inhibitory control and language processing in cocaine users remains undetermined.

The current study aims to explore whether cocaine use is associated with impairments in inhibitory control in language production. To do so, we used the semantic blocking task (Belke et

al. 2005; Damian et al. 2001; Kroll and Stewart 1994), where participants are asked to name images presented in a context where all items belong to the same semantic category (homogeneous condition: e.g., TRAIN, CAR, BIKE) or in a context in which elements belong to different semantic categories (heterogeneous condition: e.g., TRAIN, BED, DOG). The typical result is slower naming latencies to elements presented in a homogeneous context than in a heterogeneous context. This interference effect is accounted for in terms of competition among the co-activated lexical entries, by virtue of their semantic relatedness. During lexical selection, semantically-related concepts receive extra activation and they become potent competitor-distractors, relative to those concepts that are presented in a semantically-unrelated context (Roelofs 1992; Roelofs 2003; Schriefers et al. 1990). In interference paradigms, speakers have to prevent responses corresponding to highly salient competitors and selective inhibition may be involved (Roelofs and Piai 2011; Shao et al. 2013). Further evidence supporting the idea that the semantic blocking task can reflect the ability to inhibit specific unwanted responses comes from neuropsychological studies. For instance, Biegler and Martin (2008) observed exaggerated semantic blocking effects in patients with damage to the left inferior frontal gyrus (Biegler et al. 2008), which is thought to be involved in the selection among semantic competing representations (Thompson-Schill 2003; Thompson-Schill et al. 1997; Thompson-Schill et al. 2002).

In the present study, we investigated whether the abuse of cocaine predisposes an individual to showing a possible deficit in verbal inhibitory control in chronic (Experiment 1) and recreational cocaine polydrug users[1] (Experiment 2). The focus of Experiment

[1] Chronic cocaine users were screened for other drug use. We found that they only used cocaine except for one participant that 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".

1 was to examine if chronic cocaine users, who have not been using drugs other than cocaine (except alcohol and tobacco), show higher vulnerability to semantic interference - if so, we would expect larger semantic blocking effects in users than in cocaine-free controls. In Experiment 2, we hypothesized that the abuse of small amounts of cocaine predispose to a greater semantic blocking effect with respect to cocaine-free controls, and therefore we expected to find larger semantic blocking effects in the recreational cocaine polydrug users due to inefficient inhibitory mechanisms at lexical selection.

General method

Apparatus, stimuli and procedure

All participants were tested individually in a session that lasted approximately 60 minutes. They first completed a drug use questionnaire, before performing the screening tasks, followed by a Spanish version of the semantic blocking task. This task consisted of twenty images belonging to different semantic categories (faces, vehicles, vegetables, instruments and clothes) shown on a computer screen. The exemplars were selected to minimize within-category visual similarity, associative relations between exemplars, and overlap of initial phonemes of the names of the stimuli. The frequency and number of letters were controlled. The stimuli were arranged in a 5x5 item matrix. Columns corresponded to categories and formed homogeneous groups of five items, while rows formed groups of five items from different categories. Thus, there were five blocks with five items each from the same category, and five blocks with the same number of items from different categories. Each block contained four repetitions (four presentation cycles), a total of 20 trials per block. Each presentation cycle contained five different items and each item occurred once in each position within a cycle. The last item of a cycle was never the same as the first of the next cycle to avoid repetition of items on successive trials (Belke et al. 2005).

For counterbalancing purposes, we created five different homogeneous lists and five different heterogeneous lists from the combination of the 10 blocks in a Latin Square design. Homogeneous and heterogeneous lists were presented in alternating orders, with a pause after each list.

The participants were instructed to name each item as quickly and accurately as possible. We presented images on a screen using a computer, and an electronic device recorded verbal responses. The experimenter recorded errors and equipment failures. Before the naming task, participants were familiarized with the complete set of stimuli with the corresponding name printed below. A trial consisted of the following: a fixation cross at the center of the screen for 500 ms; the stimulus remained on the screen until the response or for a maximum of 3000 ms; a blank interval for 500 ms. Response latencies were measured from the presentation of the stimulus to the onset of the response.

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 et al., 2007, 2009). 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 explanations about the nature of the experiment. The local ethics committee approved the protocol and the compensation of 20 euro for participation in the study.

Experiment 1

Participants

Thirty-two adults (30 men and 2 women) participated in the experiments. They formed the two experimental groups of 16 chronic cocaine users and 16 cocaine-free controls. Chronic cocaine users were recruited from *Proyecto Hombre Granada* rehabilitation center. The inclusion criteria were: 1) meeting the DSM-IV criteria for cocaine dependence as assessed by the Structured Clinical Interview for DSM-IV disorders (SCID) (American Psychological Association 2000) – Clinician version (First et al. 1996) 2) a minimum abstinence interval of two days for all abuse substances except nicotine, observed by periodic urine toxicology tests, therapist reports 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; and 2) the presence of history of brain injury or central nervous system diseases; and 3) an excessive intake of alcohol (>280 g/week for men and >168g/week for women) (Foster and Marriott 2006). Four of the chronic cocaine users were using prescribed benzodiazepines, but they were asked not to use the medication two days before the assessment. Sixteen healthy adults formed the control group. We recruited the control participants via notes posted on community bulletin boards and by word of mouth. The control group did not meet any criteria for Axis I or Axis II psychiatric disorders, including substance abuse, and had no clinically significant medical disease (e.g multiple sclerosis or brain injury). In the last six months, prior to participation, three chronic cocaine and three cocaine-free users also smoked marijuana, whilst one chronic cocaine user reported having used MDMA (ecstasy). Although participants in the chronic 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. Researchers were also instructed to observe if participants had used alcohol prior to the experimental session.

Sample	**Chronic cocaine users**	**Cocaine-free controls**
N (M:F) [ns]	16 (15:1)	16 (15:1)
Age (years) [ns]	33.75 (4.46)	31.25 (4.97)
Raven IQ [ns]	98 (5.43)	101 (8.60)
Cigarettes (unit/day) **	12.13 (7.44)	1.69 (3.38)
alcohol (units/weeks)[1] **	24.4 (18.3)	1.8 (3.7)
Monthly Cannabis (joints) *	2.75 (6.64)	0.75 (1.61)
Years using cocaine	10.31 (4.88)	0
Monthly exposure (grams)	15.37 (16.96)	0
Maximum amount in a 12-h period (grams)	2.81 (1.52)	0
Mean weeks in abstinence	24.71 (17.68)	0
Monthly spent money (EUR)	922.5 (1017.96)	0
MDMA (grams/ last 6 months)	0.40 (1.62)	0

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

[1]Unit equals to a 10 ml or 8 grams of pure ethanol (International Center for Alcohol Policies, 2005; Spanish Ministry of Health, 2007). Chronic cocaine users are alcohol abstinent once engaged in the detoxification program.

[ns]Non-significant difference

* Significant group difference; $p<0.05$; ** Significant group difference; $p<0.01$.

Results

Demographic 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, users differed from controls in the amount of tobacco, alcohol and cannabis consumed before they entered into the rehabilitation program, although none of them were consumin alcohol or cannabis once they entered into the program.

