Doctoral thesis
Juan Carlos Bustamante Fernandiz

Psicopatología, Salud y Neuropsicología
Departamento de Psicología Básica,
Clínica y Psicobiología
Universitat Jaume I

Neural bases of cognitive and motivational processes in cocaine addiction

Castellón, Julio 2012

Departamento de Psicología Básica, Clínica y Psicobiología
Facultad de Ciencias de la salud

UNIVERSITAT JAUME·I

Bases cerebrales de procesos cognitivos y motivacionales en la adicción a la cocaína

Tesis doctoral presentada por:
Juan Carlos Bustamante Fernandiz
Para obtener el grado de doctor por la Universitat Jaume I de Castellón

Directores:
Dr. César Ávila Rivera
Dr. Alfonso Barrós Loscertales

Programa de doctorado ***Psicopatología, Salud y Neuropsicología***

Castellón, Julio 2012

Departamento de Psicología Básica, Clínica y Psicobiología
Facultad de Ciencias de la salud

Neural bases of cognitive and motivational processes in cocaine addiction

Doctoral thesis presented by:
Juan Carlos Bustamante Fernandiz
To obtain the grade of doctor by the University Jaume I of Castellón

Supervisors:
Dr. César Ávila Rivera
Dr. Alfonso Barrós Loscertales

Ph.D. program ***Psicopatología, Salud y Neuropsicología***

Castellón, Julio 2012

For my family…

"Research is to see what everybody else has seen, and to think what nobody else has thought"
Albert Szent-Gyorgyi

"Research is formalized curiosity. It is poking and prying with a purpose"
Zora Neale Hurston

"La ciencia es aquello sobre lo cual cabe siempre discusión"
José Ortega y Gasset

"La ciencia más útil es aquella cuyo fruto es el más comunicable"
Leonardo Da Vinci

Table of contents

Acknowledgments..... vi
Abbreviations list..... viii
Abstract..... xi
Resumen..... xiii
PREFACE..... 1
Justification..... 1
CHAPTER 1. GENERAL INTRODUCTION..... 5
1.1. The neurobiology of cocaine addiction..... 7
1.1.1. Dopamine circuitry implications in cocaine addiction..... 7
1.1.2. Structural and functional brain implications of cocaine addiction..... 11
1.1.2.1. Structural alterations in cocaine addiction..... 12
1.1.2.2. Functional alterations in cocaine addiction..... 13
1.1.2.2.1. Cognitive control functioning in cocaine addiction..... 14
- Inhibitory control..... 14
- Working memory..... 16
- Decision making..... 17

1.1.2.2.2 Motivational salience attribution and cocaine addiction..... 19
- Reward processing of drug-related stimuli..... 20
- Reward processing of non-drug-related stimuli..... 21

1.1.3. Drug-free state and neurobiological implications in cocaine addiction..... 22
1.2 Magnetic Resonance Imaging (MRI): the technique..... 25
1.2.1. Magnetic Resonance Imaging (MRI)..... 25
1.2.2. Functional Magnetic Resonance Imaging (fMRI)..... 26
1.2.3. Methodological toolboxes for MRI and fMRI: implications in cocaine addiction..... 28
1.2.3.1. Voxel-Based Morphometry (VBM)..... 28
1.2.3.2. Biological Parametric Mapping (BPM), statistical toolbox for multimodal analysis in neuroimaging..... 29

CHAPTER 2. EXPERIMENTAL SECTION..... 31
2.1. Overview of the studies..... 31
2.1.1 Objective and hypotheses..... 35
2.2. Barrós-Locertales A., Garavan H., Bustamante J.C., et al. (2011). Reduced striatal volume in cocaine dependent patients. *Neuroimage*, 56, 1021-1026..... 37
2.3. Bustamante J.C., Barrós-Loscertales A., Ventura-Campos N., et al. (2011). Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task. *Brain research*, 1375, 111-119……. 39
2.4. Barrós-Loscertales A., Bustamante J.C., Ventura-Campos N., et al. (2011). Lower activation in the right frontoparietal network

during a counting Stroop task in a cocaine-dependent group. *Psychiatry research*, 194, 111-118…….…….. 42

2.5. Bustamante J.C., Barrós-Loscertales A., Costumero V., et al. (submitted). Modulation of abstinence duration on striatal functioning during monetary reward processing in cocaine patients……..…….. 44

CHAPTER 3. GENERAL DISCUSSION……...…….. 47

3.1 General conclusions……...…….. 52

CHAPTER 4. FUTURE RESEARCH LINES……...……... 53

REFERENCES OF GENERAL INTRODUCTION AND GENERAL DISCUSSION……...…… 57

RESUMEN GENERAL EN CASTELLANO……...……... 83

R.1. Planteamiento y metodología utilizada…….…… 84

R.2. Objetivos e hipótesis……. 89

R.3. Principales aportaciones y conclusiones……... 91

R.4. Líneas de investigación futuras……. 94

Acknowledgements

I wish to thank all the people who have been with me while preparing this work, and who have given me their support and helped motivate me every day. Your role throughout this process has been essential for the preparation of a complex, good quality doctoral thesis.

Thanks to Dr. César Ávila Rivera for giving me the opportunity to join a research group that undertakes its work in one of my research interests, functional Magnetic Resonance Imaging (fMRI), and its application in Neuropsychology. Thank you for being the motor of a lab that grows "crescendoing" and which is developing an interesting project with much clinical and experimental applicability. I appreciate all your help with and all your advice on my PhD training.

I also wish to thank Dr. Barrós Loscertales; Alfonso, thank you for everything that you have taught me and provided me with. I feel very lucky for having the opportunity of working with a person like him. He has allowed me to obtain all the professional and personal values that I believe are essential for a good scientific and academic career.

Thanks too to Dr. Maria Antònia Parcet for her clinical contributions, and for offering me the possibility of making good use of her expertise and pragmatic vision in the Neuropsychology field.

I also thank Dr. Cristina Forn for giving me lots of advice which have made my work over these 4-5 years much more fruitful and satisfactory. Thanks too to Dr. Ana Sanjuán for being an example of attitude at work. I am also grateful to Noelia for being patient and for providing me methodological help and support, which have been basic in all the work that I am going to present. Thanks also to Víctor for his useful attitude and

for asking questions all the time, which produce interesting ideas that have improved the quality of the methodology in our papers. Thanks to Paola, Marian and Patri for providing freshness to the lab. Thanks to Maya for giving another perspective of research work, based on an open-minded style of work, which implies travelling abroad and working in different research groups. Thanks to the "new Javi" and Elisenda for showing me their motivation in doing our fieldwork, and I appreciate them motivating me more, at the same time, to continue in my work. And last but not least, thanks to Aina and the "old Javi" for giving me something, which in my opinion, is essential; their friendship and support at all times.

Thanks to my family, you are incredible! I do not know what to say, just thanks with all my heart and soul. Without you I would not have reached this point. I need you and I will always need you.

Thanks to everyone!!

The research reported in this thesis was supported by the grant "Beca de Formación de Personal Investigador UJI, PREDOC/2007/13".

Abbreviations list

ACC, Anterior Cingulate Cortex

ACG, Anterior Cingulate Gyrus

AC-PC, Anterior Commisure-Posterior Commisure

ADHD, Attention Deficit Hyperactivity Disorder

AH, Allostatic Hypothesis

BA, Brodmann Area

BOLD, Blood Oxygen Level-Dependent

BPM, Biological Parametric Mapping

DA, Dopamine

DAT, Dopamine Transporter

DLPFC, Dorsolateral Prefrontal Cortex

DS, Dorsal Striatum

DSM, Diagnostic and Statistical Manual of Mental Disorders

DTI, Diffusion Tensor Imaging

ERP, Event-Related Potentials

FDR, False Discovery Rate

fMRI, functional Magnetic Resonance Imaging

FOV, Field of View

FWE, Family Wise Error

FWHM, Full Width at Half Maximum

GM, Gray Matter

GLM, General Lineal Model

HDR, Haemodynamic Response

HMRF, Hidden Markov Random Fields

IFC, Inferior Frontal Cortex

IFG, Inferior Frontal Gyrus

IGT, Iowa Gambling Task

IPC, Inferior Parietal Cortex

IPG, Inferior Parietal Gyrus

IPL, Inferior Parietal Lobule

ISI, Intestimuli Interval

LPFC, Lateral Prefrontal Cortex

LPPs, Late Positive Potentials

MFG, Medial Frontal Gyrus

MidFG, Middle Frontal Gyrus

MIDT, Monetary Incentive Delay Task

MNI, Montreal Neurologic Institute

MPFC, Medial Prefrontal Cortex

MR, Magnetic Resonance

MRI, Magnetice Resonance Imaging

Nacc, Nucleus Accumbens

OCD, Obsesive-Compulsive Disorder

OFC, Orbitofrontal Cortex

PET, Positron Emmision Tomography

PFC, Prefrontal Cortex

RDS, Reward Deficiency Syndrome

RFT, Random Field Theory

ROI, Region of Interest

RT, Reaction Time

SD, Standard Deviation

SMA, Supplementary Motor Area

SPG, Superior Parietal Gyrus

SPM, Statistical Parametric Mapping

SSRT, Stop-Signal Reaction Time

STC, Superior Temporal Cortex

T, Tesla

TE, Echo Time

TR, Repetition Time

VBM, Voxel-Based Morphometry

VMPFC, Ventromedial Prefrontal Cortex

VS, Ventral Striatum

VTA, Ventral Tegmental Area

WAIS, Wechsler Adults Intelligence Scale

WFU, Wake Forest University

WCST, Wisconsin Card Sorting Test

WM, White Matter

Abstract

Cocaine addiction is related with neurological and neuropsychiatric complications, which need to be considered in treatment. Use of Magnetic Resonance Imaging (MRI), such as structural MRI and functional MRI, improves the neuroanatomical and neurofunctional analysis of addiction-related changes. Several studies have shown that addiction alters the dopaminergic mesocorticolimbic circuitry of self-control and incentive salience to subserve the transition from voluntary drug use to habitual, compulsive drug abuse. Some have analysed if cocaine alterations are associated with consumption patterns, effect of abstinence and treatment maintenance.

This thesis aims to give more evidence regarding the brain changes subserving alterations in cognitive and motivational processing in cocaine addiction. Four studies have been conducted in this thesis. The morphometric study shows that cocaine addicts present reduced grey matter volume in the dorsal striatum, and that the regional grey matter volume of the amygdala inversely correlates with years of cocaine use. The first functional study reveals that cocaine-dependent patients display hypoactivation in the inferior parietal gyrus during a verbal working memory n-back task. The second functional study reports that cocaine-dependent patients present hypoactivation in the inferior frontal cortex, the inferior parietal cortex and the superior temporal cortex during an interference-control Counting Stroop task. Finally, the third functional study indicates that patients present hypoactivation in the caudate during a monetary reward anticipation task. Moreover, the functional regulation of the striatum during reward processing seems to be associated with abstinence and time on treatment.

In conclusion, cocaine addiction has been associated with structural and functional alterations in the mesocorticolimbic circuitry. Attentional-cognitive changes relate to frontal and parietal hypoactivations, while striatum function and volume reduce

in cocaine addicts. Moreover, the cocaine-free time may determine the regulation of the altered striatal pattern activation during monetary reward processing. Future endeavors could focus on analysing the neural bases of the interaction between cognitive and motivational processes, and the connectivity between cortical and subcortical dopamine regions.

Resumen

La adicción a la cocaína se asocia con complicaciones neurológicas y neuropsiquiátricas que deben ser consideradas en los tratamientos. El uso de la Resonancia Magnética (RM), específicamente la RM estructural y la RM funcional, mejora el análisis neuroestructural y neurofuncional de los cambios relacionados con la adicción. La literatura previa ha mostrado que la adicción a la cocaína altera el circuito cerebral dopaminérgico mesocorticolímbico de control cognitivo y saliencia de incentivo; una alteración que está a la base del proceso de transición de un uso voluntario de la droga a un abuso compulsivo de la misma. Por otra parte, son pocos los estudios que han analizado si las alteraciones se relacionan con patrones de consumo y efectos de la abstinencia o el mantenimiento del tratamiento.

El objetivo de esta tesis es intentar dar más evidencia empírica a los cambios cerebrales asociados a las alteraciones cognitivas y motivacionales en adicción a la cocaína. Cuatro estudios se desarrollaron para la confección de la misma. El estudio de morfometría mostró que los adictos a la cocaína presentaban una reducción del volumen de sustancia gris en el estriado dorsal y que el volumen de sustancia gris en la amígdala correlacionaba inversamente con los años de consumo. El primer estudio funcional mostró que los pacientes presentaban una hipoactivación a nivel del giro parietal inferior durante una tarea n-back de memoria de trabajo verbal. El segundo estudio funcional mostró que los pacientes tenían una hipoactivación en el córtex frontal inferior, córtex parietal inferior y córtex temporal superior durante una tarea Counting Stroop de control de interferencia. El último estudio mostró que los pacientes presentaban una hipoactivación en el caudado durante la anticipación de recompensas monetarias. Además, se observó que la regulación de la funcionalidad del estriado durante el procesamiento de recompensas está relacionada con la abstinencia y el tiempo en tratamiento.

En conclusión, la adicción a la cocaína se asocia con alteraciones estructurales y funcionales en el circuito mesocorticolímbico. Cambios cognitivo-atencionales se relacionan con hipoactivaciones a nivel frontal y parietal y la función estriatal y su volumen se ven reducidos en la adicción a la cocaína. Además, el período en el que el dependiente está libre del consumo puede asociarse con una regulación de los patrones estriatales de activaciones alteradas durante el procesamiento de recompensas monetarias. Líneas de investigación futuras se pueden relacionar con el análisis de las bases neurales de la interacción entre procesos cognitivos y motivacionales, y la conectividad entre regiones dopaminérgicas corticales y subcorticales.

Preface

Justification

In the last few years, the number of cases of cocaine dependence has considerably increased to become the second most prevalent illegal psychoactive drug in Spain (National Drugs Plan, the Spanish Observatory on Drugs Report, 2009). Therefore, it is an important subject for the public health system and for professionals working on drug dependence. Responsibility is not for those who work directly with patients only; it is also necessary to study the cocaine addiction process in research environments to allow methodological controls to be able to test hypotheses and to put forward theories. Along these lines, the effort made in this research field focuses on comprehending the complex profile of a cocaine-addictive person at three levels: biological, behavioural and social. Chronic cocaine use is related with medical, neurological and neuropsychiatric complications, which have to be considered in the treatment (Bolla et al., 1998), and it is important that treatment programmes take into account a neurobiological model that has to accurately explain the patient's clinical reality.

Neuropsychology, which studies the relationship between behaviour and the brain, establishes an interesting point of view to study cocaine addiction because its efforts focus on the study of cognitive/motivational brain-behavioural processes. The technological revolution that has taken place in recent years allows the use of new technology in research. The use of techniques such as structural Magnetic Resonance Imaging (MRI) and functional Magnetic Resonance (fMRI) Imaging improves neuroanatomical and neurofunctional approaches in distinct clinical populations, such as addictive behaviours. The great spatial and good time resolutions of these techniques and their non-invasive properties provide the scientific community with interesting and

complementary data to those obtained by other techniques, such as Possitron Emission Tomography (PET), Event-Related Potentials (ERP), among others.

Nowadays, addiction emphasises uncontrolled drug use rather than tolerance and physiological dependence (O'Brien, 2008). Several studies report alteration in executive control functions in cocaine addiction (Garavan and Hester, 2007; Kubler et al., 2005, Tomasi et al., 2007a; Bolla et al., 2003). Moreover, some studies indicate that addiction alters the reward function (Garavan et al., 2000; Jia et al., 2011). The interaction of motivational and cognitive neurobehavioural components in cocaine dependence is basic in comprehending the addiction process and the different degrees of severity implicated. Compulsive drug use develops due to an inflexible behaviour, and it persists despite the considerable cost that cocaine addiction involves (Everitt et al., 2001). Addiction alters the neural bases of motivation and self-control, and affects processes like cognitive control, decision making and reward processing (Baler and Volkow, 2006; Goldstein and Volkow, 2002¸Volkow et al., 2011a, 2011b). The isolate consumption of a drug does not produce addiction, but maintaining the frequency and time of consumptions produces structural and functional brain changes (Kalivas and O'Brien, 2008). Uncertainty about the relationship between neural bases of addiction and manifestation of addictive behaviours offers this aspect, and the clinical implications that it may has, a clear value of research interest for several scientists in this particular field.

