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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 allows 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, & Beversdorff, 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.


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


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