Test	Chronic cocaine users	Cocaine-free controls
BNT [ns]	50.94 (4.64)	49 (5.5)
VFT [ns]	40.25 (7.2)	43.25 (8.9)
MST [ns]	2.68 (0.92)	3.12 (0.64)

Table 2. Mean scores obtained in neuropsychological test performance in Experiment 1.
Notes. BNT: Boston Naming Test; VF: Verbal Fluency Test; MST: Memory span Test.
[ns]Non-significant difference

No significant group differences were obtained for IQ $t(30) = 1.10$, $p = .27$; Verbal functions Boston Naming Test, $t(30) = -0.1$, $p = .29$, Verbal Fluency Test, $t(30) = 1.04$, $p = .30$ and Memory Span Test, $t(30) = 1.54$, $p = .13$. Table 2 shows performance on the neuropsychological tests.

Separate analyses were performed using IBM SPSS statistics® 20 for participants and items, yielding F_1 and F_2 statistics

respectively. Given the traditional logic in the psycholinguistics field, we report both analyses to check whether the findings could be generalized not only across participants, but also across similar stimulus materials.

We carried out a repeated measures ANOVA to compare the response latencies (RL) and errors with context (homogeneous vs. heterogeneous) as a within-subjects factor and group (chronic cocaine users vs. cocaine free controls) as a between groups factor.

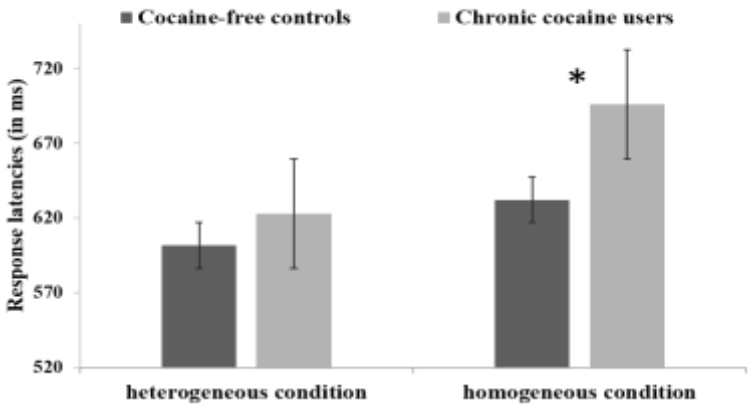
Three types of responses were excluded from the analysis (5.14%): 1) naming errors, hesitations and microphone failures; 2) responses longer than 1500 ms or shorter than 250 ms; 3) trial pictures that accounted for more than 15% of errors on overall task performance. In addition, as context effects are being targeted, following the procedure of analysis adopted by Damian et al. (2001), the first occurrence of each stimulus on each block was first excluded (first cycle), and the data from the other three cycles were collapsed. Figure 1 reports the mean RLs for correct responses and error means are reported in Table 3.

Response latencies

The RL analysis showed a significant effect of context [F_1 (1, 30) = 66.19, $p < .001$, $\eta^2_p = .68$; F_2 (1, 48) = 44.19, $p < .001$, $\eta^2_p = .47$] indicating that the homogeneous condition led to longer naming latencies (*M*=664, *SD*=80) than the heterogeneous condition (M=612, SD=65). The main effect of group was significant in the item analysis [F_1 = (1, 30) = 3.14, $p = .86$, $\eta^2_p = .09$; F_2 (1, 48) = 26.3, $p < .001$, $\eta^2_p = .35$] showing that chronic cocaine users need more time to name the stimuli (*M*=660, *SD*=89) than the cocaine-free control group (*M*=617, *SD*=57). Most importantly, the context x group interaction was significant [F_1 (1, 30) = 11.19, $p = .002$, $\eta^2_p = .27$; F_2 (1, 48) = 7.07, $p = .011$, $\eta^2_p = .12$], showing that chronic users had larger semantic interference effects than the cocaine-free controls. *Posthoc* Newman-Keuls analyses showed a reliable difference between the homogeneous

and heterogeneous condition (both *ps* < .05) for the group of chronic users (73 ms) and cocaine-free group (30 ms).

Figure 1. Mean response latencies (in milliseconds) by conditions in Experiment 1. Standard deviation in parentheses.



Errors

The main effect of context was significant in the analysis by items [F_1 (1, 30) = 3.28, p = .07, η^2_p = .09]; F_2 (1, 48) = 4.26, p = .04, η^2_p = .08] indicating that the homogeneous condition produced more errors than the heterogeneous condition. Neither the main effect of group nor the context x group interaction was significant [F< 1].

	Condition	Error (%)
Cocaine-free controls	Homogeneous	2.12
	Heterogeneous	1.74
Chronic cocaine users	Homogeneous	3.37
	Heterogeneous	1.76

Table 3. Mean error execution (in percentage) by conditions.

Correlations

To test whether the magnitude of semantic interference was proportional to the amount of cocaine consumed, we computed partial correlation coefficients 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 both semantic blocking (the result of the subtraction between homogeneous and heterogeneous response latencies) and error, when controlling for other drug use (tobacco, MDMA and alcohol). The variable error commission correlated positively with times per week of cocaine use $r = .681$ ($p = .01$) (figure 2) and maximum peak of cocaine used in 12 hours $r = .718$ ($p = .006$) (figure 3). Although the variable semantic effect followed the same trend, no correlations reached significance ($r_s \leq .41$, $p_s \geq .15$). Thus, it seems that the heavy cocaine usage (more times per week and high picks in 12 hours) may impair performance on the semantic blocking task. No other significant correlations were found ($p_s > .05$).

Figure 2. Scatter diagram of the partial correlation between the error commission and weekly comsuption of cocaine (residuals) in experiment 1, controlling for the use of other drugs.

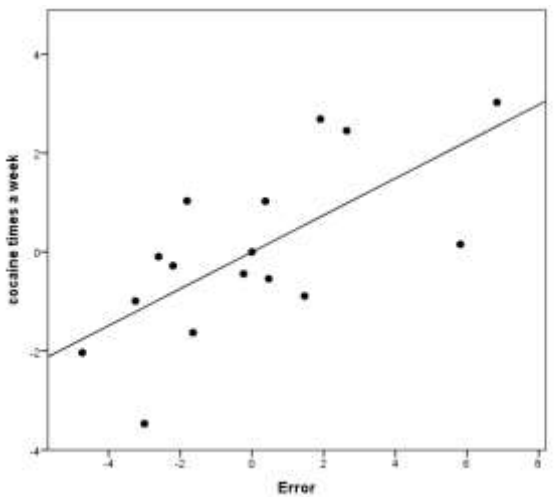
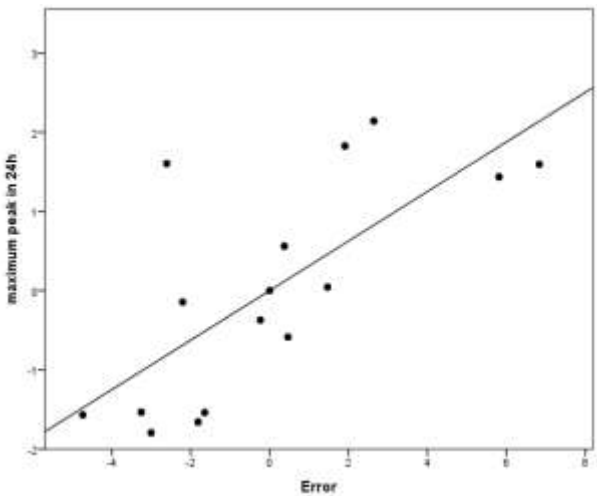


Figure 3. Scatter diagram of the partial correlation between the error commission and maximum comsuption of cocaine in 12 h (residuals) in experiment 1, controlling for the use of other drugs.