The neurobehavioural study of both cognitive aspects (e.g., cognitive control) and motivational aspects (e.g., reward processing), and also the possible structural changes associated with cocaine addiction, will offer possibilities to produce empirical evidence to develop theoretical models. These models not only implicate one "psychopathology of the patient" dimension, but also a "biological" dimension (a neural substrate of addiction processes), which could be modulated by genetic and environmental variables. The neuroimaging studies methodology provides an understanding of the cocaine patients profile by considering aspects like neurotransmission systems, brain structural and functional bases, cognitive state, personality traits, personal-social situation and clinical situation. This amount of

knowledge will relate with the establishment of more complete, effective and efficient treatments (Kampman, 2010; Volkow et al., 2011a, 2011b, 2011c).

The general aim of this doctoral thesis is to provide the addictions field with more empirical evidence for the possible structural and functional implications in the cognitive and motivational alterations relating with maintenance of the compulsive/impulsive substance use behavioural pattern in cocaine addiction by generalising them to therapeutics approaches to confer clinical significance to the results.

Chapter 1.General Introduction

Behavioural disinhibition associated with cognitive and motivational components, which are related with failures in the top-down control of fronto-striatal circuits and overactivity within striatal circuitry, may explain both the impulsive and compulsive patterns in some disorders (Fineberg et al., 2010). These psychopathological disorders are often highly heritable and include obsessive-compulsive disorder (OCD), body dysmorphic disorder, Tourette's syndrome, trichotillomania, attention deficit hyperactivity disorder (ADHD), pathological gambling and substance addictions (Fineberg et al., 2010).

Impulsivity is defined as a predisposition towards rapid, unplanned reactions to internal or external stimuli with diminished regard to negative consequences (Chamberlain and Sahakian, 2007; Potenza, 2007). Compulsivity represents a tendency to unpleasantly perform repetitive acts habitually, leading to functional impairment (Hollander and Cohen, 1996; Chamberlain et al, 2006). Longitudinal studies have demonstrated that individuals who demonstrate poor behavioural self-control or high novelty seeking as young children are substantially more likely to initiate substance use in adolescence (King et al., 2004; Màsse and Tremblay, 1997). On the other hand, prolonged consumption can lead to drug-taking compulsion, and addicted losses control habitual behaviour and are unable to reverse repetitive response patterns no longer driven by drugs (Koob and Volkow 2010). Some neurobiological models establish that psychostimulant addiction could be a transition between impulsive and compulsive behaviours (Dalley et al. 2011; Koob and Volkow, 2010; Everitt et al., 2008; Pierce and Vanderschuren, 2010). These neurobiological models establish the existence of separate, yet intercommunicating, 'compulsive' and 'impulsive' cortico-striatal circuits that are differentially modulated by neurotransmission, and which play different roles in the various stages of the transition process of addiction from social drug use to habitual and compulsive drug use (Robbins, 2007; Brewer and Potenza, 2008; Everitt et al., 2008; Pierce and Vanderschuren, 2010). In the impulsive circuit, a ventral striatal

component (VS/nucleus accumbens) may drive the impulsive behaviours underlying cocaine seeking and intake over extended periods of time (Everitt et al., 2008); in the compulsive circuit, a dorsal striatal component (DS/caudate nucleus) may drive compulsive behaviours. Compulsive behaviours result from maladaptative stimulus-response habits in which the ultimate goal of behaviour has been devalued and responding is governed by drug-related stimuli, which also function when presented as a result of instrumental responses. The persisting quality of these habits has been likened to a pathological wanting of drugs and also relates simultaneously with lack of control of habitual behaviours.

Goldstein and Volkow (2002) and Volkow et al. (2011b) proposed that at the core of drug addiction, we find the processes of loss of self-directed behaviours to become "automatic sensory-driven formulas", as well as the attribution of primary salience to the drug of abuse at the expense of natural reinforcers, which are related with the impulsive behavioural pattern. Then, when these processes become chronic, behavioural compulsion patterns appear as relapse and mental compulsion patterns like withdrawal or craving. The proposed syndrome of impaired response inhibition and salience attribution (I-RISA syndrome) consists in four behavioural dimensions that are interrelated in a positive loop (Goldstein and Volkow, 2002): drug intoxication, drug craving, compulsive drug administration and drug withdrawal. Drug intoxication is related with the experience of strong effects of the drug based on positive and negative reinforcement, and the repeated associations between the drug and these effects allow the attribution of primary salience to drugs. Craving is associated with the learned response that links drug-related stimuli to a pleasurable experience, producing drug expectation and its desire. Moreover, compulsive drug taking is maintained to avoid unpleasant withdrawal symptoms, or even when the drug is no longer perceived as pleasurable and adverse physical reactions to it appear.

In short, addictive drugs like cocaine are initially taken simply to achieve their pleasant drug effects, and after addiction, they are consumed to escape withdrawal symptoms due to only the sensitisation to the drug of the incentive salience brain system, but also to impaired response inhibition (Robinson and Berridge, 2003; Volkow et al., 2011b).

1.1. The neurobiology of cocaine addiction

1.1.1. Dopamine circuitry implications in cocaine addiction

Prefrontal components (e.g., orbitofrontal cortex, OFC; inferior frontal cortex, IFC; Anterior Cingulate Cortex, ACC) may exert inhibitory control over the formerly cited impulsive and compulsive dopaminergic circuitries (Robbins, 2007; Brewer and Potenza, 2008). Hyperactivity or hypoactivity within the striatal components and abnormalities (presumably hypoactivity) in the prefrontal components may, thus, result in increased impulsive or compulsive behaviours (Fineberg et al., 2010). In addiction impairment typically begins in the more primitive subcortical areas of the brain that process reward to then move on to other neocortical areas relating with more complex cognitive functions (Volkow et al., 2010). Thus, in addition to reward (see Figure 1), addiction can produce severe disruptions in learning (memory, conditioning, habituation), executive function (impulse inhibition, working memory, decision making, delayed gratification), cognitive awareness (interoception), and even emotions (mood and stress reactivity) (Volkow et al., 2010).

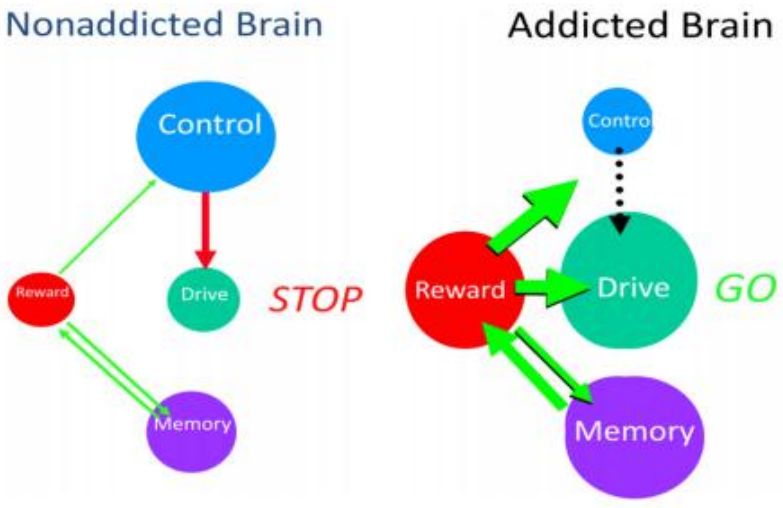


Figure 1. During addiction, the enhanced value of the drug in the reward, motivation, and memory circuits overcomes the inhibitory control exerted by the prefrontal cortex, thereby favoring a positive-feedback loop initiated by the consumption of the drug and perpetuated by the enhanced activation of the motivation/drive and memory circuits. Extracted from Volkow et al. (2011d).

The mesocortical dopamine circuit, which includes the prefrontal cortex (PFC), the OFC and the ACC, seems to be involved in the conscious experience of drug intoxication, drug incentive salience, craving and compulsive drug administration. The mesolimbic dopamine circuit, which includes the nucleus accumbens (VS component), the caudate (DS component), the amygdala and the hippocampus, has been associated with acute reinforcing drug effects, and also with memory and conditioned responses, which have also been linked to craving and to compulsive drug processes. This circuit is also likely to be involved in emotional and motivational changes during withdrawal (Goldstein and Volkow, 2002). Cocaine produces its reinforcing effects by potentiating these dopamine circuits (Hurd and Pontén, 2000). Indeed, enhancement of cocaine-evoked dopamine (DA) levels in a terminal projection area of mesocorticolimbic neurons like the nucleus accumbens, which is related with behavioural sensitisation (Zapata et al. 2003; Kalivas et al., 1998), is thought to be responsible for the development of the impulsive and compulsive drug-taking behaviour related with addictive disorders (Robinson & Berridge, 1993).

Scientific literature has shown that addiction implicates alterations in the neural circuitry normally involved in pleasure, incentive motivation and learning (Wise 1989, Robbins and Everitt 1996, Berridge and Robinson 1998, Di Chiara 1999, Kelley 1999, Hyman and Malenka 2001, Kelley & Berridge 2002). DA pathways in the mesolimbic system perform an important function in reward and reinforcement (Wise, 2002). Addiction is related with a sensitisation of the reward system due to repeated stimulation of mesolimbic DA pathways, increasing reward-seeking behaviours (Robinson and Berridge, 1993). This fact relates with inhibitory control (associated with poor prefrontal functioning) and may facilitate DA impulsive-motivated behaviours. Excessive DA release and stimulation may deplete DA stores and lead to anhedonia and depression (Koob and Le Moal, 1997), producing compulsion to seek stronger rewards to avoid DA deficiency. The demonstration of decreased DA receptors in chronic cocaine users (Volkow et al, 1999a) suggests a down-regulation in response to persistently elevated postsynaptic DA concentrations, which is consistent with the hypothesis of a dysregulated DA system after repeated stimulation of DA release. As Volkow et al. (2002a) reported, in drug abusers, lower striatal dopamine receptors

correlate significantly with lower brain glucose metabolism in the OFC (involved with salience attribution, whose disruption results in compulsive behaviours) and in ACC (involved with inhibitory control and error monitoring, whose disruption results in impulsivity). The dopamine transporter (DAT) removes dopamine from the extracellular space, thus terminating signalling, and it is also critically involved in the rewarding and stimulating effects of psychostimulants. DAT blockers, like cocaine, inhibit the uptake of DA (Ferris et al., 2011), increasing DA levels and extending the magnitude and duration of DA signalling (see Figure 2). Psychostimulant-induced DA elevations are related with regulation of motor, mood, motivation, fronto-attentional functioning, learning and addiction processes (Wanat et al., 2009; Schultz, 2007). What starts as an increased DA release, leading to increased ventral ACC activity and increased reward seeking (Wise, 2002), may end up as a compulsive drive towards increased levels of reward stimulation to restore resultant DA deficiency. This compulsive drive may be exacerbated by deficient impulse control and decision making, linked to the OFC, ventromedial prefrontal cortex (VMPFC) and ACC (Adinoff, 2003).

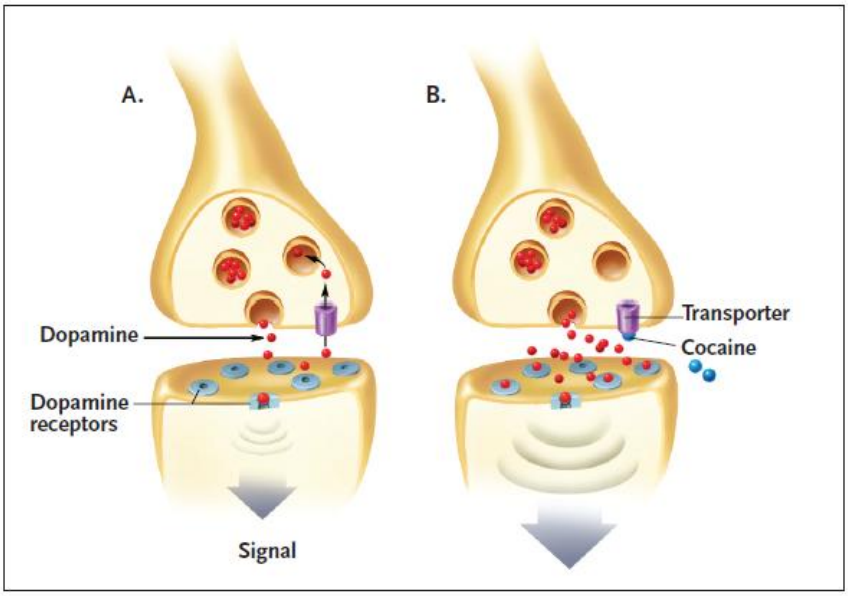


Figure 2. Cocaine blocks the dopamine transporters and dopamine molecules are accumulated in the intercellular space striking the receiving cell's receptors and causing an intensified response in the receiving cell. Also a downregulation of the dopamine receptors in the receiving cell may take place. Extracted from Fowler et al. (2007).

Low dopamine D2 receptor (DRD2) availability is associated with drug liking for stimulants (Volkow et al., 1999b) and the reinforcing effect of cocaine has also been related to its ability to block the DA transporter (Ritz et al., 1987). As animal studies report, drug intoxication is associated with higher extracellular dopamine concentrations in striatal, limbic and frontal brain regions (Ritz et al., 1987; Hurd et al., 1989; Goeders and Smith, 1986), which relate with positive reinforcing effects. On the other hand, although increased DA has been frequently associated with positive affective states, it is possible that, under certain conditions, DA levels increasingly stimulate the neuronal systems associated with aversion, thus causing an animal to increase cocaine intake to block these negative experiences (Hurd and Pontén, 2000). Human studies have shown that increasing extracellular DA concentrations in the nucleus accumbens is thought to be a final common pathway for cocaine (Everitt and Robbins, 2005). In non-dependent drug abusers, cocaine self-administration increases the extracellular DA levels within the ventral limbic striatum (Cox et al., 2009).

DA release is also related with craving mechanisms. DA agonists produce an enhancement in cocaine cue reactivity (Robbins et al., 1992). Re-exposure to the environmental cues previously associated with cocaine use produces a strong conditioned response, which increases subjective measures of cocaine craving, while DA release may also mediate some conditioned responses to cocaine cues (Berger et al., 1996). High concentrations of DA metabolites (plasma homovanillic acid), which represents high concentrations of DA, correlate with cocaine craving in newly abstinent patients (Berger et al., 1996). When non-treatment seeking cocaine-dependent volunteers listen to cocaine-related scripts or view cocaine-related videos, a DA release is selectively induced within the associative and sensorimotor regions of the DS (Volkow et al., 2006a; Wong et al., 2006). Sensitisation mechanisms in animals, such as locomotor activating and dopamine-releasing effect (Fontana et al., 1993), occur after repeated use of cocaine, and are believed to enhance the incentive salience of drug-related stimuli related to craving and drug seeking (Robinson and Berridge, 2003).

DA deficiency during withdrawal evidences the fact that DA agonists effectively reverse post-cocaine deficits in brain stimulation reward in rats (Markou and Koob, 1992), and confirms a link between withdrawal and DA neurotransmission in

mesolimbic areas and attenuated brain stimulation reward (Weiss et al., 2001). By taking into account that dopamine partial agonists can reverse psychostimulant withdrawal, it has been suggested that DA tone dysregulation relates with the motivational effects of withdrawal (Koob, 2009). Regarding relapse, DA neurotransmission mediates cocaine-induced reinstatement (Self and Nestler, 1998; Shalev et al., 2002; Spealman et al., 1999). Increasing the DA release in the nucleus accumbens (Nacc) can reinstate cocaine-seeking behaviour (Stewart et al., 1984). Moreover, a lot of dopaminergic agonists are greater inducers of relapse in cocaine and heroin addiction (De Wit and Stewart, 1983; Wise et al., 1990; Self et al., 1996a; 1996b), and DA antagonists can block the priming effects of heroin, amphetamine and cocaine (Ettenberg, 1990; Shaham and Stewart, 1996; Weissenborn et al., 1996).

In short, DA mesocorticolimbic circuitry plays an essential role in the cocaine addiction process, and is related with alterations in this neurotransmission system based on the dysregulation of DA levels in the synaptic space to produce cognitive and motivational changes in distinct phases of addiction, which allow a transition from voluntary drug use to habitual and compulsive drug abuse (Everitt et al., 2008).