Discussion

Experiment 1 tested the hypothesis that chronic cocaine users have an impairment in inhibitory processes in the verbal domain. If so, chronic cocaine users would show a more pronounced semantic blocking effect due to an inefficient selection mechanism when items became stronger competitors during lexical selection. This is exactly what we observed: both groups showed similar performance on naming items in a semantically-unrelated condition, but chronic cocaine users showed larger naming latencies for the items to be named in a semantically-related condition in comparison to the cocaine-free controls. In addition, partial correlations showed that heavy cocaine (more times per week and high picks in 12 hours) seems to contribute to the greater semantic effect. Based on the assumption of there being impaired inhibitory processes in long-term cocaine users (Ersche et al. 2012; Fillmore and Rush 2002; Goldstein and Volkow 2002; Rosselli et al. 2001; Volkow et al. 2010), we consider that the greater semantic

interference that chronic cocaine users show reflects a deficit in the inhibitory mechanism involved during lexical selection.

Experiment 2

Participants

Forty healthy adults (20 men and 20 women) served as participants for partial fulfillment of course credits or financial compensation. They formed the two experimental groups of 20 recreational cocaine polydrug users and 20 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 the snorting route for a minimum of two years; 2) no Axis I or Axis II psychiatric disorders [Diagnostic and Statistical Manual of Mental Disorders IV DSM-IV; (American Psychological Association 2000)], including substance abuse; 3) no clinically significant medical disease; 4) no use of prescription medication and 5) non-excessive below-risk intake of alcohol (>280 g/week for men and >168 g/week for women) (Foster and Marriott 2006). Cocaine free-controls met the same criteria but they reported no history of past or current cocaine use.

In the six months prior to participation, fourteen recreational cocaine polydrug users and two cocaine-free users also smoked marijuana, while fourteen recreational users reported having used MDMA (ecstasy) and six reported using ketamine. Participants were asked to refrain from taking all psychoactive drugs for at least two days, not to consume alcohol the night before the experimental session, and to have a normal night of rest. Researchers were instructed to observe if participants had used alcohol prior to the experimental session. Participants were selected by means of a telephone interview using the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al. 1997). The sample was obtained from a pool of 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, alcohol abuse or medication.

Sample	Recreational cocaine polydrug users	Cocaine-free controls
N (M:F) ns	20 (10:10)	20 (10:10)
Age (years) ns	24.7 (4.26)	23.35 (3.24)
Raven IQ ns	103 (9.2)	101 (9.5)
Cigarettes (unit/day) *	7.6 (8)	1.95 (3.30)
alcohol (units/weeks) **[1]	15 (9.89)	4.75 (5.31)
Monthly Cannabis (joints) **	25.6 (26.57)	1.2 (4.51)
Years using cocaine	4 (2.43)	0
Monthly exposure (grams)	2.56 (1.74)	0
Maximum amount in a 12-h period (grams)	1.61 (0.76)	0
Mean days in abstinence	13.25 (10)	0
Monthly spent money (EUR)	98 (46.29)	0
MDMA (grams/ last 6 months)	1.95 (1.92)	0

Table 4. Demographic 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.

[1]Unit equals to a 10 ml or 8 g of pure ethanol (International Center for Alcohol Policies, 2005; Spanish Ministry of Health, 2007.

ns Non-significant difference

* Significant group difference; $p<0.05$: ** Significant group difference; $p<0.01$

Results

Demographic and drug use statistics are provided in Table 4. Recreational cocaine polydrug users significantly used more tobacco, alcohol and cannabis than the control group in the last six months prior to the test. No significant group differences were obtained for intelligence, $t(38) = .66$, $p = .51$; Boston Naming Test, $t(38) = 1.18$, $p = .24$, Memory span, $t(38) = .99$, $p = .32$ or verbal fluency test, $t(38) = 1.12$, $p = .26$. Table 5 shows performance on the neuropsychological tests.

Test	Recreational cocaine	Cocaine-free controls
BNT ^{ns}	50.25 (3.1)	51.75 (4.74)
VFT ^{ns}	43.20 (10.43)	46.7 (9.22)
MST ^{ns}	3.23 (0.90)	3.50 (0.76)

Table 5. Mean scores obtained in neuropsychological test performance in Experiment 2.
Notes. BNT: Boston Naming Test; VF: Verbal Fluency Test. MST: Memory span Test.; ns: Non-significant difference.

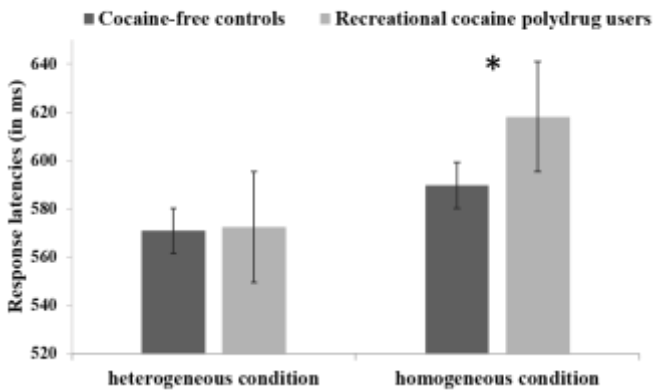
As for Experiment 1, three types of responses were excluded from the analysis (3.56%): 1) naming errors, hesitations and microphone failures; 2) responses longer than 1500 ms or shorter than 250 ms; 3) trial pictures that accounted for more than 15% of errors on overall task performance.

Response latencies

The RL analysis showed a significant effect of context [F_1 (1, 38) = 40.15, $p < .001$, $\eta^2_p = .51$; F_2 (1, 48) = 22.26, $p < .001$, $\eta^2_p = .31$] indicating that the homogeneous condition led to longer naming latencies (M=604, SD=80) than the heterogeneous condition (M=572, SD=78.5). The main effect of group was marginally significant in the item analysis [F_1 (1, 38) = .37, $p = .54$, $\eta^2_p = .009$; F_2 (1, 48) = 3.62, $p = .063$, $\eta^2_p = .07$] showing that recreational polydrug cocaine users needed more time to name the

stimuli (M=595, SD=87.6) than cocaine-free control group (M=580, SD=73.6). Most importantly, the context x group interaction reached significance [F_1 (1, 38) = 6.95, p = .012, η^2_p = .15; F_2 (1, 48) = 4.02, p = .05, η^2_p = .07], showing that recreational polydrug cocaine users had stronger semantic interference than the cocaine-free controls. *Posthoc* Newman-Keuls analyses showed a reliable difference between the homogeneous and heterogeneous condition (both p_s< .05) for the group of recreational cocaine polydrug users (46 ms) and cocaine-free group (19 ms). Figure 4 reports the mean RLs for correct responses.

Figure 4. Mean response latencies (in milliseconds) by conditions in Experiment 2. Standard deviation in parentheses.



Errors

The main effect of context was not significant in either the subject and items analysis. The main effect of group was significant in the item analysis [F_1 (1, 38) = 8.43, p = .006, η^2_p = .18; F_2 (1, 48) = 12.35, p < .001, η^2_p = .20] showing a higher rate of error commission in the recreational cocaine polydrug group compared to the cocaine free control group. Interestingly, the context x group interaction reached significance in the item analysis [F_1 (1, 38) = 3.76, p = .06, η^2_p = .08; F_2 (1, 48) = 5.6, p = .022, η^2_p = .10]. *Posthoc*

Newman-Keuls analyses showed that the recreational cocaine polydrug users committed a higher rate for semantically-related items than the control group. Error means are reported in Table 6.

	Condition	Error (%)
Cocaine-free controls	Homogeneous	0.95
	Heterogeneous	1.16
Recreational cocaine polydrug users	Homogeneous	3.04
	Heterogeneous	1.65

Table 6. Mean error execution (in percentage) by conditions in Experiment 2.

Correlations

To test whether the magnitude of semantic interference is proportional to the amount of cocaine consumed, we computed partial correlation coefficients between relevant cocaine use variables (such as lifetime amount consumed, maximum peak in 12 hours, and cocaine grams consumed per month) and both the semantic blocking effect and error commission, when controlling for other drug use (tobacco, MDMA and alcohol). However, no correlation reached significance ($r_s \leq .41, p_s \geq .10$).

Discussion

As expected in Experiment 1, recreational cocaine polydrug users showed larger semantic blocking effects in comparison with a cocaine-free group, reflecting vulnerability to semantic interference in a language production task. The results are in line with those studies in which recreational cocaine polydrug users show decreased performance in tasks tapping inhibition (Colzato and Hommel 2009; Colzato et al. 2007; Sellaro et al. 2013). Taken together, these results suggest that even small amounts of cocaine may predispose to inefficient selection mechanisms for

lexical selection during language production. However, the possible causal role of drug consumption in language selection has to be taken with caution since recreational cocaine polydrug users significantly used more tobacco, alcohol, and cannabis than the control group and, partial correlations between cocaine use and semantic blocking did not reach significance. It is also important to note the possibility that preexistent endophenotypes that are known to contribute to behavioral performance in cocaine users may have a role to play in the impairment of language competition in recreational users (Ersche et al. 2012; Verdejo-Garcia et al. 2008).

General discussion

This study investigated for the first time whether the chronic and recreational use of cocaine leads to a detectable increase in semantic interference. The magnitude of the semantic effect was substantially larger in the chronic and recreational cocaine groups relative to cocaine-free controls during the naming of semantically-related objects. This semantic interference can be accounted for by the competition between co-activated lexical entries in a homogeneous context that affects selection latencies (Roelofs 1992; Schriefers et al. 1990). To ensure the success of the lexical selection, the inhibitory system must act to selectively suppress semantically-related lexical entries that are strong competitors for the correct answer (Roelofs and Piai 2011; Shao et al. 2013). Following the study of Biegler and Martin (2008), patients with left inferior frontal gyrus damage showed an exaggerated semantic blocking effect, suggesting that the brain adjusts the weight derived from the co-activation of semantic-related items (Biegler et al. 2008). Thus, we propose that the chronic and recreational cocaine users may suffer from the same deficit, albeit in a milder form. Our results are in line with the available studies on recreational and chronic users of cocaine, which report impairments on tasks measuring inhibition in non-verbal domains (Colzato et al. 2007; Fillmore and Rush 2002; Sellaro et al. 2013; Verdejo-García et al. 2007). However, this is the first study in

which a semantic blocking task is used as an indicator of interference resolution in the verbal domain in cocaine users. Both chronic and recreational cocaine-users showed larger semantic blocking, probably due to inefficient use of verbal inhibitory processes.

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 on these variables. Similarly, the present results cannot be explained by factors related to 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 conducted extensive screening using the MINI to exclude any preexisting psychiatric disorders (e.g. ADHD).

Nevertheless, the results of the study for the recreational polydrug group do not allow us to completely rule out an account of their deficit in terms of preexistent underlying neurocognitive endophenotype for stimulant drug addiction that may contribute to task performance (Ersche et al. 2012; Verdejo-Garcia et al. 2008). However, the fact that the impairment was found for both chronic and recreational users with very different social and personal profiles may suggest that recreational cocaine use is also related to the larger blocking effects found in the recreational polydrug users relative to the controls.

Another possible shortcoming of our study is that, given the abuse rate of other drugs when consuming cocaine among recreational users (Grov 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. It should be noted that the difference in significance in the use of tobacco, alcohol and cannabis between the groups may also be influencing difference in the semantic effect. We tried to minimize this fact by selecting a sample of users who predominantly used cocaine and, avoiding as far as possible the selection of 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 are strongly correlated with objective measures of drug abuse (Glintborg et al. 2008; Zaldívar 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 the effects 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).

A more important limiting factor of our study is the fact that cocaine and alcohol are more often than not, consumed together and our sample of cocaine users was not an exception (see Table 1). Given the fact that acute alcohol use impairs inhibitory control (Fillmore and Vogel-Sprott 2000; Fillmore 2007; Noël et al. 2010), it is difficult to determine whether the obtained effects are the result of cocaine, or the effects of alcohol and cocaine together (Jatlow et al. 1996). In this regard, the screening of alcohol consumption in both groups was particularly important, 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, the group of chronic users were undergoing regular urine toxicology screens as part of their treatment. However, whilst we used self-report measures and provided specific instructions not to consume alcohol or other drugs before the experimental session, we cannot be sure that participants in Experiment 2 may have actively used either alcohol or cocaine shortly before the session, with 24 to 48 hours prior to the experimental session potentially affecting performance on the semantically-blocked naming task. Although this suggestion should be treated 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.

The outcomes from both experiments show that the use of high and low amounts of cocaine may be influencing vulnerability to interference in verbal cognitive processes in which inhibitory control is required. Although the role of some preexisting factor such as impulsiveness, risky behavior, driving or illegal activity (Verdejo-Garcia et al. 2008) cannot be ruled out, the present results support the broader notion that cocaine use may impair inhibitory processes including those that subserve speech production.

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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. 2013 a, 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 stimulants 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

[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 familiarise 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 asses 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 (η^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 >168g/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.

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

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
[ns]Non-significant difference
*Significant group difference; $p < 0.05$; ** $p < 0.01$

Results

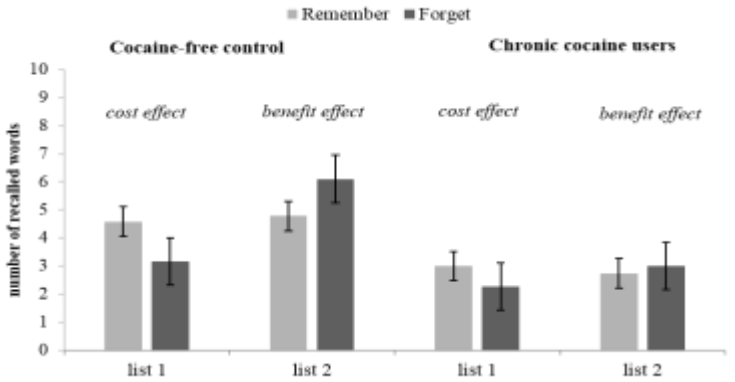
Demographics and drug use statistics are provided in Table 1. As mentioned, we assessed the alcohol habits of the participants through a self-reported questionnaire enquiring about their weekly intake of alcoholic drinks. Since the strengths of different types of alcoholic beverages vary significantly, 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.

Test	Chronic cocaine users in rehabilitation	Cocaine-free controls
BNT ^{ns}	51.8 (4.9)	49.6 (5.4)
VFT ^{ns}	44.4 (8.3)	47 (10.8)
MST ^{ns}	3.2 (0.7)	2.78 (1.03)

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 [$F(1, 36) = 11.64$, $p < 0.01$,

η^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, $p < 0.001$, η^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, $p = 0.039$, η^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.

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

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; $p < 0.05$; ** $p < 0.01$

Test	Recreational cocaine polydrug users	Cocaine-free controls
BNT [ns]	50.6 (4.2)	50 (5.51)
VFT [ns]	43.5 (10.0)	41.3 (10.0)
MST [ns]	2.9 (0.7)	3.2 (0.7)

Table 4. Mean neuropsychological test performance scores in Experiment 2.