1.1.2. Structural and functional brain implications of cocaine addiction

Cocaine addiction is associated with neural changes in the frontostriatal brain system, which may be related with impulsivity and drug-related compulsivity (Jentsch and Taylor 1999; Everitt and Robbins, 2005; Porrino et al., 2007; Schoenbaum and Shaham, 2008). Imaging studies have shown functional and structural alterations in PFC regions that play an important role in executive functions such as cognitive control, decision making, emotional regulation, motivation and salience attribution, demonstrating the catastrophic consequences of PFC disruption in cocaine addiction (Volkow and Fowler, 2000; Volkow et al.,2006b). Impaired cognitive control plays a fundamental role in drug-seeking behaviours in abusers, and successful functionality requires top-down control of the PFC to the striatum and limbic regions involved in reward and emotion processing (Heatherton and Wagner, 2011). Motivational/emotional alterations in cocaine addiction are related with structural and functional alterations in several regions, including the ACC, the OFC, the dorsolateral

PFC (DLPFC), the amygdala, the striatum, and other limbic brain regions (see Figure 3). Neurobiology of cocaine addiction results in not only an enhanced motivational value of the drug at the expense of other natural reinforcers, but in an impaired ability to inhibit the intentional actions associated with strong desires to take the drug, resulting in impulsive and compulsive drug taking in cocaine addiction (Volkow et al., 2003).

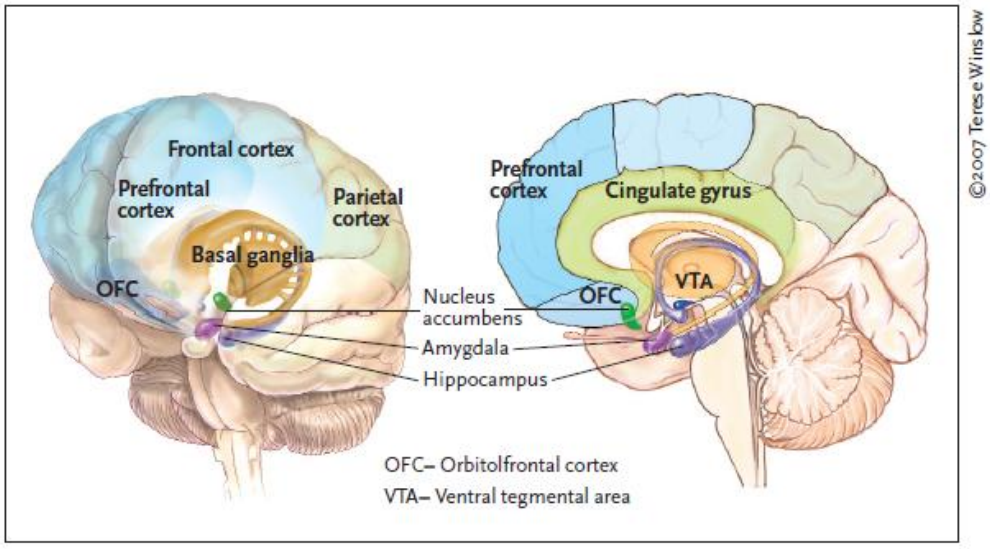


Figure 3. Major brain regions with structural and functional alterations, including the Prefrontal cortex regions (as the OFC, DLPFC), ACC, the OFC, the amygdala, hippocampus, the striatum (Nacc, caudate, putamen) with a clear role in cocaine addiction. Extracted from Fowler et al. (2007).

1.1.2.1. Structural alterations in cocaine addiction

Cocaine dependence is associated with the structural neuroadaptations related to behavioural and brain functional changes in cocaine users. Many studies based on these neuroadaptations have focused on DA circuitry, and particularly on the striatum (Koob et al., 1994; White and Kalivas, 1998). Nonetheless, cocaine addiction is also related to spread reductions in grey matter (GM) density and volume in cortical brain regions (Matochik et al., 2003; Tanabe et al., 2009; Franklin et al., 2002; Bartzokis et al., 2000a; Sim et al., 2007; Ersche et al., 2011), as well as in frontal (Lim et al., 2002, 2008), insular (Lyoo et al., 2004) and callosal (Moeller et al., 2005) white matter (WM).

Previous studies applying Voxel-Based Morphometry (VBM), based on morphometric changes (Ashburner and Friston, 2000), have reported GM reductions in

the volume of the OFC, the ACC, the insula, the superior temporal cortex (Matochik et al., 2003; Franklin et al., 2002; Lim et al., 2008; Tanabe et al., 2009) and the cerebellum (Sim et al., 2007) in cocaine addiction. Yet others have failed to find these differences (Connolly et al., 2009; Narayana et al. 2010). On the other hand, and by means of manual volume segmentation, Jacobsen et al. (2001) showed an increased volume of the striatal structure, like the caudate head and putamen, based on brain volume differences. Martínez et al. (2004) do not find these differences. The last structural findings have shown loss of GM in the following: OFC, IFC, medial frontal cortex (MPFC), DLPFC, insula, ACC, temporoparietal cortex, amygdala, parahippocampus, caudate and cerebellum (Ersche et al., 2011; Weller et al., 2011; Moreno-López et al., 2012), as well as increased GM in the putamen, the caudate, globus pallidum and the cerebellum in cocaine-dependent men (Ersche et al., 2011). Moreno-López et al. (2012) also found lower WM volumes in the inferior and medial frontal cortices, the superior temporal cortex, the ACC, the insula and the caudate. Lack of consensus among studies could be related with methodological and sample differences.

All these structural changes associated with cocaine addiction process affect the striato-cortico-limbic circuitry linked to the cognitive and motivational/emotional component of the process. These effects could be related with long-term drug use based on maintenance of drug-seeking and drug-consuming behaviours due to impulsive and compulsive behaviours.

1.1.2.2. Functional alterations in cocaine addiction

Volume differences in a given brain area related to drug use may affect functional activation, as measured by brain Blood Oxygen Level Dependent (BOLD) patterns (Aron and Paulus, 2007). Thus, the cell numbers in a structure, as reflected by its volume measure, could be important for capillary recruitment associated with brain activity (Makris et al., 2004), suggesting reduced functionality in an area of reduced volume. Cocaine dependence has been related to a wide range of cognitive and motivational/affective dysfunctions, and fMRI has proven an invaluable technique to study these drug-related changes (Aron and Paulus, 2007). Different fMRI studies have shown cognitive (Garavan et al., 2008), motivational (Goldstein et al., 2007a; Garavan

et al., 2000) and motor (Hanlon et al., 2009) deficits in cocaine-dependent patients, which directly relates with the functionality of dopamine-mediated regions.

1.1.2.2.1. Cognitive control functioning in cocaine addiction

Stimulant abusers present significant deficits in executive control processes (Bechara, 2005). Mental flexibility or cognitive monitoring, and decision-making processes become altered executive functions in cocaine addiction (Bolla et al., 1998). Moreover, there are differences between cocaine abstinent and controls in selective (Verdejo-García et al., 2005) and sustained (Morgan et al., 2006) attention, visuospatial functions, memory and concentration (Berry et al., 1993). It has been suggested that executive control implicates not only one simple network, but two different connected networks: a frontoparietal network comprising DLPFC, inferior parietal lobe (IPL), dorsal frontal cortex, intraparietal sulcus, precuneus and middle cingulate cortex; and a cingulo-opercular network composed of anterior prefrontal cortex, anterior insula/medial frontal operculum, dorsal anterior cingulate/medial superior frontal cortex and thalamus (Dosenbach et al., 2008). These two networks may be affected by cocaine addiction to an unknown extent.

- Inhibitory control

Some studies have demonstrated that cocaine-dependent individuals exhibit an attentional system that is biased to detect and process cocaine-related stimuli; in drug Stroop tasks, substance abusers have been seen to take longer to name the colour of drug-words than neutral words (Cox et al., 1999; Mogg and Bradley, 2002; Copersino et al., 2004; Hester et al., 2006; Vadhan et al., 2007). Moreover, other research works have indicated an association between long-term cocaine use and impairments of inhibitory processes (Ardila et al., 1991; Horner et al., 1996; Volkow et al., 1996; Biggins et al., 1997; Fillmore and Rush, 2002; Colzato et al., 2007). Cocaine abuse is related with patterns of premature responding (Bauer, 2001), persevering behaviour, and the inability to adapt behaviour to environmental changes (Lane et al., 1998).

Previous research, which compared patients and controls using the Stroop task, has found differences in several frontal and cingulate areas. Bolla et al. (2004) revealed how the ACC and the right lateral prefrontal cortex (LPFC) were less active in a group of cocaine-dependent individuals during the execution of a manual version of the Stroop task. Although Goldstein et al. (2001) did not find brain functional differences between cocaine-dependent patients and a group of matched controls while performing an event-related colour-word Stroop task, their results reveal increased activation in the OFC, which is associated with lesser and greater conflict in controls and patients, respectively, while groups did not differ in terms of task performance.

Cocaine-using subjects have shown impaired behavioural performance in GO–NOGO tasks (Fillmore and Rush, 2002). Kaufman et al. (2003) demonstrated that the ACC, which is critical for cognitive control, is less responsive in chronic cocaine users during a GO-NOGO task. They showed STOP-related hypoactivity in the right insula and a rostral region of the ACC, two regions that have been identified with emotional processes (Whalen et al., 1998). The ACC has also been seen to be implicated in inhibitory control (Casey et al., 1996; Ponesse et al., 1998). In one of our studies (Bustamante et al., 2008), we showed lower activation in the MPFC of cocaine-dependent patients during a GO-NOGO task with reward contingencies, as in previous studies (Hester and Garavan, 2004; Kaufman et al., 2003). Moreover, compensatory hyperactivation in the right IFC has shown in cocaine patients during a GO-NOGO task (Kaufman et al., 2003).

In a stop-signal task, Fillmore and Rush (2002) established that cocaine users display less ability to inhibit a response, less likelihood of inhibiting responses, and that they required more time to inhibit responses as estimated by their higher stop-signal reaction time (SSRT) in comparison with controls. Li et al. (2008) showed hypoactivation in the rostral ACC as a specific deficit in controlling the inhibitory response in men with chronic cocaine abuse. Moreover, they found greater activation in the visual and posterior parietal regions in controls when compared with cocaine users. These results are also consistent with an earlier work demonstrating frontal and temporo-parietal hypoperfusion associated with chronic cocaine use (Strickland et al,

1993), while greater activation of the posterior parietal and visual cortical regions suggests that healthy individuals pay more attention to the task (Li et al., 2008).

These alterations in the frontal brain regions relating with inhibitory control functioning may be associated with the cocaine-related cognitive deficits linked to the relationship between drug cues and compulsive drug self-administration in drug dependence (Goldstein et al., 2001; Carpenter et al., 2006). These dysexecutive consequences of drug abuse indicate that cocaine users may be compromised in the endogenous and volitional control of their behaviour. Consequently, their behaviour may be disproportionately determined by environmental cues (e.g., drug-craving cues) and by habitual and compulsive behavioural patterns. The effect of this would be to compound drug abuse maintenance: if chronic cocaine users are influenced especially by environmental contingencies and cues, then an inhibitory dysfunction may reduce their capacity to inhibit these external influences (Kaufman et al., 2003).

- Working memory

In general, cocaine patients poorly perform a verbal working memory task, such as the n-back task (Beatty et al., 1995; Bolla et al., 2000; Goldstein et al., 2004; Verdejo-García et al., 2006; Tomasi et al., 2007a). Some studies have reported a functional alteration in the PFC in cocaine dependence (Adinoff et al., 2001; 2003; Goldstein and Volkow, 2002; Goldstein et al., 2004; Kosten et al., 2004), which could be related with patients' limited working memory capacity (Tomasi et al., 2007a). However, there is also evidence to establish that cocaine patients, in comparison to controls, hypoactivate the anterior cingulate gyrus (ACG) (Tomasi et al., 2007a; Kubler et al., 2005), the medial frontal gyrus (MFG), the middle frontal gyrus (MidFG) and the parietal cortex (Kubler et al., 2005). For control subjects, parametric increases of working memory load enhance brain activation bilaterally in the prefrontal and the parietal cortices (Tomasi et al., 2007a). In patients, an increased working memory load produces lower BOLD signal increases in these brain regions. These dysfunctional patterns in a fronto-parietal network could be related with limitations in working memory capacity among cocaine patients. Another study (Tomasi et al., 2007b) has revealed greater activations in the frontal and parietal brain regions in cocaine-

dependent users in comparison to a control group, such as engagement of attentional resources for supporting working memory functions. Thus, the dysfunctional activation frontoparietal pattern in cocaine users (Adinoff & cols., 2001, 2003; Goldstein et al., 2004; Goldstein & Volkow, 2002; Kosten et al., 2004; Volkow et al., 1988, Bolla et al., 2004) could be associated with limitations in the capacity of the working memory frontoparietal network (Tomasi et al., 2007a; Nyberg et al., 2009). Specifically, the parietal cortex is related with attentional response-orienting processes (Corbetta y Shulman, 2002) and limitations in the working memory load (Nyberg et al., 2009).

In short, the literature establishes differential patterns of activation between cocaine addicts and controls in a frontoparietal network related with the working memory function and attentional-related processes. There is evidence for an impaired integrative function of those regions involved with executive control and attention in cocaine abusers, and it is likely to underlie the cognitive disruption in cocaine patients. Diverse studies have established the prefrontal cortex to be the main neural substrate holding the neurocognitive pattern and the addiction process in cocaine-dependent subjects, but other cortical brain regions are relevant in cognitive control functioning in cocaine addiction.

- Decision making

Cocaine addicts' inability to consider the consequences of both their behaviour with a view to modifying it and their poor risk assessment is similar to the impairment noted in patients with VMPFC lesions (Damasio, 1985; Bechara et al., 1994; 1998; Grant et al., 1997; Bartzokis et al., 2000b). The Iowa gambling task (IGT) proves a valid decision-making measure (Bechara et al., 1998). A study reported that polydrug abusers perform worse in the Gambling Task when compared to controls (Grant et al. 1997). Cocaine use impairs risk assessment and advantageous decision making (Bartzokis et al., 2000b; Bolla et al., 2003). Cocaine-dependent subjects show impaired performance in decision-making tasks such as the Gambling task (Reavis and Overman, 2001; Adinoff et al., 2003).

Tanabe et al. (2007) reported that substance-dependent individuals display lower ventral medial frontal activity during decision-making processes, as well as less right prefrontal activity. Cocaine abusers exhibit greater activation during the IGT in the right OFC, but less activation in the right DLPFC, which are involved in planning and working memory required for IGT, and in the left MFC involved in planning and performance in the IGT (Bolla et al., 2003). For compensation processes, cocaine abusers may overactivate the right OFC. OFC hyperactivity in cocaine abusers during the IGT may reflect an abnormally intense focus because they are thinking about the winning/rewarding emotional aspects of the task, and this thought process could exaggerate the value of the high reward and suppress the negative value of high loss. OFC dysfunction could be a predisposing factor which may lead to poor decision making that relates with certain "myopia" for the future consequences of their choices (Cunha et al., 2011) and to the social dysfunction among cocaine patients. Thus in cocaine subjects, Adinoff et al. (2003) reported less regional cerebral blood flow in the OFC, the ACC and the DLPFC during gambling task execution, which could be related with impaired performance.

In conclusion, cocaine abusers display functional abnormalities in the prefrontal neural networks involved in decision-making. This compromised decision-making is likely to contribute to maintaining addiction, thus making abstinence difficult (Bolla et al., 2003). Specifically, the important social behaviour deficits, risk-taking tendencies and personality alterations seen in cocaine addiction are related with the link between the OFC and the decision-making dysfunction (Cunha et al., 2011).

The neuroscientific literature has concentrated on the involvement of DA in the drug addiction process because the ability of drugs of abuse to increase brain DA concentrations in the limbic and striatal brain regions is considered crucial for their reinforcing effects (Di Chiara, 1999). Otherwise in drug addiction, we can observe functional and structural changes in dopamine circuits, including not only limbic areas, but also the frontal cortex (Goldstein and Volkow, 2002). As Tomasi et al. (2007a) remarked, multiple neuroimaging studies have been done to characterise the neurocircuitry involved in cocaine addiction, mostly focussing on reward processing (related with the motivational and emotional aspects implicating addiction), but also on

complex cognitive functions (related with executive functions; e.g., cognitive control). The literature clearly places importance on the structural and functional alterations in the striato-cortico-limbic system as a neural substrate of altered processes of the top-down control and incentive sensitisation presented in cocaine addiction.