Notes. BNT: Boston naming Test; VF: Verbal fluency test; MST: Memory span test.
[ns]Non-significant difference.

Results

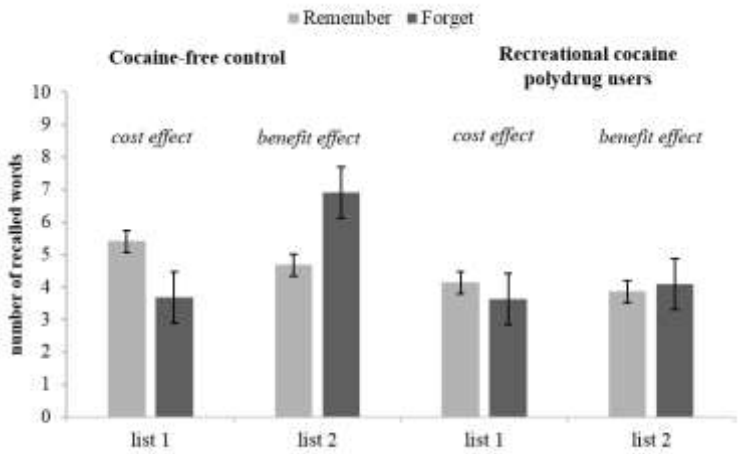
Demographics and drug use statistics are provided in Table 3. No significant group differences were obtained for intelligence, $t(42) = 0.18$, $p = 0.85$; memory span test, $t(42) = 1.40$, $p = 0.47$; Boston naming task, $t(42) = -0.36$, $p = 0.71$ or verbal fluency, $t(42) = -0.72$, $p = 0.47$. Table 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 (Grov 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; Zaldívar 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.

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Chapter 8

Conclusions

In line with the general aim of this thesis, we investigated whether the use of khat and cocaine impacts particular mechanisms that underlie the control of thoughts and actions. With this purpose we carried out several experiments to observe the performance of khat users on tasks that tap into cognitive control functions, namely inhibitory control, mental flexibility, working memory updating, and interference control. Moreover, we specifically assessed inhibitory control in cocaine users through tasks that tap into the ability to overcome semantic interference during verbal production and to suppress inappropriate memories at encoding and retrieval of information. In addition, we reviewed in this dissertation the behavioral and physiological effects of the natural psychomotor stimulant khat and the cathinone-derived designer drug mephedrone. We paid special attention to the pharmacokinetics and pharmacodynamics and its potential to produce withdrawal and dependence. The principal outcomes of this investigation are the following.

First, in chapter two we reviewed the historical and geographical backgrounds and mechanisms of the khat alkaloid cathinone and the designer drug mephedrone. We addressed an emerging consensus about their toxicity and the liability potential, as well as the effect of producing abuse and dependence. Available scientific evidence agrees that the use of these substances may be harmful and requires further and extensive research, especially mephedrone, which is more dangerous due to its availability and the lack of information about it.

Second, the data reported in chapters three and four suggest that khat users, compared to khat-free users show deficiencies in the three major functions of cognitive control. The results from the different tasks and experiments show that 1) khat

users and non-users are comparable in terms of response execution, but khat users needed significantly more time to inhibit prepotent responses than non-users; 2) khat use may be associated with impairments in working memory updating. This implies that khat users were less efficient at discriminating which information is old and no longer relevant, which means that no longer relevant information is more likely to enter in working memory and interfere; and 3) khat users, as compared to controls, needed more time to shift between mental sets, as indicated by a higher switching cost. These results suggest that khat use may be associated with a broad and general impact on human cognition. Taking into account the chemical and action resemblance between cathinone and amphetamine, our results are in line with those of previous studies of humans that show impairments in cognitive control functions as a consequence of long-term amphetamine and methamphetamine abuse (Baicy & London, 2007; Daumann et al., 2003, 2004; Monterosso et al., 2005; Nordahl et al., 2003; Rubia et al., 2011; Salo & Leamon, 2003; Salo et al., 2009a, 2009b, 2009c; van der Plas et al., 2009). We suggest that these impairments may be due to the long term use of khat, which leads to dysfunctions in prefrontal cortex and fronto-striatal dopaminergic receptors.

Third, in chapter five, we presented evidence of the impact of long-term use of khat on the emergence and resolution of interference by measuring performance on a Simon task (Simon, 1969). In line with studies showing the impact of acute and long-term use of amphetamines and methamphetamines on this cognitive process (Fillmore, Rush, & Abroms, 2005; Rubia et al., 2011; Salo et al., 2009a, 2009b, 2009c), we showed that long-term users were more strongly affected by stimulus-induced response conflict, showing a slower and poorer performance on the interference task. The stimulant effect of cathinone may act as a cognitive enhancer during acute consumption, supporting the view of khat as a "natural amphetamine" (Kalix, 1992). However, in the long–term it may impair the mechanisms underlying the control of interference in response conflict, possibly by altering the dopamine

pathways and prefrontal areas that play a key role in resolving response conflict (Botvinick, 2007; Cools, 2006).

Fourth, in chapters six and seven, we presented evidence that supports the idea of impaired inhibitory control in the domain of language and memory. Previous research shows that the chronic and recreational use of cocaine impacts the correct functioning of executive control, notably affecting inhibitory processes in the cognitive non-verbal domain (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002; Verdejo-García, Perales, & Pérez-García, 2007). In our experiments we assessed chronic and recreational cocaine users through a blocked-cycled naming task (Belke, Meyer, & Damian, 2005; Damian, Vigliocco, & Levelt, 2001) and a directed forgetting procedure (Bjork, 1970, 1989) where inhibitory mechanisms are engaged to suppress and reduce interference in language production (Roelofs & Piai, 2011; Shao, Meyer, & Roelofs, 2013) and in episodic memory retrieval (Anderson, 2003), respectively. We tapped into the inhibitory mechanisms that act selectively to suppress semantically-related competitors during lexical selection in users of cocaine and drug-free controls. Chronic and recreational cocaine users showed substantially larger vulnerability to semantic interference as compared to cocaine-free controls. This is probably due to inefficient performance of verbal inhibitory processes. Moreover, we used the directed forgetting procedure to observe the ability to suppress recently learned information that becomes irrelevant due to instructions to forget. We found that inhibitory mechanisms acting on the self-initiated forgetting may be impaired due to the use of cocaine. Chronic cocaine and recreational cocaine users' ability to suppress non-relevant memories was inefficient. To explain the results, we suggest that chronic long-term usage of cocaine and even small but continuous amounts of cocaine usage is connected to a hypoactive prefrontal cortex and a relative state of dopaminergic dysfunction, which may impair the cognitive processes engaged in episodic memory. Notwithstanding, the cessation of cocaine use makes a partial-recovery of cognitive functioning possible (Connolly, Foxe, Nierenberg, Shpaner, &

Garavan, 2012; Sclafani, Tolou-Shams, Price, & Fein, 2002; Vonmoos et al., 2014), but this process needs time and complete abstinence to show its effect.

Lastly, this work, together with previous research, has considerable implications for the understanding and treatment of drug abuse. The findings of these studies are rather worrying because, first, many real-life situations require correct cognitive control, as it plays an important role in the interaction between our inner and external world. The use of stimulant drugs such as khat or cocaine may lead to a marked deterioration of psychophysical functions, affecting everyday behavior ranging from car driving to work performance and social behavior. Second, defining the nature of impaired cognitive control will be an important step for the development of future therapeutic targets, improvement of the detoxification process, and the encouragement of drug abusers to achieve and maintain abstinence.

In summary, the mechanisms that control thought and action vary with the fluctuating and dynamic nature of both internal physiological states and external environmental constraints. In addition, we suggest that the abuse of stimulant drugs like khat or cocaine somehow impact cognitive control processes. There are currently limitations and unresolved issues associated with the performance of these stimulant drugs on the body and mind that will need to be addressed in future investigations. We hope that other investigators who are interested in cognitive control and drug abuse will join in these research efforts in understanding the relationship between them.

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Samenvatting

Het onderzoek dat in dit proefschrift wordt beschreven is toegespitst op de vraag of het gebruik van khat en cocaïne bepaalde mechanismen beïnvloedt die aan de basis liggen van ons denken en handelen. Hiertoe hebben we verschillende experimenten uitgevoerd. Wij hebben khat gebruikers taken laten uitvoeren op het gebied van cognitieve hersen functies en observeerden hierbij hun gedrag. Deze taken hadden vooral betrekking op het onderdrukken van acties (inhibitie), mentale flexibiliteit, het updaten van het werkgeheugen, en controle met betrekking tot de interferentie van acties. Meer specifiek hebben we met name het inhibitievermogen bij cocaïne gebruikers beoordeeld door middel van taken die aansluiten op het vermogen om semantische interferentie tijdens verbale productie te overwinnen. Daarnaast hebben we taken gebruikt die gericht zijn op het onderdrukken van ongepaste of misplaatste herinneringen bij het coderen en terughalen van informatie. Aanvullend hebben we in deze dissertatie gekeken naar gedrags- en psychologische effecten van de natuurlijke psychomotorische stimulant khat, en de uit cathinone verkregen designer drug mephedrone. Onze aandacht ging specifiek uit naar de rol die farmacokinetiek en farmacodynamica spelen bij onthouding en afhankelijkheid. Hieronder volgen de belangrijkste resultaten.

Ten eerste blikten wij in hoofdstuk twee terug op de historische en geografische achtergronden en mechanismen van de khat alkaloïde cathinone en de designer drug mephedrone. Wij richten ons op de ontstane consensus betreffende toxiciteit en de mogelijk verantwoordelijke effecten die leiden tot misbruik en afhankelijkheid. Het reeds beschikbaar wetenschappelijk bewijs komt overeen met onze hypothese dat het gebruik van deze stoffen schadelijk kan zijn en dat dit meer en uitgebreider onderzoek behoeft. Dit geldt met name voor mephedrone, deze stof is namelijk gevaarlijker omdat het makkelijk verkrijgbaar is en er bovendien weinig informatie over beschikbaar is.

Ten tweede blijkt uit de resultaten uit hoofdstuk drie en vier dat khat gebruikers in vergelijking met niet- gebruikers deficiënties in de drie belangrijkste functies van cognitieve controle laten zien (Miyake, 2000). De onderzoeksresultaten in de verschillende taken en experimenten tonen het volgende aan: 1) Hoewel khat gebruikers en niet-gebruikers vergelijkbaar zijn wat betreft het uitvoeren van een actie, blijken khat gebruikers significant meer tijd nodig te hebben om dominante acties te onderdrukken dan niet-gebruikers. 2) Het gebruik van khat kan in verband gebracht worden met tekortkomingen in het werkgeheugen. Dit houdt in dat khat gebruikers minder efficiënt onderscheid kunnen maken met betrekking tot oude en irrelevante informatie; deze informatie komt daardoor makkelijker in het werkgeheugen en interfereert met nieuwe en relevantie informatie.3) Khat gebruikers hadden, vergeleken met de controle groep, meer tijd nodig om te schakelen tussen mind-sets, zoals blijkt uit een hogere 'switch cost', die ontstaat wanneer mensen moeten schakelen tussen twee taken. Deze resultaten doen vermoeden dat khat geassocieerd is met een negatieve impact op de algemene menselijke cognitie. Wanneer men daarbij kijkt naar de gelijkenis tussen de algemene en chemische werking van cathinone en amfetamine, dan zijn onze resultaten in lijn met die van vorige studies, die beschadigingen aantonen in de cognitieve controlefuncties bij mensen als gevolg van langdurig gebruik van amfetamine en methamfetamine (Baicy & London, 2007; Daumann et al., 2003, 2004; Monterosso et al., 2005; Nordahl et al., 2003; Rubia et al., 2011; Salo & Leamon, 2003; Salo et al., 2009a, 2009b, 2009c; van der Plas et al., 2009). Wij gaan er dan ook van uit dat deze beschadigingen het gevolg zouden kunnen zijn van langdurig khat gebruik, hetgeen leidt tot disfuncties in de prefrontale cortex en fronto-striatale dopaminerge receptoren .

Ten derde hebben wij in hoofdstuk vijf bewijs aangedragen met betrekking tot de impact die langdurig gebruik van khat heeft op zowel het opkomen als verdwijnen van interferentie bij de uitvoering van een Simon taak (Simon, 1969). Lange termijn gebruikers worden sterker beïnvloed door conflicten

in reacties die ontstaan door de presentatie van een stimulus. Hierbij laten lange termijn gebruikers namelijk een slechtere en langzamere uitvoering van de taak zien. Op de lange termijn kan khat gebruik leiden tot beschadigingen aan mechanismen die ten grondslag liggen aan de controle die men heeft over het uitvoeren van de juiste actie wanneer er een conflict ontstaat, wellicht doordat zich wijzigingen voordoen in de bestaande dopaminerge banen en prefrontale gebieden die een sleutelrol spelen bij het oplossen van zo'n conflict (Botvinick, 2007; Cools, 2006).

Ten vierde hebben wij in de hoofdstukken zes en zeven bewijs gevonden voor het idee dat de cognitieve functie met betrekking tot het inhiberen van acties is beschadigd in zowel het taal- als geheugendomein. Eerder onderzoek toont aan dat het chronisch gebruik van cocaïne, evenals recreatief gebruik, een negatief effect heeft op de cognitieve controle met betrekking tot het uitvoeren van acties. Met name wordt het vermogen om actie te stoppen in het cognitieve, non-verbale domein aangetast (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002; Verdejo-García, Perales, & Pérez-García, 2007). In onze experimenten hebben we chronische en recreatieve gebruikers van cocaïne beoordeeld aan de hand van een *blocked-cycled naming task* (Belke, Meyer, & Damian, 2005; Damian, Vigliocco, & Levelt, 2001) en een *directed forgetting procedure* (Bjork, 1970, 1989). In deze taken zijn inhibitie mechanismen betrokken die conflicten in taalproductie en het terughalen van episodische herinneringen onderdrukken en verminderen (Roelofs & Paiai, 2011; Shao, Meyer, & Roelofs, 2013) (Anderson, 2003). We hebben vooral gekeken naar de inhibitiemechanismen die selectief betrokken zijn bij het onderdrukken van semantisch gerelateerde concurrenten tijdens lexicale selectie, bij cocaïne gebruikers en een drugs-vrije controlegroep. Chronische en recreationele gebruikers van cocaïne toonden een substantieel hogere kwetsbaarheid voor semantische interferentie, vergeleken met niet-gebruikers. Mogelijkerwijs is dit te wijten aan de ondoelmatige uitvoering van verbale inhibitieprocessen. Bovendien gebruikten wij de *directed forgetting procedure*, deze heeft als doel de vaardigheid met betrekking tot het