1.1.2.2.2. Motivational salience attribution and cocaine addiction

Environmental stimuli associated with effects of self-administered drugs gain incentive salience through the Pavlovian conditioning process. Drugs produce sensitisation of autonomic activity or distortions in sensory processing, and exaggeration of incentive salience of stimuli that already predict important environmental events such as drug-related cues (Everitt and Robbins, 2005).

There are theories to explain the role of the brain reward pathways in mediating relapse, which is the core motivational symptom of compulsive drug taking and intense drug craving. Impulsivity theories have determined that addicted users are characterised by prominent traits of impulsivity resulting from some combinations of overactive mesolimbic reward approach circuitry and deficient frontocortical punishment avoidance circuitry to produce a greater functional engagement of the dopaminergic-motivational brain circuitry during reward processing (Bechara, 2005; Bickel et al., 2007; Newman and Wallace, 1993). On the other hand, the reward deficiency syndrome (RDS) hypothesis (Blum et al., 2000) has established that addicted individuals display deficit to recruit the dopaminergic-motivational circuitry by non-drug rewards, but abused drugs are able to normalise DA levels, thus motivating drug-taking behaviour (Bjork et al., 2008). The allostatic hypothesis (AH) (Koob and Le Moal, 1997; Koob et al., 2004) has posited that neurochemical effects of chronic drug use also cause an under-responsiveness in the mesolimbic incentive neurocircuitry to non-drug rewards and cues (Koob and Le Moal, 2005). These effects produce anhedonia and a generalised dysphoric mood (Bjork et al., 2008), and relapse risk implicates the alleviation of that discomfort and negative affect (Weiss et al., 2001). However, this theory has its limitations; as regards the positive incentive processes caused directly by drugs themselves, withdrawal states are not especially powerful in motivating drug-seeking behaviour (Stewart & Wise 1992; Robinson and Berridge, 2003). Besides, this theory

cannot explain why addicts so often relapse into drug-taking, even after being free from withdrawal (Robinson and Berridge, 2003).

There is another theory, the Incentive-Sensitisation Theory, which suggests that relapse is explained by drug-like processes that activate reward pathways, such as the acute effect of the drug itself (Stewart et al., 1984; Wise and Bozarth, 1987; Robinson and Berridge, 1993; Self and Nestler, 1995). Drugs, like cocaine, can alter the reward brain circuits mediating the attribution of incentive salience (see Figure 4), a basic incentive-motivational function (Robinson and Berridge, 2003). These neural circuits become hypersensitive (neural sensitisation) to specific drug effects and to drug-related stimuli at both the micro (neurotransmission) and macro (brain systems) levels. Thus, excessive attribution of incentive salience to drug-related representations could cause "pathological wanting" (Goldstein and Volkow, 2002; Robinson and Berridge, 2003; Volkow et al., 2011a, 2011b). Thus, the next two points go on to present the main neuroimaging findings in cocaine addiction relating with processing drug and non-drug-related stimuli to compare evidence for highly responsiveness to drug-associated cues in brain reward regions, and for altered responsiveness of brain reward regions to non-drug rewards.

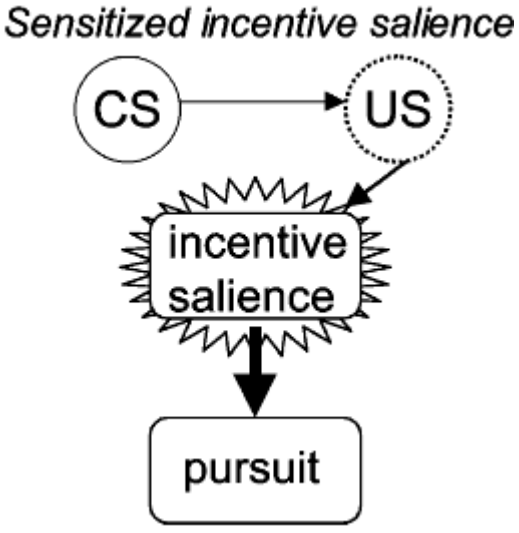


Figura 4. According to the incentive-sensitisation theory the critical change is in the ability of drug cues (the dashed US evoked by a drug cue) to engage a sensitized motivational response of incentive salience (as indicated by the starbust). This enhanced motivational response is primarily responsible for compulsive drug pursuit in addiction. Extracted from Robinson and Berridge (2003).

- Reward processing of drug-related stimuli

If compared with neutral stimuli, drug-related stimuli elicit enhance physiological reactivity in addicted individuals (Carter & Tiffany, 1999). Some authors

have demonstrated that larger late positive potentials (LPPs) are elicited by drug-related pictures if compared with neutral pictures in cocaine, heroin and alcohol addiction (Franken et al., 2003; 2004; van de Laar et al., 2004; Namkoong et al., 2004). These results have been interpreted as an increased centralisation of neural resources in drug-related stimuli if compared with neutral stimuli (Dunning et al., 2011).

Goldstein et al. (2009) demonstrated that drug words increase brain activations in the mesencephalon, a major source of dopamine release during motivationally salient situations or conditioned stimuli appearances (Robinson and Berridge, 1993; McClure et al., 2003). When cocaine-related stimuli are presented, and if we compare this scenario with non-drug-rewarding stimuli presentation (i.e., erotic stimuli), various brain regions become activated in cocaine abusers: ACG, OFC, DLPFC, retrosplenial cortex, peristriate cortex, IFL and temporal pole (Maas et al., 1998; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Wexler et al., 2001; Bonson et al., 2002; Grant et al., 1996; Wang et al., 1999). In cocaine addicts, even a brief exposure to drug cues evokes limbic system activation (Childress et al., 2008) as with exposure to natural-sexual cues. In this sense, cocaine users' brain response to "unseen" drug and sexual cues reflects Pavlovian learning, but has evolutionary implications; rapid response to reward signals for food and sex would have a survival advantage. Cocaine confers no such advantage, but strongly activates the reward circuitry. The limbic brain treats cocaine cues "as if" they were signals for highly desirable natural rewards (Childress et al., 2008).

- Reward processing of non-drug-related stimuli

A deficient electrophysiological response to pleasant and unpleasant images has been shown to be evident during current use of cocaine (Dunning et al., 2011), as occurs in other drug addiction and dependence cohorts (Lubman et al., 2009; Zijlstra et al., 2009), and is related with impairments in sustaining non-drug-related goal-oriented motivation and predisposition of addicted patients to drug use as a compensation mechanism (Dunning et al., 2011).

Goldstein et al. (2007) showed altered sensitivity to gradients in monetary value in the OFC in cocaine-dependent men. Asensio et al. (2010) showed that, if compared with controls, a cocaine group displayed hypoactivated DS and VS, thalamus, parietal cortex and dorsomedial prefrontal cortex while processing erotic-related pictures. On the other hand, some studies have suggested that some cocaine-addicted individuals are hypersexual (Washton and Stone-Washton, 1993) and that some substance-dependent individuals may be hyperresponsive to monetary rewards (Bechara et al., 2002; Jia et al., 2011). These results could indicate impairments that may reflect inefficient processing, reward hypersensitivity, greater salience, or other possibilities or combinations (Knutson et al., 2000; Bjork et al., 2008; Jia et al., 2011). It can be postulated that reactivity to monetary rewards in cocaine patients increases in comparison with control subjects as money acts as a secondary reinforcer towards substance use, thus increasing anticipation and outcome responses (Jia et al., 2011).

Briefly, the neuroimaging literature shows a functional alteration in reward processing neural systems in cocaine addicts, which is characterised by hyperactivity to drug-related cues, and by either hyperactivity or hypoactivity regarding other rewarding stimulus processing. Alterations have been found in the emotional processing related with cocaine addict patients' reduced ability to experience pleasure by natural reinforcers, thus attributing excessive incentive salience to drugs and stimuli, which remain associated with drugs after repeated drug use.

1.1.3. Drug-free state and neurobiological implications in cocaine addiction

As shown in this introduction, in different neuroimaging studies into cocaine addiction, no consensus between studies has been reached as regards results. Perhaps methodological issues could represent the main reason for this lack. Thus, characteristics of samples in relation to illness severity or treatment-seeking status are one of the most common methodological differences (Moeller et al., 2012). In this sense, most studies into cocaine addiction have not reached an agreement on the clinical situation of cocaine patients that have participated in their works using short-term or long-term abstinents, or even using active cocaine users. Indeed, the marked heterogeneity of treatment-seeking samples (determined by length of abstinence, in-

patient status, remission status, etc.) in the same study could lead to an increase in data variability and to effects on the power of the neuroimaging results (Moeller et al., 2012).

The literature has shown differences in brain structure and brain functioning in those who have attained relatively long periods of abstinence, and also in those who have recently abstained. Regarding the acute effects of cocaine, they could affect the brain structure and function in a wide range of dopaminergic brain regions including, but not limited to, regions involved in reward and executive control functions (Breiter el al., 1997; Breiter and Rosen, 1999; Bartzokis et al., 1999a, 1999b; Hanlon et al., 2009; Kaufman et al., 2003; Lyoo et al., 2004; Hester and Garavan, 2004; Kubler et al., 2005; Goldstein et al., 2007, 2009; Garavan et al., 2008; Li et al., 2008; Sim et al., 2007; Franklin et al., 2002; Ersche et al., 2011). Specifically, if we take into account the neuroimaging data on abstinence duration, abstinent patients were those who showed reduced GM volume in the PFC (Fein et al., 2002), the medial OFC (Tanabe et al., 2009; Matochik et al., 2003; Moreno-López et al., 2012), the lateral OFC (Matochik et al., 2003), the right inferior frontal gyrus (IFG) (Moreno-López et al., 2012), the right ACG (Matochik et al., 2003), the right insula (Moreno-López et al., 2012), the left amygdala and the bilateral caudate (Moreno-López et al., 2012) in comparison to controls. Bell et al. (2011) showed that a short-term abstinent group, a mid-term abstinent group and a long-term abstinent group differed in terms of the WM integrity of the bilateral inferior longitudinal fasciculus, the right anterior thalamic radiation, the right ventral posterolateral nucleus of the thalamus, the left superior corona radiata, superior longitudinal fasciculus bilaterally, the right cingulum and the right precentral gyrus. Moreover, all abstinent patients, if compared with controls, exhibited WM differences in left anterior callosal fibres, the left genu and the splenium of the corpus callosum, right superior longitudinal fasciculus, right callosal fibres and the superior corona radiata bilaterally (Bell et al., 2011). In a PET study during a Stroop task (Bolla et al., 2004) recently abstinent cocaine patients displayed less activation in the left ACC and the right lateral PFC, but greater activation in the right ACC when compared to controls. Recently abstinent cocaine patients also showed greater activation in the right OFC while performing the IGT, but less activation in the right DLPFC and the left MFC (Bolla et al., 2003). On the other hand, in an fMRI study during a verbal working

memory task, longer abstinent patients presented attention-related functional alterations in the putamen, the ACC, the MidFG, the MFG, the superior parietal gyrus (SPG), the parahippocampal gyrus, the amygdala, the mesencephalon and the thalamus (Tomasi et al., 2007). Another sample of longer abstinent patients (at least two months) showed an altered activation in the right IFG and the right MFG during an inhibitory control task (Bustamante et al., 2008).

Otherwise, there are very few data available that elucidate structural and functional recovery with abstinence. Thus, a PET study has shown that striatal dopaminergic dysregulation may partly recover with abstinence (Volkow et al. 2001). A diffusion tensor imaging (DTI) study (Xu et al., 2010) found that self-reported abstinence correlated positively with white matter integrity in the right superior longitudinal fasciculus, the right body of the corpus callosum, the right posterior limb of the internal capsule and the left cerebellum. One fMRI study found positive correlations between self-reported duration of abstinence and activation during a cognitive control task in the left posterior ACC, the left ventral MPFC and the right putamen (Brewer et al., 2008). Additionally, Moeller et al. (2012) demonstrated a partial recovery of brain response during an interference control drug Stroop task in the dopaminergic midbrain and the thalamus in relation to maintained abstinence. Moreover, Connoly et al (2012) showed that short-term abstinence is related with increased inhibition-related dorsolateral and inferior frontal activity, indicative of the need for increased inhibitory control while long-term abstinence relates with increased error-related ACC activity, indicative of heightened behavioural monitoring. On the other hand, little is known about the effects of abstinence on functional effects during motivational reward processing in cocaine addiction. Specifically, only one fMRI study has shown that activation in the thalamus, the culmen and the Nacc during a monetary reward processing task is correlated with self-reported abstinence (Jia et al., 2011)

In short, we observe that a drug-free state in cocaine patients brings about changes in the brain's structure and function, conferring protracted abstinence therapeutic implications. However, very little is known about the neurobiology of those who successfully avoid relapse, maintain the guidance of treatment and remain abstinent over long periods of time (Bell et al., 2011; Connoly et al., 2012).

1.2. Magnetic Resonance Imaging (MRI): the technique.

1.2.1. Magnetic Resonance Imaging (MRI)

MRI is based on the application of intense magnetic fields for creating biological tissues. These magnetic fields use the Tesla (T, 1T are 1000 Gauss) as a unit measure and are generated by an electromagnet in the MRI scanner. In human studies, the intensity of magnetic fields is between 0.5 and 9.4 T. In the scanner, MRI sequences, which are series of oscillatory magnetic gradients and electromagnetic fields, are applied to detect properties and types of tissues. These tissues are, principally, GM, WM and cerebrospinal fluid.

Pulses sequences with a specific frequency are absorbed by the atomic nuclei of the tissue of interest. These frequencies are specific for each atomic nucleus. Hydrogen is the most common nucleus in the human body and the frequencies of pulses are adjusted for that nucleus with a unique proton. After absorption, protons emit the electromagnetic energy that they have captured, and this energy is the "signal". Signal intensity depends on the concentration of these nuclei in the tissue and their magnetic properties. Therefore, if diverse tissues are differentiated in the concentration of hydrogen nuclei, the electromagnetic energy emitted by each tissue will differ. However, another important aspect is the spatial localisation of the tissues in MRI images. This spatial localisation is established in units called "voxels", like spatial localisation in a digital image in pixels. Thus, a voxel is a unit of volume with three dimensions (x, y, z). The spatial resolution of MRI images is determined by the size of the voxel in each dimension; if the voxel is smaller, then we will have more possibilities to delimit small brain structures.

The signal obtained from each voxel has an intrinsic variability that is independent of the tissue, but dependent on the measuring technique used, called "noise". Then, the MRI image is not an absolute measure of the signal emitted by a tissue, but is a measure of the contrast between the signal emitted by a tissue and the noise inherent to the technique used, called "signal to noise ratio". The "signal to noise ratio" is the magnitude of the difference in intensity between diverse amounts of signal

divided by the variability of the measures. The "signal to noise ratio" is bigger the larger the voxel size.

In summary, to obtain brain structural images in an MRI scanner:

1. An electromagnet generates a magnetic field for the alignment of hydrogen protons in a specific direction.

2. Sequences of pulses are applied at a specific frequency (radiofrequency pulses) to change the orientation of the hydrogen protons at a specific angle.

3. The interruption of the pulse causes hydrogen protons to return to their original position, as established by the electromagnet.

4. When protons return to their original position, they emit energy, that is captured by a receptor and transformed into images by considering the position of each voxel and the signal emitted by each one.

1.2.2. Functional Magnetic Resonance Imaging (fMRI)

MRI allows us to study the brain structure as a static representation. With this technique, specifically Functional Magnetic Resonance Imaging (fMRI), we can study short-term physiologic changes related with brain functionality; we can also visualise functional dynamic changes.

The main characteristic of the images obtained for the brain structure study by MRI is their "spatial resolution". The study of brain functioning by MRI (fMRI) introduces an important variable: "temporal resolution". This variable establishes the velocity of registering the physiologic changes related with brain functioning. This temporal resolution depends on the "sampling rate", which is the frequency of the fMRI signal measure over time, and is between 2 and 4 seconds. It means that physiologic changes are measured every 2-4 seconds in the acquisition process.