onderdrukken van recent opgenomen informatie, die irrelevant is geworden als gevolg van de instructie, te vergeten. Wij ontdekten dat inhibitie mechanismen, werkzaam bij het door de persoon zelf-geïnitieerde- vergeten, beschadigd kunnen zijn tijdens cocaïne gebruik. Het vermogen van recreationele gebruikers van cocaïne om niet relevante herinneringen te onderdrukken was onvoldoende. Hoewel chronische cocaïne gebruikers blijk gaven van een slechtere geheugenonderdrukking dan de controle groep, bleken zij succesvol in het opzettelijk afremmen van ongewenste herinneringen. De vraag blijft hoe dit mogelijk is. Om de onderzoeksresultaten te verklaren, suggereren wij dat zelfs kleine maar continu toegediende hoeveelheden cocaïne in verband gebracht worden met een hypoactieve prefrontale cortex en een relatieve staat van dopaminergisch dysfunctioneren. Deze kunnen de cognitieve processen beschadigen die betrokken zijn bij de werking van het episodische geheugen. Toch kan het beëindigen van cocaïne gebruik cognitieve functies deels herstellen (Connolly, Foxe, Nierenberg, Shpaner, & Garavan, 2012; Sclafani, Tolou-Shams, Price, & Fein, 2002; Vonmoos et al., 2014).

Als laatste willen wij benoemen dat ons werk, samen met het reeds gedane wetenschappelijk onderzoek, belangrijke implicaties heeft voor het begrip en de behandeling van drugs misbruik. De uitkomsten van deze studies zijn zeer zorgwekkend. Ten eerste omdat vele situaties in het dagelijks leven vragen om efficiënte en juiste cognitieve controle, wat een belangrijke rol speelt in de interactie tussen onze innerlijke en uiterlijke wereld. Het gebruik van stimulerende drugs zoals khat of cocaïne kunnen leiden tot een aanzienlijke verslechtering van de psychofysische functies die het dagelijks gedrag beïnvloeden. Denk hierbij aan een scala van activiteiten die variëren van autorijden tot het uitvoeren van werkzaamheden en sociaal gedrag. Ten tweede zal het definiëren van de aard van beschadigde cognitieve controlefuncties een belangrijke stap zijn in zowel de ontwikkeling van therapeutische doelen als voor het aanbrengen van verbeteringen in het detoxificatie proces en het aanmoedigen van druggebruikers, opdat onthouding wordt bereikt en behouden.

Samenvattend: de mechanismen die gedachten en acties sturen en controleren variëren als gevolg van het fluctuerende en dynamische karakter van zowel interne, psychische toestanden als externe, beperkende omgevingsfactoren. Bovendien willen wij erop wijzen dat misbruik van stimulerende drugs zoals khat of cocaïne op de een of andere manier cognitieve controlefuncties beïnvloedt. Momenteel bestaan er nog onopgeloste kwesties die in verband gebracht worden met de werking van deze stimulerende drugs op zowel lichaam als geest, waar toekomstig onderzoek nader op in zal moeten gaan. Wij hopen dan ook dat onderzoekers die eveneens zijn geïnteresseerd in cognitieve controle en misbruik van drugs hun steentje zullen bijdragen aan het creëren van inzicht in deze materie.

Resumen

El control cognitivo es una característica extraordinaria de la mente humana. Este control consiste en la configuración de los propios mecanismos mentales en el desempeño y ejecución de tareas específicas a través de los ajustes apropiados en la selección perceptual, las tendencias de las respuestas y en el mantenimiento continuo de la información contextual (Botvinivk, 2001). Además, esta tesis pretende subrayar que desde una perspectiva psicológica y neurológica hay un consenso en entender que, en la adicción, la alteración de los procesos ejecutivos que controlan el comportamiento juega un papel central.

Las investigaciones realizadas hasta la fecha sobre las habilidades cognitivas de los consumidores de cocaína presentan un escenario en el que los procesos de control que median en la toma de decisiones, atención, memoria y aprendizaje se encuentran alterados. Muchos de estos procesos cognitivos necesitan de participación de regiones prefrontal dorsolateral y orbitofrontal, vías ricas en dopamina y regiones con importantes papeles en las funciones ejecutivas, y todas ellas, parecen estar mal reguladas cuando se consume cocaína. Muchos investigadores de este campo señalan las incidencias que tiene el consumo de sustancia estimulantes como la cocaína en los procesos inhibitorios que se ven seriamente dañados en quienes la consumen (Colzato, van den Wildenberg, & Hommel, 2007; Fillmore & Rush, 2002; Verdejo-García, Bechara, Recknor, & Pérez-García, 2006).

Aunque se ha realizado un importante progreso para entender la actuación de la cocaína sobre los procesos mentales, solo un reducido número de estudios han investigado las características sociales y psicológicas de los consumidores de khat. Precisamente la inexistencia de estudios que pongan el foco en los mecanismos neurobiológicos de esta droga, o de otros que se centren en la investigación sistemática del efecto en el consumo agudo y a corto y medio plazo, demuestra que se adolece de ese

análisis social y psicológico. Sin embargo, dada la similitud entre el principio activo de la planta khat (catinona) y las anfetaminas en estructura y actividad farmacológica tiene sentido asumir que el consumo agudo y las consecuencias del consumo a largo plazo de khat afectan al mismo sistema de neurotransmisores y regiones cerebrales que las anfetaminas.

De acuerdo con el objetivo principal de esta tesis, he investigado si el consumo de khat y cocaína altera mecanismos específicos que subyacen en el control del pensamiento y de la acción. Con este propósito he llevado a cabo varios experimentos encaminados a observar el rendimiento de consumidores de khat ejecutando tareas que acceden a procesos de control cognitivo, principalmente control inhibitorio, flexibilidad mental, actualización de la memoria de trabajo y en el control de la interferencia. Además, de forma específica he evaluado el control inhibitorio en consumidores de cocaína a través de tareas experimentales que acceden en la habilidad para controlar interferencias semánticas en la producción de lenguaje y la habilidad para suprimir trazos de memoria irrelevantes durante la codificación y la recuperación de los recuerdos. Igualmente, en esta tesis hemos revisado los efectos fisiológicos y comportamentales del psicoestimulante natural khat y la droga de diseño derivada de la catinona, Mefedrona. He puesto especial atención en los procesos de farmacocinética y farmacodinámica y en el potencial de estas sustancias para producir síndrome de abstinencia y dependencia. Los principales resultados de esta investigación son los siguientes:

Primero, en el capítulo dos he revisado la literatura que analiza el aspecto histórico y geográfico del alcaloide de la planta khat (catinona) y la droga de diseño mefedrona. Examino estas sustancias sabiendo que hay un cierto consenso sobre su toxicidad y el potencial dañino, además de la potencia de estas drogas para producir abuso y dependencia. La literatura científica sobre estas sustancias coincide en que su consumo puede ser dañino y sería necesario investigar más al respecto, especialmente acerca de la

sustancia mefedrona, la cual, es aún más peligrosa debido a su fácil disponibilidad y la falta de información sobre ella.