These physiologic changes, which represent variations or changes in the quantity of deoxyhaemoglobin in the blood (Huettel et al., 2004), are related with functional changes in a given brain region. Functional changes are defined as the intensity and variation of the oxyhaemoglobin changes in a brain region related with the neural

response during a cognitive function or task (emotional regulation, behavioural inhibition, etc). Thus, a brain region is implicated in a cognitive function depending on the magnitude of the signal change associated with the deoxyhaemoglobin concentration. The signal which originates from the physiologic changes related with deoxyhaemoglobin is based in the magnetic properties of haemoglobin. Oxyhaemoglobin is diamagnetic and enhances the magnetic signal, while deoxyhaemoglobin is paramagnetic and diminishes the magnetic signal. The content changes in deoxyhaemoglobin that are relative to oxyhaemoglobin generate contrast in terms of signal in the fMRI sequences; this contrast is named BOLD contrast. In this sense, the fMRI signal intensity increases with augmented oxidative metabolism and is an indirect measure of the neuronal response produced by the deoxyhaemoglobin/oxyhaemoglobin contrast.

The neuronal response occurs in milliseconds and produces changes in the oxygen metabolism rate leading to the BOLD Haemodynamic Response (HDR). However, the first haemodynamic changes do not appear until 1 or 2 seconds later. We have to take into account that the HDR begins with a reduction in the signal produced by incremented deoxyhaemoglobin during 1 or 2 seconds. Then, blood flow is regulated, incrementing the oxyhaemoglobine level and enhancing the HDR, which reaches its peak 5 seconds after the initial decrement. Finally, a slow return to baseline is completed by about 12 seconds. When the neuronal response is maintained over time (for example, during a block of a task in a block design), the HDR peak also extends over time (Huettel et al., 2004).

The development of experimental fMRI designs is based on Donders' substractive method (1868). Hence, it is necessary to establish a baseline or a control condition, as well as events of an activation or activation condition in our design. Then, with the subtraction between activation during the control condition and activation during the experimental condition, we can determine the brain regions implicated in the functional process of interest.

Basically, the dependent variable in fMRI is the HDR, which depends on the intensity of the signal related with the MRI principles and the magnetic properties of

haemoglobin. The unit of measure in the MRI is the voxel, which has three dimensions, but in fMRI, we have to include a new dimension: time.

1.2.3. Methodological toolboxes for MRI and fMRI: implications in cocaine addiction

1.2.3.1. Voxel-Based Morphometry (VBM)

Voxel-Based Morphometry (VBM) is a toolbox (Structural BrainMapping group, Department of Psychiatry, University of Jena, http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/) for comparing groups at a voxel level in terms of grey and white matter density and volume. This toolbox needs a preprocessing of the MRI images because the images for all the subjects have to be normalised in the same stereotaxic space. In relation to this normalisation process, there are modulation processes for correcting volumetric differences due to the elastic deformations produced during normalisation. Moreover, a segmentation process of grey matter, white matter and cerebrospinal fluid in normalised images takes place. In order to compensate inter-individual variability at a morphometric level and to eliminate noise in the data, it is necessary to apply Gaussian filters during the smoothing process. Then, statistical parametric tests based on the General Lineal Model are run to obtain t-maps showing the regions where GM and WM may statistically differ.

Good et al. (2001a) developed the "Optimised" VBM, which offers a VBM analysis with improvements in segmentation, including additional steps in this process to spatially process data. These improvements are based on: the normalisation of the segmented GM and WM images to GM and WM templates, with a second segmentation process of those normalised images, a correction process of brain volume changes and, finally, the standard smoothing process. Thus, the "Optimised" VBM implicates the creation of separate GM and WM templates, a normalisation process of the GM and WM data, which has been segmented to the new templates, a second segmentation of the normalised images and correction for volume changes.

The VBM is a useful toolbox for determining possible patterns of affectation or improvement in GM and WM when comparing between two groups, as some studies

with cocaine patients have shown, thus empirically supporting possible structural alterations that could affect diverse brain networks implicated in their interaction and the function of complex motivational and cognitive processes. Thus, cocaine dependence could produce changes GM and WM volume (Matochik et al., 2003; Tanabe et al., 2009; Franklin et al., 2002; Bartzokis et al., 2000a; Ersche et al., 2011; Lim et al., 2002, 2008; Lyoo et al., 2004; Weller et al., 2011; Moreno-López et al., 2012). Otherwise, and as mentioned earlier, clearly there is no consensus between structural studies into cocaine dependence, so it would be interesting to provide evidence for a better understanding of the neurostructural substrate of cocaine addiction. Additionally, morphometric alterations in cocaine-addicted users could be related with the measured affectation of functional activations based on the BOLD signal (Aron and Paulus, 2007). Therefore, it is interesting to contemplate cocaine-related structural alterations because they could be associated with the neurofunctional and behavioural profile of addicted individuals.

1.2.3.2. Biological Parametric Mapping (BPM), statistical toolbox for multimodal analysis in neuroimaging

BPM is an approach for integrated analysis of multimodal imaging which analyses specific neuroimaging data from one mode using other data from a different mode. This toolbox uses biological information as a covariate in the analyses of data from another mode (Casanova et al., 2007). Thus, the BPM can determine changes in morphometric, spectroscopy or DTI data relating with functional data in fMRI experiments, and vice versa. BPM is a voxel-wise covariation method that can be applied in Regions of Interest (ROI) analyses. This toolbox is based on the General Lineal Model (GLM) for statistical estimation and the Random Field Theory (RFT) or False Discovery Rate (FDR) for correcting statistical Type I errors for multiple comparisons (Friston et al., 1995, Worsley et al., 1996; Benjamini and Hochberg, 1995; Genovese et al., 2002), and for statistical inference on T- and F-maps which result from neuroimaging analyses.

With the application of the BPM, we can establish different results in our neuroimaging studies if we take into account the association between anatomic and

functional variables. A functional activation effect could be, or not be, affected (potentiated or diminished) if we covariate the possible intersubject morphometric variability which we may find in our samples (Oakes et al., 2007). BPM helps develop statistical complex methods of analyses that could offer the scientific community interesting neuroimaging results. Combination of images from different modes could avoid possible study limitations related with neuroimaging unimodal analyses.

There are no studies available into cocaine addiction which use the BPM. In this sense, this toolbox offers great applicability in cocaine-related studies because we can establish associations between cocaine-related structural and functional alterations and, at the same time, the association of these alterations with behavioural compulsive patterns. If we consider that changes GM and WM volume could improve the interpretation of cocaine-related functional alterations in relationships with behavioural changes, this would confer more significance to the conclusions drawn from the study (Barrós-Loscertales et al., 2008; Casanova et al., 2007). The positive and negative correlations between morphometric and functional results could provide evidence to the question on BOLD response alterations in cocaine patients being due to altered brain pattern activations or to possible structural alterations (Aron and Paulus, 2007).

Chapter 2. Experimental Section

2.1. Overview of the studies

The cocaine dependence literature shows that addiction implicates an alteration in the mesolimbic circuit related with motivational components, but also an alteration of a mesocortical circuit that implicates both complex cognitive functions and motivational functions (Goldstein and Volkow, 2002; Garavan et al., 2002; Lim et al., 2002, 2008; Matochik et al., 2003; Kubler et al., 2005; Tomasi et al., 2007; Goldstein et al., 2007a, 2007b; Bjork et al., 2008; Tanabe et al., 2009; Goldstein et al., 2009; Asensio et al., 2010; Jia et al., 2011; Ersche et al., 2011). Cocaine patients could present a complex neurobiological profile that implicates frontal, parietal, limbic and striatal brain areas. Understanding this complexity could provide an interesting value for the success of treatment procedures (Aron and Paulus, 2007). Moreover, it could offer the scientific community more evidence to clarify the neurocognitive reality of cocaine addiction.

The basic methodology that I present in this doctoral thesis relates to the application of a technique with important scientific relevance as the MRI, given its great spatial and good temporal resolutions, which allow researchers to obtain data of much scientific value (Aron and Paulus, 2007). Moreover, in the four studies that I present, we obtained behavioural and clinical data to render more validity to our functional interpretation and more clinical value. This fact implicates technical complexity for the preparation, programming and adaptations of paradigms to the MRI environment.

Men and women show differences in behavioural patterns and clinical profiles related with drug abuse, and are affected differently by drugs of abuse (Brady and Randall, 1999; Sinha and Rounsaville, 2002; Becker y Hu, 2008). Moreover, humans display differences in brain structure (Chen et al., 2007; Fan et al., 2010; Good et al., 2001b; Takahashi et al., 2011; Koscik et al., 2009) and brain functioning (Wager et al., 2003; Kim et al., 2005; Goldstein et al., 2005; Li et al., 2006; Adinoff et al., 2006).

Therefore in our studies, we have used only men to control the possible effect of this variable on the functional and structural results. We have also employed matched groups in handedness, level of education and general intellectual functioning in all our studies. Regarding users' substance consumption pattern that we used in the patients sample in our studies, we recruited patients who have an addiction pattern only for cocaine and a consumption pattern with no abuse of other substances.

Cocaine compulsive drug use is related with GM and WM volume alterations in the mesocorticolimbic brain areas (White and Kalivas, 1998; Bartzokis et al., 2000; Franklin et al., 2002; Matochik et al., 2003; Lyoo et al., 2004; Moeller et al., 2005; Lim et al., 2008; Tanabe et al., 2009; Ersche et al., 2011). In this sense, we did a study to compare the differences in grey matter volume between a cocaine patient group and a comparison group. For this purpose, we applied a morphometric analysis toolbox such as the VBM 5.1 toolbox.

Clear evidence has been established of an executive dysfunction in cocaine dependence (Bolla et al., 1998; Cunha et al., 2004) with a deficient attentional mechanism (Jovanovski et al., 2005; Simon et al., 2000; Verdejo-García et al., 2005; Morgan et al., 2006), which could be related with an altered pattern of activation in the frontoparietal network in terms of the executive function. Thus, we conducted two studies which attempted to compare a cocaine-dependent group and a matched control group during two different tasks adapted to the MRI context (to minimise difficulties in data collection; for example, motion during scanning or loss of behavioural data): an auditory 2-BACK working memory task, which has been validated for its use in fMRI (Forn et al., 2007), and an interference-control Counting Stroop task (Bush et al., 2006). Moreover, these two tasks were adapted in difficulty terms to match the behavioural performance between the groups involved in the studies and to allow for a better interpretation of the functional data. This methodological approach confers validity to our functional results of the two cognitive studies because we could establish that the alterations in brain activation patterns in cocaine patients are associated with consumption-related cognitive deficit, but not with the fact that participants could have problems with task performance (Price et al., 2006; Li et al., 2008).

Cocaine chronic consumption is also related with the fact that brain anatomic alterations could affect the BOLD brain response (Aron and Paulus, 2007). Therefore in these two studies, we applied two neuroimaging analysis toolboxes to confer our results further experimental validity and significance, and also to facilitate the interpretation of the results. On the one hand, we applied the VBM toolbox to study the effects of grey matter volume on functional data by using, on the other hand, BPM to analyse the covariance effects between morphometric and functional data (Casanova et al., 2007).

Finally, the incentive processing/reward processing alterations in cocaine dependence could highlight the implication of dopaminergic subcortical limbic brain regions. These subcortical regions in tandem with cortical (prefrontal) areas represent the neural substrate of salience attribution to drug-related and non-drug related stimuli (Goldstein and Volkow, 2002; Bjork et al., 2008; Volkow et al., 2011a). Reward brain circuits become hypersensitive to drug effects and to drug-associated stimuli (Robinson and Berridge, 2003). There are some studies (Maas et al., 1998; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Wexler et al., 2001; Bonson et al., 2002; Grant et al., 1996; Wang et al., 1999) which reveal a sensitised functional brain system when cocaine patients process drug-related stimuli. Yet, as mentioned before, there are very few studies which attempt to elucidate the neurofunctional affectation of non-drug reward processing (Goldstein et al., 2007a; Asensio et al., 2010; Jia et al., 2011). Specifically, our fourth study is an attempt to provide empirical evidence of possible alterations in monetary reward processing in cocaine dependence by applying an adapted version of the Monetary Incentive Delay task (MIDT) developed by Knutson et al. (2001).

Cocaine addiction has a clear relapsing nature (Connolly et al., 2012). A significant proportion of treatment-seeking cocaine-dependent individuals do not achieve long-term abstinence (Ahmadi et al, 2006; Carroll, 1997; Dutra et al, 2008; Elkashef et al, 2007; Knapp et al, 2007; Shearer, 2007). Impaired neurocognitive performance linked to regional brain functions has been implicated in the poor outcome of behavioural therapy for cocaine dependence (Xu et al., 2010). Brain activation may be a more sensitive measure than self-report or task performance assessments for predicting treatment outcomes (Brewer et al., 2008). Thus, it is interesting to study the

relationship between functional effects and treatment-related variables to help interpret the results and to render them clinical significance based on therapeutic-related brain changes and their implication in abstinence maintenance or relapse. As reported before, very little is known about the neurobiology of successful long-term abstinence, and as others have reported, time of abstinence could modulate brain functions in patients (Moeller et al., 2010). There are only two studies that conclude that functional dysregulation related with cognitive control demands may be partly recovered with protracted cocaine-free periods in cocaine abstinents (Connolly et al., 2012; Moeller et al., 2012). Conversely, there are no studies into the long-term abstinence effects on functional effects during reward processing in reward-related dopaminergic brain areas such as the striatum. Thus, we propose to characterise brain striatal functioning in motivational-reward processing of those who become abstinent for long periods. Moreover, in order to know which neurofunctional and neurostructural implications have variables related with severity of illness (e.g., number of years of consumption or onset age of consumption), in all our studies, we have done exploratory correlation analyses between functional and structural effects, and those variables confer more clinical significance to the results.

To summarise, the doctoral thesis that I present studies the neurobiological basis of the two main components that conceptualise the vicious circle of addiction (Goldstein and Volkow, 2002): alteration of salience attribution to non-drug-related stimuli and cognitive control. The first study explores the possible structural alterations related with cocaine addiction. The next two studies are based on analysing altered brain pattern activation in cocaine patients during two complex cognitive processes: working memory and interference control. The last study also examines altered brain pattern activation in cocaine patients during a motivational task related with monetary reward processing by taking in account the possible effects of abstinence on brain functioning.

2.1.1.Objectives and hypotheses

The general aim of this work is to elucidate the neurobiological substrates that implicate alterations in cognitive and motivational processing in cocaine addiction that lead to maintainance of compulsive drug-seeking behaviours, and also their possible treatment-related implications. The specific aims are to:

- Detect structural changes in important subcortical structures, such as the striatum, in a cocaine-dependent group in comparison with a control group by means of VBM analyses.

- Compare the brain activation pattern between a comparison group and a cocaine-dependent group in an auditory verbal working memory task by matching both groups in the performance level of the task.

- Identify the brain regions that are differently involved in interference-control functioning for a cocaine group and a comparison group by applying a counting Stroop task and by matching both groups in terms of performance.

- Show striatal alterations in a cocaine dependent group and the neurofunctional changes of cocaine protracted abstinence on striatum activation during anticipation and reactivity to monetary outcomes in a cross-sectional study adapting the MIDT.

Regarding previous objectives, we have developed the following hypotheses:

- We would find GM volume changes in those brain areas that are functionally affected by cocaine addiction, which are dependent on dopaminergic neurotransmission, and which are mainly expected in the striatum.

- Cocaine-dependent patients would show reduced activation in the attentional-working memory brain system in comparison to a control group during an auditory working memory task.

- The cocaine-dependent group would show less activation in the frontoparietal areas involved in the Stroop effect, which are affected by cocaine dependence, if compared with controls.

- We would expect to find striatal functional differences between our cocaine patients group and the control group, and a regulation of striatum functionality during the monetary reward processing associated with abstinence and time on treatment.

In the next sections I will present the four studies that I include in this work to test the aforementioned hypotheses. The studies are to be presented with the same format they have been published in (the three first papers) and with which they have been submitted (the last paper).

Section 2.2. Barrós-Loscertales A., Garavan H., Bustamante J.C., Ventura-Campos N., Llopis J.J., Belloch V., Parcet M.A., Ávila C. (2011). Reduced striatal volumen in cocaine dependent patients. 'Neuroimage', 56, 1021-1026.

NeuroImage 56 (2011) 1021–1026

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Reduced striatal volume in cocaine-dependent patients

Alfonso Barrós-Loscertales [a,*], Hugh Garavan [b,c], Juan Carlos Bustamante [a], Noelia Ventura-Campos [a], Juan José Llopis [a], Vicente Belloch [a,d], María Antonia Parcet [a], César Ávila [a]

[a] Dpto. Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castellón de la Plana, Spain
[b] Institute of Neuroscience, School of Psychology, Trinity College Dublin, Dublin, Ireland
[c] Departments of Psychiatry and Psychology, University of Vermont, VT, USA
[d] Departamento de Radiología. ERESA, Valencia, Spain

ARTICLE INFO

Article history:
Received 8 October 2010
Revised 7 February 2011
Accepted 11 February 2011
Available online 19 February 2011

Keywords:
Cocaine
Addiction
Voxel-based morphometry
MRI
Striatum
Amygdala

ABSTRACT

Long-term cocaine consumption is associated with brain structural and functional changes. While the animal literature on cocaine use and dependence has traditionally focused on the striatum, previous human studies using voxel-based morphometry have reported reduced volumes of gray matter in several brain areas, but not in the striatum. Brain magnetic resonance imaging was performed with 20 cocaine-dependent patients and 16 healthy age-, education- and intelligence-matched control men. The cocaine-dependent group had lower gray matter volumes in the striatum and right supramarginal gyrus compared to controls. Within the cocaine-dependent group, years of cocaine use were inversely associated with the volume of the bilateral middle frontal gyrus, left superior frontal gyrus, parahippocampus, posterior cingulate, amygdala, insula, right middle temporal gyrus and cerebellum. These results show that cocaine dependence is associated with reduced gray matter volumes in the target structures of the dopaminergic system. These findings are the first to suggest reduced gray matter in the striatum by means of voxel-based morphometry in human users, thereby linking human results to animal models of addiction. In addition, the relationship between years of use and gray matter volumes in numerous brain regions are consistent with these volume reductions arising as a consequence of the cocaine use.

Introduction

Structural neuroadaptations in the central nervous system are related to the changes in behavior and brain function associated with cocaine dependence. Much of the research on these neuroadaptations has focused on dopamine circuitry and particularly on the ventral striatum (Koob et al., 1994; White and Kalivas, 1998). For example, animal and human studies have shown altered functional activity in the ventral striatum associated with cocaine consumption (Lyons et al., 1996; Porrino et al., 2002, 2007; Volkow et al., 2006; Risinger et al., 2005; Hanlon et al., 2009). Chronic effects of cocaine on the striatum have also been reflected in the concentration of dopamine receptors (Volkow et al., 1993), dendrites and dendritic spines (Robinson and Kolb, 2004). A central role for the striatum in drug addiction is suggested by its involvement in drug incentive salience processes (Robinson and Berridge, 2003, 2008), drug-related neuroadaptations (Koob and Le Moal, 2008), and in the proposed change in the locus of behavioral control from the ventral to dorsal striatum associated with drug-seeking behavior after chronic drug self-administration (see Everitt and Robbins, 2005; Everitt et al., 2008). Therefore, theories of addiction and the empirical animal literature lead to the prediction of changes in the striatum in cocaine-dependent patients.

Neurobiological differences related to cocaine addiction at the macrostructural brain level are widespread across the brain as shown by voxel-based morphometry (VBM). Previous studies on the morphometric changes associated with drug use and abuse which applied VBM have reported gray matter (GM) reductions in the volume of the orbitofrontal cortex, the anterior cingulate cortex, the insula, the superior temporal cortex (Matochik et al., 2003; Franklin et al., 2002; Lim et al., 2008) and the cerebellum (Sim et al., 2007). Although the studies cited above have suggested that structural changes should be found in the striatum, they have not been reported by means of VBM. It is possible that the micro-structural changes observed in animal studies may not be detectable by a macro-structural technique such as VBM. However, the possibility of detecting structural changes in important subcortical structures such as the striatum by means of this non-invasive tool in human studies would prove valuable as it could provide an assay of cocaine's effects while linking the human and animal literatures.

A few human studies on the structural changes associated with cocaine addiction have specifically analyzed brain volume differences in the striatum (Jacobsen et al., 2001; Martínez et al., 2004) by means of manual volume segmentation. Jacobsen et al. (2001) showed an

* Corresponding author at: Dpto. Psicología Básica, Clínica y Psicobiología, Avd. Vicente Sos Baynat s/n, Universitat Jaume I, 12071 Castellón, Spain.
E-mail address: barros@psb.uji.es (A. Barrós-Loscertales).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.02.035

increased volume of the caudate head and putamen while Martínez et al. (2004) found no such differences. This lack of consensus in human research may reflect methodological and sample characteristic differences between studies. Compared to these previous studies, the present investigation was restricted to a sample of cocaine-dependent males for two main reasons. First, gender considerably influences GM values, even in healthy subjects (Good et al., 2001; Giedd et al., 1996; Filipek et al., 1994; Ahsan et al., 2007); therefore limiting analyses to one gender should reduce unwanted variance. Second, and more importantly, gender differences in cocaine dependence have been described in perfusion abnormalities (Levin et al., 1994), treatment outcomes (Weiss et al., 1997), patterns of abuse (Griffin et al., 1989), situations that lead to consumption (Waldrop et al., 2007) and the brain's stress response (Li et al., 2005). Particularly, it seems that some cocaine-related phenomena, like craving, specifically involve the striatum in males (Kilts et al., 2004, 2001). Therefore, it seems plausible that cocaine neuroadaptations may depend on gender, and that striatum changes might be more pronounced in males. Therefore, we hypothesized that we would find GM volume changes in those brain areas functionally affected by cocaine addiction which are dependent on dopaminergic neurotransmission, and our main expectations focused on the striatum.

Methods and materials

Participants

Twenty male cocaine-dependent patients and 16 matched controls participated in this study. The cocaine patients were recruited from the Addiction Treatment Service of San Agustín in Castellón, Spain. The inclusion criteria included cocaine dependence based on the DSM-IV criteria. Control subjects were required to have no diagnosis of substance abuse or dependence. The exclusion criteria for all the participants included neurological illness, prior head trauma, positive HIV status, diabetes, Hepatitis C, or other medical illness and psychiatric diagnoses such as schizophrenia or bipolar disorder. Some patients reported a background of depressive symptoms ($n=3$), and anxiety symptoms ($n=3$), but never a DSM IV Axis I disorder, and these symptoms were absent at the time they were recruited and tested. The patients reported a history of consumption of other psychoactive drugs without involving dependence (Table 1). The control and patient groups did not differ in terms of the distribution of smokers (56% controls vs. 65% patients, $p>0.1$). Cocaine consumption was assessed with a urine toxicology test, which ensured a minimum period of abstinence of two to four days prior to MRI data acquisition. Groups were matched on the basis of age (mean controls $=33.38\pm-9.17$; patients $=33.30\pm6.94$), level of education (mean controls $=8.53\pm1.45$; patients $=9.20\pm1.70$ years) and general intellectual functioning (mean control $=10.86\pm2.58$; patients $=9.55\pm2.37$; standardized scores in the Matrix Reasoning Test from WAISIII; 32, Wechsler, 2001); there were no inter-group differences for any of these variables ($p>0.1$). All the participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971; Bryden, 1977). They all signed an informed consent prior to participating in the study.

Table 1
Descriptive scores for frequency of cocaine consumption and consumption patterns of other psychoactive substances without abuse in the cocaine-dependent group ($n=20$).

	n	Percentage
Daily frequency of cocaine consumption	8	40%
Frequency of cocaine consumption: 1–2 days/week	4	20%
Frequency of cocaine consumption: 3–5 days/week	6	30%
Frequency of cocaine consumption: weekends	2	10%
Cigarettes	13	65%
Alcohol	10	50%
Cannabis	4	20%
Amphetamines	1	5%
Heroin	0	0%
Other psychoactive substances	1	5%

n = number of subjects at the time of their first visit to the clinic.

MRI imaging

Images were acquired on a 1.5T Siemens Avanto (Erlangen, Germany) with a standard quadrature head coil. Subjects were placed in a supine position in the MRI scanner. A high resolution three-dimensional T1-weighted gradient echo pulse sequence was acquired (TE = 4.9 ms; TR = 11 ms; FOV = 24 cm; matrix = $256\times224\times176$; voxel size = $1\times1\times1$).

Image processing

Image processing was conducted with the voxel-based morphometry toolbox (Structural BrainMapping Group, Department of Psychiatry, University of Jena, http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/) implemented in Statistical Parametric Mapping (SPM5) running on Matlab® 7.0. VBM combined tissue segmentation, bias correction and spatial normalization into a unified model (Ashburner and Friston, 2005; Rosario et al., 2008). The parameter settings were: warp frequency cutoff to 25 mm, warping regularization light to (0.001), a thorough clean up of segmentations and a 1-mm^3 voxel size resolution for normalization. Iteratively weighted hidden Markov Random Fields (HMRF) were applied to improve the accuracy of tissue segmentation (Cuadra et al., 2005) by removing isolated voxels which were unlikely to be a member of a certain tissue class and closing hole in the clusters of connected voxels of a certain class, resulting in a higher signal to noise ratio of the final tissue probability maps (Koutsouleris et al., 2010). We did a visual inspection to check the accuracy of the segmentation in those areas where the distinction between gray and white matter is known to be problematic (e.g., thalamus and basal ganglia). Otherwise, default parameters were used (Rosario et al., 2008). Each subject's brain was normalized to the tissue probability maps provided by the International Consortium for Brain Mapping (ICBM, http://www.loni.ucla.edu/Atlases/). These transformations involve a first linear transformation and a second nonlinear shape transformation. Segmented GM images were modulated to restore tissue volume changes after spatial normalization. The GM images modulation was performed by multiplying the voxel intensities by the Jacobian determinant of the spatial transformation matrix derived from normalization. Modulated GM segmented images were corrected for nonlinear warping only (http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/), making correcting for total intracranial volume of the individual unnecessary (see Scorzin et al., 2008). Thus, global brain volume effects were removed from the data to allow inferences on local GM volume changes. An 8-mm FWHM Gaussian kernel was applied to the segmented GM maps.

Statistical and image analyses

Group differences were evaluated in an ANCOVA analysis with age as the covariate. An absolute threshold mask of .1 was used to restrict the analysis to gray matter tissue, thus equaling the use of an implicit mask. Statistical significance was defined at a statistical threshold at the voxel level of $p<0.001$ (uncorrected for multiple comparisons), and at an extent threshold of $p<0.05$, corrected for multiple comparisons with family-wise error (FWE). To ensure the validity of cluster-level statistics on smoothed data, a nonisotropic smoothness correction was applied (Hasayaka et al., 2004). This correction is related to a methodological issue about how smoothness on VBM data depends on the underlying anatomy in order to apply a cluster extent threshold (Ashburner and Friston, 2000). Thus, Random Field corrections for multiple dependent comparisons based on the extent statistic need the smoothness of the residuals to be spatially invariant

throughout the brain (Mechelli et al., 2005). This fact was solved by means of a nonstationary cluster extent correction (as implemented at http://dbm.neuro.uni-jena.de/vbm/non-stationary-cluster-extent-correction/) which adjusts the sensitivity of the test in accordance with image smoothness by means of a nonstationary permutation test (Hasayaka et al., 2004). Lastly, a limited set of exploratory correlations was performed between drug-use variables and the observed volumetric effects.

Results

Group differences

Whole brain voxel-wise analyses with an age-adjusted ANCOVA showed significantly reduced GM in the left striatum (x, y, z MNI coordinates = −5, 2, −1; T-value = 4.46, $p<0.001$; cluster size = 833) and the right supramarginal gyrus (x, y, z MNI coordinates = 50, −60, 32, T-value = 5.20, $p<0.001$; cluster size = 1086) for the cocaine group. Fig. 1 charts voxel means for these clusters revealing that the percentage of volume change between controls and patients was 14.8% for the striatum and 12.1% for the supramarginal gyrus. Opposite contrasts between groups (patients>controls) revealed no significant areas of increased GM volume in patients. Correlation analyses found no significant relationship between GM volumes in these two regions and the age of first cocaine use and years of cocaine use. Whole-brain voxel-wise regression analyses based on these same variables were then conducted and were thresholded at $p<0.001$ (uncorrected) and cluster-corrected with a threshold at $p<0.05$. The age of first cocaine use variable (mean = 19.60, SD = 5.97, ranging from 14 to 40) showed no positive or negative association with brain volume in any region. On the other hand, the years of cocaine use variable (mean = 13.2, SD = 5.97, ranging from 2 to 21 years) inversely related to local GM volumes in bilateral middle frontal gyri, left superior frontal gyrus, parahippocampus, posterior cingulate cortex, bilateral amygdala, parietal operculum (insula), right middle temporal gyrus and cerebellum (culmen) (T-values ranged from 5.95 to 4.53, see Table 2 and Fig. 2).

Table 2
Brain regions in which gray matter volume reduction was associated with years of cocaine use in the patient sample.

Brain region	Hemisphere	MNI coordinates	T-value	Cluster size
Middle frontal gyrus	R	49, 19, 25	5.95	702
	R	38, 27, 41	5.87	686
	R	30, 58, 24	5.81	1764
	L	−41, 32, 31	5.39	951
Superior frontal gyrus	R	25, 41, 40	5.48	859
Amygdala	L	−18, 2, −17	5.41	1083
Posterior cingulate	L	−11, −49, 40	5.16	655
Amygdala/parahippocampus	R	23, −5, −24	4.97	1274
Uncus	R	31, 7, −26	4.67	1498
Middle temporal gyrus	L	−47, −72, 25	4.54	770
Insula	L	−43, −18,1	4.53	700
Cerebellum	R	32, −38, −33	4.80	1121

Discussion

We provide the first evidence of gray matter (GM) volume reduction in the striatum of cocaine-dependent patients by means of VBM as well as a volume reduction in the right supramarginal gyrus. The detection of striatal volume reduction in the cocaine group in this report may be explained by sample characteristics or methodological improvements. For example, unlike prior studies that applied this same image-analysis technique (http://dbm.neuro.uni-jena.de/vbm/) to substance-dependence individuals (Tanabe et al., 2009), we applied an iterative weighting of a Hidden Markov Random Field to improve tissue segmentation (see Cuadra et al., 2005). Furthermore, we used a slightly lower spatial smoothing (8 mm in our case as opposed, for example, to 12 mm in Tanabe et al., 2009). In fact, when we applied a bigger spatial smoothing kernel (12-mm FWHM), the between-group structural differences disappeared (data not reported). This suggests that the choice of smoothing kernel and its relationship to the size of the structure under study can impact on the sensitivity of the analysis.

The striatum is identified as a key target structure in cocaine addiction. Volume differences in a given brain area related to drug use

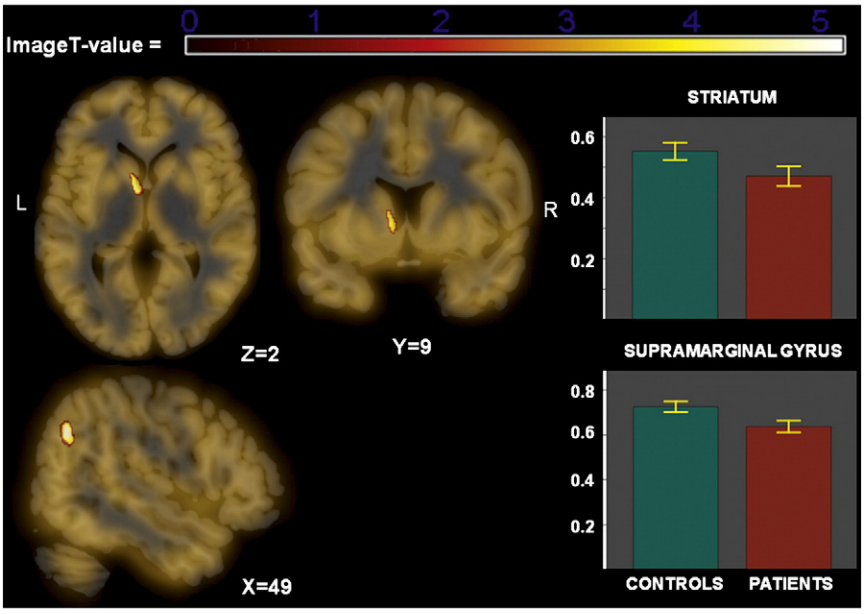


Fig. 1. Regions of reduced gray matter volume in cocaine-dependent patients compared to matched controls. Footnote: Golden gray matter volume maps are shown overlapped on T1 template from MRIcroN. Image T-value bar represents statistical t-contrast values for significant voxels within the image. Left is left. Charts represent the mean gray matter volumes of those voxels within the clusters which show a significant difference from a confirmatory ROI analysis.