Segundo, los datos presentados en los capítulos tres y cuatro señalan que consumidores de khat, en comparación con no consumidores, muestran deficiencias en las tres principales funciones de control cognitivo (Miyake, 2000). Los resultados en las diferentes tareas y experimentos muestran que i) los consumidores de khat y no consumidores son similares en términos de ejecución de respuesta, sin embargo, los consumidores de khat en comparación con los no consumidores necesitan más tiempo para inhibir las respuestas prepotentes; ii) el consumo de khat parece estar asociado con problemas en la actualización de memoria de trabajo. Los consumidores de khat son menos eficientes en la discriminación de qué información es antigua y no relevante. Esto significa que la información no relevante tiene mayor posibilidad de entrar en memoria de trabajo y convertirse en interferencia, y iii) los consumidores de khat, comparados con el grupo de control, necesitaban más tiempo para cambiar entre configuraciones mentales, indicado esto por un mayor índice de coste de cambio. Estos resultados indican que el consumo de khat puede tener un impacto amplio y general sobre la cognición. Además, teniendo en cuenta la similitud farmacológica entre catinona y anfetamina, nuestros resultados están en línea con estudios anteriores que muestran daños en las funciones de control cognitivo como consecuencia del consumo a largo plazo de anfetaminas (Baicy & London, 2007; Daumann et al., 2003, 2004; Monterosso et al., 2005; Nordahl et al., 2003; Rubia et al., 2011; Salo & Leamon, 2003; Salo et al., 2009a, 2009b, 2009c; van der Plas et al., 2009). Este estudio señala que estos daños en las funciones de control cognitivo pueden deberse al consumo a largo plazo de khat debido a disfunciones en los receptores dopaminérgicos de áreas fronto-estriatales y la corteza prefrontal.

Tercero, en el capítulo cinco, se demuestran pruebas del impacto del consumo a largo plazo de khat en la aparición y resolución de interferencia medida a través de la observación de los

participantes un una tarea Simon (Simon, 1969). De acuerdo con algunos estudios que muestran el impacto del consumo agudo y a largo plazo de anfetamina y metanfetamina en este proceso cognitivo (Fillmore, Rush, & Abroms, 2005; Rubia et al., 2011; Salo et al., 2009a, 2009b, 2009c), se muestra cómo el consumo agudo de khat a largo plazo altera la habilidad de inhibir información irrelevante y seleccionar la respuesta correcta en la aparición de conflicto inducido por incompatibilidad de respuesta, mostrando una pobre ejecución en la tarea de interferencia. Por un lado, el efecto estimulante de la Catinona actúa como un potenciador cognitivo a nivel agudo mientras se consume, apoyando de este modo la idea del khat como una "anfetamina natural" (Kalix, 1992). Por otro lado, el consumo a largo plazo de khat puede producir un efecto nocivo sobre los mecanismos cognitivos que subyacen al proceso del control de la interferencia en la respuesta de conflicto, posiblemente debido a la alteración de las vías dopaminérgicas y las áreas prefrontales que tienen un papel muy importante en la resolución de conflicto de respuesta (Botvinick, 2007; Cools, 2006).

Cuarto, en los capítulos seis y siete, he presentado los datos que apoyan la hipótesis de los posibles daños en el control inhibitorio en los dominios del lenguaje y la memoria. Existen investigaciones previas que muestran que los consumidores de cocaína, tanto recreativos como crónico, muestran alteraciones en el correcto funcionamiento del control ejecutivo notablemente, afectando procesos inhibitorios del dominio no verbal de funciones cognitivas (Colzato et al., 2007; Fillmore & Rush, 2002; Verdejo-García, Perales, & Pérez-García, 2007). En estos experimentos se evalúo a consumidores crónicos y recreativos de cocaína usando una tarea de bloqueo semántico en el nombrado (Belke, Meyer, & Damian, 2005; Damian, Vigliocco, & Levelt, 2001) y una tarea experimental mediante el procedimiento de olvido dirigido (Bjork, 1970, 1989) en la que los mecanismos inhibitorios son requeridos para suprimir y reducir la interferencia en la producción de lenguaje (Roelofs & Piai, 2011; Shao, Meyer, & Roelofs, 2013) y en la recuperación de memoria episódica (Anderson, 2003) respectivamente. En los experimentos del capítulo siete he usado la

tarea de bloqueo semántico para observar los mecanismos que selectivamente suprimen competidores semánticamente relacionados durante el proceso de selección léxica en consumidores de cocaína y no consumidores de la sustancia. Los consumidores crónicos y recreativos de cocaína mostraron una vulnerabilidad a la interferencia semántica en comparación con los grupos controles no consumidores de cocaína. Esto, probablemente, puede que sea producido por una ejecución ineficiente de los procesos inhibitorios en el ámbito de la producción verbal. Además he usado el procedimiento de olvido dirigido para observar la habilidad de suprimir información recientemente aprendida que se convierte en información interferente debido a instrucciones de olvidar. En los experimentos que he llevado a cabo observo que los mecanismos que actúan durante olvido auto-iniciado pueden estar dañados durante el consumo de cocaína y la habilidad para suprimir trazos de memoria no-relevantes es ineficiente en consumidores crónicos y recreativos de cocaína. Este resultado sugiere que, además de un consumo crónico y continuado, pequeñas cantidades de cocaína consumidas continuadamente está asociado con una hipofunción de la corteza prefrontal y un estado relativo de disfunción dopaminérgica que puede alterar los procesos cognitivos implicados en la recuperación de la memoria episódica. No obstante, hay diversos estudios que demuestran que el cese de consumo de cocaína parece favorecer una recuperación parcial del funcionamiento cognitivo (Connolly, Foxe, Nierenberg, Shpaner, & Garavan, 2012; Sclafani, Tolou-Shams, Price, & Fein, 2002; Vonmoos et al., 2014), aunque se necesita tiempo y abstinencia para pueda manifestarse alguna mejoría.

Por último, este trabajo, junto con la investigación previa sobre el tema, hace varias consideraciones sobre el funcionamiento y el tratamiento cuando se abusa de sustancias adictivas. Los resultados de esta serie de investigaciones son de notable preocupación; primero, muchas situaciones de la vida diaria requieren un correcto funcionamiento de control cognitivo que juega un papel muy importante en la interacción entre nuestro

fuero interno con el mundo exterior. El uso de drogas estimulantes del comportamiento como el khat o la cocaína conducen al deterioro de funciones psicológicas y físicas que influyen en el comportamiento diario, desde la conducción de un vehículo al desempeño de actividades laborales o el comportamiento en sociedad; segundo, definir la naturaleza del posible daño del control cognitivo es un paso importante en el desarrollo de los objetivos terapéuticos, así como la mejora del proceso de desintoxicación y alentar a los consumidores de estas sustancias a lograr y mantenerse en abstinencia.

En conclusión, sostengo que los mecanismos que controlan el pensamiento y la acción varían en la fluctuante y cambiante naturaleza de los estados fisiológicos internos y en las limitaciones ambientales externas y además apunto que el consumo de sustancias psicoestimulantes como el khat o la cocaína, de alguna manera, impactan más en estos proceso de control cognitivo. Sin embargo, siguen habiendo una serie de limitaciones y aspectos poco conocidos acerca de cómo actúan estas sustancias en el cuerpo y en la mente que a mi juicio deben ser estudiados en futuras investigaciones. Espero que otros investigadores interesados en los procesos de control cognitivo y el consumo de drogas se sumen al esfuerzo de entender la relación existente entre ambos.

Curriculum vitae

Manuel Jesús Ruiz Muñoz was born on May 15, 1985, in Úbeda, Spain. In 2003, he took up studies in psychology at the University of Granada (Spain), where he graduated in July 2009. From September 2008 until October 2010, he attended the Master in Behavioral and Cognitive Neuroscience at the University of Granada, where he was instructed in the fields of cognitive psychology and neuropsychology. Since October 2011 he works as a PhD student at Leiden University and the Mind, Brain and Behavior Research Center (CIMCYC) of the University of Granada.

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Notes