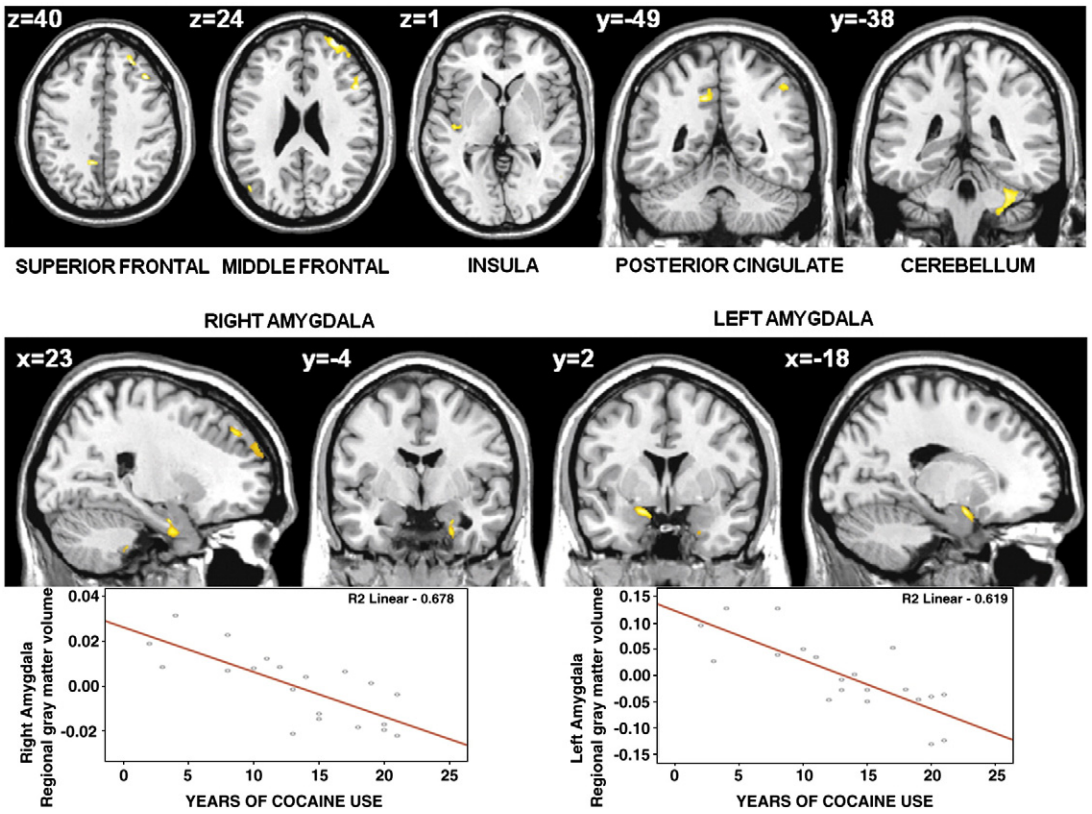


Fig. 2. The related mean-centered volume of the bilateral amygdala with the years of cocaine abuse variable and other region-related volumes. The X-, Y- and Z-related MNI coordinates for each coronal, saggital and axial slice, respectively.

may affect functional activation as measured by brain BOLD patterns (Aron and Paulus, 2007). Thus, the cell numbers in a structure as reflected by its volume measure would be important for capillary recruitment associated with brain activity (Makris et al., 2004), suggesting a reduced functionality in an area of reduced volume. In line with this idea, different fMRI studies have shown cognitive (Garavan et al., 2008), motivational (Goldstein et al., 2007; Garavan et al., 2000) and motor (Hanlon et al., 2009) deficits in cocaine dependent patients which directly related with either striatum functionality or other dopamine-mediated regions. On the other hand, the right supramarginal gyrus function has been related to executive functioning and craving in this population (Garavan et al., 2000). Furthermore, early reports suggest GM recovery in the right supramarginal gyrus after cocaine abstinence (Connolly et al., 2009).

We did not find regions of significantly increased GM in the cocaine group compared with controls. In contrast, other previous studies report a quantitative volumetric increase of the GM volume in the caudate and putamen of cocaine addicts (Jacobsen et al., 2001) or a lack of differences (Martínez et al., 2004) by means of ROI-based methods. Jacobsen et al. (2001) used volumetric measures by manually outlining the caudate head and body as a single structure, while our analyses were based on voxel-wise statistics. Their cocaine and control group samples were equal in numbers of males and females, but differed in terms of the racial ratio (Caucasian-African American) whereas the present sample contained only Caucasian males. Jacobsen and colleagues reported that race was apparently important for the effect of cocaine dependence on caudate volume because when this variable was regressed out, the group difference was no longer significant. Furthermore, Jacobsen et al. (2001) reported a mean 2-week period of abstinence in the cocaine group; however, we cannot assume abstinence of more than two to four days given the sensitivity of the urine test (Vearrier et al., 2010). Therefore, methodological and sample differences may explain the apparent contradiction between the present results and the small extant literature.

Another discrepancy between the present and previous results (e.g., Makris et al., 2004; Sim et al., 2007) is the relative scarcity of between-group GM volume differences in other brain areas. In light of the sizeable numbers of regions that showed significant relationships between years of cocaine use and volume, we surmise that the variability within the cocaine group that drove these correlations served to reduce the statistical power to detect between-group effects. These structures (the amygdalae, the lateral prefrontal cortex, the insula and the posterior cingulate) have all been implicated in cocaine addiction and craving (Grant et al., 1996; Bonson et al., 2004). Cognitive control-related activation in the lateral prefrontal cortex and the posterior cingulate regions have been identified as predictors of treatment outcome in a sample of cocaine dependent patients (Brewer et al., 2008), the structural changes associated with the insula are in agreement with the role this region may play in interoception and awareness in addiction (Naqvi et al., 2007; Garavan, 2010; Volkow et al., 2010) while reduced GM volume in the amygdalae of cocaine addicts has previously been reported by Makris et al. (2004). In contrast to these regions showing a relationship between volume and years of use, the striatum showed no such relationship but did show a significant between-group difference. This suggests either a neuroadaptation that occurs relatively early in use (i.e., one that does not continue to deteriorate with continued years of use) or a pre-existing condition that might predispose to cocaine abuse or addiction (Nader and Czoty, 2005; Dalley et al., 2007). Future longitudinal studies that assess the emergence of structural volume changes in the striatum as an effect of cocaine exposure will better characterize these relationships. Likewise, it would be useful to know the functional correlates of the reduced striatal volumes of the patients. Although the present study did not include a psychometric psychological/cognitive assessment, the reduced volumes are plausibly related to

the deficits that are well known in cocaine addicts, such as impulsivity or compulsivity.

As far as we are aware, this study is the first to analyze the structural volumetric differences of a male-only cocaine group; an earlier study (Franklin et al., 2002) focused on structural gray matter concentration or density in male cocaine-dependent patients. Whereas the gray matter concentration measure used by Franklin and colleagues reflected the proportion of gray matter in relation to all other tissue types within each voxel, the present study employed a volumetric measure which is optimal for identifying regional differences (the modulation step compensated for spatial expansion or shrinkage when warping to a standard space) (Good et al., 2001). The volumetric measure is thought to reflect volume differences since the relative concentration of gray matter, coded in intensities of voxels (the concentration measure), is corrected by the relative spatial transformations before and after normalization allowing inferences about volume (Mechelli et al., 2005). Otherwise, restricting the present study to males had the advantage of maximizing the homogeneity of the cocaine group, this selection limits the scope of the present results. Further research will test whether gender differences contribute to the structural changes associated with cocaine addiction. The screening for alcohol and cannabis consumption habits was not considered in the control group, and may involve structural effects on the cohorts as reported by previous studies (Lorenzetti et al., 2010; Mechtcheriackof et al., 2007; Fein et al., 2006). In the case of cannabis and amphetamine, as they involved a small group of participants of our already small cocaine group, we excluded them from the control group and repeated the analyses. Excluding the patient who reported amphetamine use did not change the results. Moreover, excluding the four cannabis users from the cocaine group ($n = 16$) did not significantly change the statistical significance value of the difference ($p < 0.001$, uncorrected), but slightly lessened the statistical significance of the cluster extent ($p < 0.052$, FWE-corrected). The reduced effect of excluding these four patients from the cocaine group may be due to a similar unknown use of cannabis in the control group, or more probably to the effect of losing degrees of freedom in the statistical model. Other limitations of the study relate to the colinearity between the years of cocaine use and age variables in the cocaine group. Logically, older individuals had been consuming cocaine for more years than younger ones. One solution for the colinearity effects would be to recruit a cohort of cocaine addicts of similar ages, but of a wide range of years of cocaine use. That said, all areas with the exception of the insula continued to show a significant relationship to years of cocaine use when age was included in a multiple regression analysis. Another matter for consideration was the size of the isotropic Gaussian kernels applied in this study. Usually, smoothing kernels in VBM studies range from 8 to 12 mm (Ashburner, 2009). It is likely that the use of a reduced kernel in our dataset favored the detection of significant effects in smaller sized regions (e.g., striatum) (Mechelli et al., 2005). Likewise, smoothing compensates for the imperfect registration of spatial normalization, and it is necessary to apply bigger kernels for less intersubject accuracy during normalization (Ashburner, 2009). This effect was seen to be particularly important for a region like the striatum, in which systematic ventricles dilation and, consequently, misregistration led to a significantly reduced volume of the striatum in a sample of patients with Herpes Simplex Encephalitis (Gitelman et al., 2001). However, other studies on samples with no systematic dilation of the ventricles have reported differences in the striatum between a patient group and a matched control group (e.g., Lázaro et al., 2009; Huey et al., 2009). Replicating these results is the best approach to compensate this tradeoff.

In conclusion, we report reduced GM volume in the striatum, a target structure in cocaine addiction, dependent behavior and motivation, but also in the supramarginal gyrus. Likewise, another set of cortical and subcortical structures, such as the amygdalae, the insula and dorsolateral prefrontal cortex, were seen to have volume reductions related to years of cocaine exposure. All these structural changes associated with cocaine addiction seem to merge in the striato-cortico-limbic circuitry linked not only to addiction, but also to the wider set of disinhibitory disorders. Although causal relationships are very difficult to determine in human studies, the significant relationship between years of use and reduced GM volumes are consistent with these volumetric effects arising from the cumulative exposure to cocaine or the concomitant lifestyle (e.g., stress) that accompanies prolonged drug use (Yücel et al., 2008).

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgments

We thank the professional group at the Addictive Behaviors Unit San Agustín of Castellón (UCA, Unidad de Conductas Adictivas San Agustín de Castellón) for their collaboration. This study was supported by grants from FEPAD (Fundación para el Estudio, Prevención y Asistencias a la Drogodependencia), from the "National Plan of Drugs" (Plan Nacional de Drogas) and from the funding agency CONSOLIDER-INGENIO 2010 Program (CSD2007-00012).

References

Ahsan, R.L., Allom, R., Gousias, I.S., Habib, H., Turkheimer, F.E., Free, S., et al., 2007. Volumes, spatial extents and a probabilistic atlas of the human basal ganglia and thalamus. Neuroimage 38, 261–270.
Aron, J.L., Paulus, M.P., 2007. Location, location: using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. Addiction 102 (1), 33–43.
Ashburner, J., 2009. Computational anatomy with the SPM software. Magn. Reson. Imaging 27, 1163–1174.
Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.
Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. Neuroimage 11, 805–821.
Bonson, K.R., Grant, S.J., Contoreggi, C.S., Links, J.M., Metcalfe, J., Lloyd, W., Kurian, V., Ernst, M., London, E.D., 2004. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology 26, 376–386.
Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Potenza, M.N., 2008. Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. Biol. Psychiatry 65, 998–1004.
Bryden, M.P., 1977. Measuring handedness with questionnaires. Neuropsychologia 15, 617–624.
Connolly, C.G., Bell, R., Jones, J., Nierenberg, J., Hoptman, M., Butler, P., et al., 2009. Changes in grey matter volumes related to cocaine abstinence. Neuroimage 47, S39–S41 (Abstracts: Organization for Human Brain Mapping 2009 Annual Meeting).
Cuadra, M.B., Cammoun, L., Butz, T., Cuisenaire, O., Thiran, J.P., 2005. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. IEEE Trans. Med. Imaging 24, 1548–1565.
Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Lääne, K., et al., 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315, 1267–1270.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.
Everitt, B.J., Belin, D., Economidou, D., Pelloux, Y., Dalley, Y., Jeffrey, W., et al., 2008. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addition. Philos. Trans. R. Soc. Lond. B Biol. Sci. 363, 3125–3135.
Fein, G., Landman, B., Tran, H., McGillivray, S., Finn, P., Barakos, J., Moon, K., 2006. Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. Neuroimage 32, 1465–1471.
Filipek, P.A., Richelme, C., Kennedy, D.N., Caviness Jr., V.S., 1994. The young adult human brain: an MRI-based morphometric analysis. Cereb. Cortex 4, 344–360.
Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., et al., 2002. Decreased gray matter concentration in the insular, orbitofrontal, cingulated and temporal cortices of cocaine patients. Biol. Psychiatry 51, 134–142.
Garavan, H., 2010. The insula and drug cravings. Special issue on Insula. Brain Struct. Funct. 214, 593–601.
Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.K., Sperry, L., Ross, T.J., et al., 2000. Cue-induce cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am. J. Psychiatry 157, 1789–1798.
Garavan, H., Kaufman, J.N., Hester, R., 2008. Acute effects of cocaine on the neurobiology of cognitive control. Philos. Trans. R. Soc. Lond. B Biol. Sci. 363, 3267–3276.

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., et al., 1996. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb. Cortex 6, 551–560.
Gitelman, D.R., Ashburner, J., Friston, K.J., Tyler, L.K., Price, C.J., 2001. Voxel-based morphometry of herpes simplex encephalitis. Neuroimage 13, 623–631.
Goldstein, R.Z., Tomasi, D., Alia-Klein, N., Zhang, L., Telang, F., Volkow, N.D., 2007. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am. J. Psychiatry 164, 43–51.
Good, C.D., Johnsrude, I., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 14, 685–700.
Grant, S., London, E.D., Newlin, D.B., Villemagne, V.L., Liu, X., Contoreggi, C., Phillips, R.L., Kimes, A.S., Margolin, A., 1996. Activation of memory circuits during cue-elicited cocaine craving. Proc. Natl Acad. Sci. USA 93, 12040–12045.
Griffin, M.L., Weiss, R.D., Mirin, S.M., Lange, U., 1989. A comparison of male and female cocaine abusers. Arch. Gen. Psychiatry 46, 122–126.
Hanlon, C.A., Wesley, M.J., Porrino, L.J., 2009. Loss of functional specificity in the dorsal striatum of chronic cocaine users. Drug Alcohol Depend. 102, 88–94.
Hasayaka, S., Phan, K.L., Liberzon, I., Worsley, K.J., Nichols, T.E., 2004. Nonstationary cluster-size inference with random field and permutation methods. Neuroimage 22, 676–687.
Huey, E.D., Pardini, M., Cavanagh, A., Wassermann, E.M., Kapogiannis, D., Spina, S., et al., 2009. Association of ideomotor apraxia with frontal gray matter volume loss in corticobasal syndrome. Arch. Neurol. 66, 1274–1280.
Jacobsen, L.K., Giedd, J.N., Gottschalk, C., Kosten, T.R., Krystal, J.H., 2001. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. Am. J. Psychiatry 158, 486–489.
Kilts, C.D., Schweitzer, J.B., Quinn, C.K., Gross, R.E., Faber, T.L., Muhammad, F., et al., 2001. Neural activity related to drug craving in cocaine addiction. Arch. Gen. Psychiatry 2001 (58), 334–341.
Kilts, C.D., Gross, R.E., Ely, T.D., Drexler, K.P., 2004. The neural correlates of cue-induced craving in cocaine-dependent women. Am. J. Psychiatry 161, 233–241.
Koob, G.F., Le Moal, M., 2008. Neurobiological mechanisms for opponent motivational processes in addiction. Philos. Trans. R. Soc. B 363, 3113–3123.
Koob, G.F., Caine, B., Markou, A., Pulvirenti, L., Weiss, F., 1994. Role for the mesocortical dopamine system in the motivating effects of cocaine. NIDA Res. Monogr. 145, 1–18.
Koutsouleris, N., Gaser, C., Bottlender, R., Davatzikos, C., Decker, P., Jäger, M., Schmitt, G., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2010. Use of neuroanatomical pattern regression to predict the structural brain dynamic of vulnerability and transition to psychosis. Schizophr. Res. 123, 175–187.
Lázaro, L., Bargalló, N., Castro-Fornielles, J., Falcón, C., Andres, S., Calvo, R., Junqué, C., 2009. Brain changes in children and adolscents with obsessive-compulsive disorder before and after treatment: a voxel-based morphometric MRI study. Psychiatry Res. 172, 140–146.
Levin, J.M., Holman, B.L., Mendelson, J.H., Teoh, S.K., Garada, B., Johnson, K.A., et al., 1994. Gender differences in cerebral perfusion in cocaine-abuse: technetium-99m-HMPAO SPECT study of drug abusing women. J. Nucl. Med. 35, 1902–1909.
Li, C.S., Kosten, T.R., Sinha, R., 2005. Sex differences in brain activation during stress imagery in abstinent cocaine users: a functional magnetic resonance imaging study. Biol. Psychiatry 57, 487–494.
Lim, K.O., Wozniak, J.R., Mueller, B.A., Franc, D.T., Specker, S.M., Rodriguez, C.P., Silverman, A.B., Rotrosen, J.P., 2008 Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug Alcohol Depend. 92, 164–172.
Lorenzetti, V., Lubman, D.I., Whittle, S., Solowij, N., Yücel, M., 2010. Structural MRI findings in long-term cannabis users: what do we know? Subst. Use Misuse 45, 1787–1808.
Lyons, D., Friedman, D.P., Nader, M.A., Porrino, L.J., 1996. Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. J. Neurosci. 16, 1230–1238.
Makris, N., Gasic, G.P., Seidman, L.J., Goldstein, J.M., Gastfriend, D.R., Elman, I., et al., 2004. Decreased absolute amygdale volume in cocaine addicts. Neuron 44, 729–740.
Martínez, D., Broft, A., Foltin, R.W., Slifstein, M., Hwang, D.-R., Huang, Y., et al., 2004. Cocaine dependence and D2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. Neuropsychopharmacology 29, 1190–1202.
Matochik, J.A., London, E.D., Eldreth, D.A., Cadet, J.L., Bolla, K.I., 2003. Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance study. Neuroimage 19, 1095–1102.
Mechelli, A., Price, C.J., Friston, K.J., Ashburner, J., 2005. Voxel-based morphometry of the human brain: methods and applications. Curr. Med. Imaging Rev. 1, 105–113.
Mechtcheriackof, S., Brenneis, C., Egger, K., Koppelstaetter, F., Schocke, M., Marksteiner, J., 2007. A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. J. Neurol. Neurosurg. Psychiatry 78, 610–614.
Nader, M.A., Czoty, P.W., 2005. PET imaging of dopamine D2 receptors in monkey models of cocaine abuse: genetic predisposition versus environmental modulation. Am. J. Psychiatry 162, 1473–1482.
Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A., 2007. Damage to the insula disrupts addiction to cigarette smoking. Science 315, 531–534.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Porrino, L.J., Lyons, D., Miller, M.D., Smith, H.R., Friedman, D.P., Daunais, J.B., et al., 2002. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. J. Neurosci. 22, 7687–7694.
Porrino, L.J., Smith, H.R., Nader, M.A., Beveridge, T.J., 2007. The effects of cocaine: a shifting target over the course of addiction. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 1593–1600.
Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., Hoffmann, R.G., et al., 2005. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. Neuroimage 26, 1097–1108.
Robinson, T.W., Berridge, K.C., 2003. Addiction. Annu. Rev. Psycol. 54, 25–53.
Robinson, T.W., Berridge, K.C., 2008. The incentive sensitization theory of addiction: some current issues. Philos. Trans. R. Soc. B 363, 3137–3146.
Robinson, T.E., Kolb, B., 2004. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47, 33–46.
Rosario, B.L., Ziolko, S.K., Weissfeld, L.A., Price, J.C., 2008. Assessment of parameter settings for SPM5 spatial normalization on structural MRI data: application to type 2 diabetes. Neuroimage 41, 363–370.
Scorzin, J.E., Kaaden, S., Quesada, C.M., Müller, C.-A., Fimmers, R., Urbach, H., Schramm, J., 2008. Volume determination of amygdala and hippocampus at 1.5 and 3.0T MRI in temporal lobe epilepsy. Epilepsy Res. 82, 29–37.
Sim, M.E., Lyoo, I.K., Streeter, C.C., Covell, J., Sarid-Segal, O., Ciraulo, D.A., et al., 2007. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology 32, 2229–2237.
Tanabe, J., Tregellas, J.R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., et al., 2009. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. Biol. Psychiatry 65, 160–164.
Vearrier, D., Curtis, J.A., Greenberg, M.I., 2010. Biological testing for drugs of abuse. EXS 100, 489–517.
Volkow, N.D., Fowler, J.S., Wang, G.-J., Hitzemann, R., Logan, J., Schlyer, D., et al., 1993. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14, 169–177.
Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Childress, A.R., et al., 2006. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J. Neurosci. 26, 6583–6588.
Volkow, N.D., Fowler, J.S., Wang, G.J., Telang, F., Logan, J., Jayne, M., et al., 2010. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. Neuroimage 49, 2536–2543.
Waldrop, A.E., Back, S.E., Brady, K.T., Upadhyaya, H.P., McRae, A.L., Saladin, M.E., 2007. Daily stressors sensitivity, abuse effect and cocaine use in cocaine dependence. Addict. Behav. 32, 3015–3025.
Wechsler, D., 2001. Weschler Intelligence Scale for Adults, WAIS-III (Escala de Inteligencia de Wechsler Para Adultos-III, WAIS-III). TEA Ediciones, Madrid.
Weiss, R.D., Martínez-Raga, J., Griffin, M.L., Greefield, S.F., Hufford, C., 1997. Gender differences in cocaine dependent patients: a 6 month follow-up study. Drug Alcohol Depend. 44, 35–40.
White, F.J., Kalivas, P.W., 1998. Neuroadaptations involved in amphetamine and cocaine dependence. Drug Abuse Depend. 51, 141–153.
Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., et al., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. Arch. Gen. Psychiatry 65, 694–701.

Section 2.3. Bustamante J.C., Barrós-Loscertales A., Ventura-Campos N., Sanjuán A., Llopis J.J., Parcet M.A., Ávila C. (2011). Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task. 'Brain Research', 1375, 111-119.

BRAIN RESEARCH 1375 (2011) 111–119

available at www.sciencedirect.com

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task

Juan-Carlos Bustamante[a,*,1], Alfonso Barrós-Loscertales[b,1], Noelia Ventura-Campos[c], Ana Sanjuán[c], Juan-José Llopis[d,e], María-Antonia Parcet[f], César Ávila[g]

[a]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2242DL, 12071, Castellón de la Plana, Spain
[b]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2241DD, 12071, Castellón de la Plana, Spain
[c]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2212DL, 12071, Castellón de la Plana, Spain
[d]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2240DD, 12071, Castellón de la Plana, Spain
[e]UCA (Unidad de Conductas Adictivas San Agustín de Castellón), Av. Diputación, s/n, 12004, Castellón de la Plana, Spain
[f]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2206DD, 12071, Castellón de la Plana, Spain
[g]Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Av. de Vicent Sos Baynat, s/n, Room: HC2205DD, 12071, Castellón de la Plana, Spain

ARTICLE INFO

Article history:
Accepted 11 December 2010
Available online 21 December 2010

Keywords:
Cocaine
Functional magnetic resonance imaging
Parietal cortex
Attention
Working memory
Behavioral performance

ABSTRACT

It has been suggested that cocaine addiction affects the engagement of the frontoparietal networks in executive functions, such as attention and working memory. Thus, our objective was to investigate brain differences between cocaine-dependent subjects and healthy controls during the performance of a verbal working memory task. Nineteen comparison men and nineteen cocaine-dependent men performed a 2-back task. Data were acquired on a 1.5-T Siemens Avanto. Image processing and statistical analyses were carried out using SPM5; Biological Parametric Mapping (BPM) was used for further morphometric and correlation analyses. No performance differences were found between groups. However, the dorsal part of the right inferior parietal cortex (BA 40) was less activated in the cocaine-dependent group. Cocaine patients did not overactive any brain area when compared with controls. Our results show reduced activation in the brain areas related to the attention system in cocaine-dependent men while performing a verbal working memory task. Chronic cocaine use may affect the attentional system in the right parietal lobe, making patients more prone to attentional deficits.

* *Corresponding author*. Fax: +34 964729267.
E-mail addresses: jbustama@psb.uji.es (J.-C. Bustamante), barros@psb.uji.es (A. Barrós-Loscertales), venturan@psb.uji.es (N. Ventura-Campos), asanjuan@psb.uji.es (A. Sanjuán), jllopis@psb.uji.es (J.-J. Llopis), parcet@psb.uji.es (M.-A. Parcet), avila@psb.uji.es (C. Ávila).
[1] These two authors equally contributed to this work.

0006-8993/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2010.12.042

1. Introduction

Neuropsychological studies report that chronic stimulant-dependent subjects, such as cocaine addicts, have problems in executive tasks (Beatty et al., 1995; Mcketin and Mattick, 1997; Iwanami et al., 1998). These processes share the involvement of the frontoparietal networks at different degrees. A recent meta-analysis with neuropsychological data found that the principal differences between abstinent cocaine abusers and matched controls lay in attentional functioning (Jovanovski et al., 2005). Specifically, cocaine users perform poorly in measures of selective (Simon et al., 2000; Verdejo-García et al., 2005) and sustained attention (Morgan et al., 2006). It is known that such functions involve the parietal, frontal, and anterior cingulate cortices (Cabeza and Nyberg, 2000).

Cocaine addiction has been suggested to affect the engagement of the frontoparietal networks in attention (Hester and Garavan, 2004; Tomasi et al., 2007; Kubler et al., 2005). Tomasi et al. (2007) showed the involvement of the frontoparietal network during a working memory task and noted performance differences between groups. The frontal and parietal regions were seen to be hyperactivated in cocaine-dependent patients. Particularly, right parietal activation lowered as memory load increased (Hester and Garavan, 2004; Tomasi et al., 2007). These results were interpreted as a larger involvement of frontoparietal networks to support working memory in cocaine-dependent patients as a compensatory mechanism of performance deficits. However, an equivalent performance between groups of participants is particularly important in this kind of study since (1) it reduces the number of false-positive and false-negative activations (Murphy and Garavan, 2004), (2) group differences in performance can create artifactual differences in activation patterns (Kubler et al., 2005; Murphy and Garavan, 2004), (3) abnormal functional activations are difficult to interpret as a cause or a consequence of the performance deficit (Price and Friston, 1999).

Another possible source of variability in cocaine addiction is the transient change in the reduction of gray matter volume. Several studies have found a reduction in gray matter volume in the frontal and cingulate areas (Lim et al., 2008; Matochik et al., 2003; Tanabe et al., 2009), and more importantly, this reduction positively correlates with impaired performance in frontal tests (Tanabe et al., 2009; Fein et al., 2002). Assumedly, underlying anatomy is a related factor with brain functionality but is rarely taken into account jointly with functional activations. Therefore, beyond the interactions between task-related activation and level of performance, anatomical differences should be carefully controlled to obtain conclusive results (Barrós-Loscertales et al., 2008; Casanova et al., 2007).

The aim of this study is to compare the brain activation patterns between a comparison group and a cocaine-dependent group in an auditory verbal working memory task. In order to better interpretation of functional differences, good performance on 2-back tasks was expected of all the subjects and individual differences in gray matter volume were controlled within regions of functional differences. Typically, 2-back tasks yield bilateral and wide activations in the frontoparietal networks and the anterior cingulate. As neuropsychological tests reveal, specific attentional (but not working memory) problems in cocaine-dependent men, we hypothesized that cocaine-dependent patients would show reduced activation in the shared attention-working memory brain areas.

2. Results

Table 1 shows the behavioral results obtained during the functional Magnetic Resonance Imaging (fMRI) experiment. As expected, a repeated measure 2 condition (0-back, 2-back)×2 group (controls, patients) ANOVA analysis showed no group effect. There was only a significant condition effect in the accuracy and response time (RT) data ($p<0.01$) with more errors and longer RTs in the 2-back condition than in the 0-back condition for both groups. The interaction group×condition analysis was not significant.

Both the comparison group and the cocaine-dependent group showed a similar activation pattern in the [2-back>0-back] condition contrast (see Table 2, Fig. 1), which is in agreement with previous studies in our research group (Forn et al., 2007a, 2007b) as well as another (Tomasi et al., 2007). Regression analyses using first-used-cocaine age and years of cocaine use as covariates did not present any significant association with task-related activation ($p>0.01$).

The comparison made between groups revealed that the right inferior parietal cortex was more activated in the comparison group than in the cocaine-dependent group ($p<0.001$, uncorrected; activation cluster size threshold (k)=20; $Z=4.00$ at the local maximum $x, y, z=53, -36, 40$); see Fig. 2a. Notice that this result is not significant at an *a priori* defined FWE corrected cluster extend threshold (see Experimental procedures section). In order to test for the effects on functional activation of the transient changes of gray matter volume reduction due to cocaine addiction, we conducted a voxelwise gray matter volume correlation with functional activation within the restricted ROI (right inferior parietal cortex) for each group separately. These analyses did not report any significant association ($p>0.01$). Furthermore, anatomical differences in terms of GMV were not present before a threshold of $p>0.02$ was reached. However, when gray matter volume effects were regressed out in the ANCOVA analysis, the statistical significance increased the magnitude and size of functional effect cluster surviving a FWE correction at cluster level ($p<0.05$, FWE corrected; $Z=4.77$ at the local maximum $x, y, z=60, -42, 39$; $k=125$ when a FWE-corrected cluster extent threshold at $p<0.05$ was set at 54 voxels/cluster) in the right inferior parietal cortex (Fig. 2b). There was no other focal point of significant functional differences between groups across the whole brain when applying a $p<0.001$, uncorrected.

3. Discussion

The results of our study show differences in the pattern of brain activation in the right inferior parietal cortex (BA40) in a cocaine-dependent group compared to a matched control group during a working memory task, while task performance did not differ between groups. Moreover, we show that the

Table 1 – Mean scores (standard deviations in parentheses) of the main demographic characteristics and the behavioral results of the percentage of correct responses, percentage of commissions, and response time (RT) of the cocaine-dependent and comparison groups.

	Comparison group $n=15$	Cocaine-dependent group $n=15$	Difference ($p>0.05$) [a]
Age	34.20 (8.86)	32.40 (7.56)	n.s.
Years of education	8.53 (1.46)	9.00 (1.73)	n.s.
General intellectual functioning [b]	10.87 (2.59)	9.27 (2.31)	n.s.
Percentage of correct responses (0-back condition) [c]	99.39% (2.35)	100% (0)	n.s.
Percentage of correct responses (2-back condition) [c]	88.49 % (6.40)	87.88 % (8.87)	n.s.
Percentage of commissions (0-back condition) [d]	0.33% (0.69)	0.56% (0.81)	n.s.
Percentage of commissions (2-back condition) [d]	2.99% (3.42)	3.10% (3.00)	n.s.
RT (0-back condition) [e]	540.85 (51.67)	531.76 (96.84)	n.s.
RT (2-back condition) [e]	711.36 (91.20)	700.16 (128.02)	n.s.

[a] Differences between groups (n.s.=no significance).
[b] Standard score in the Matrix Reasoning test (WAIS-III).
[c] Percentage obtained from the total of possible correct responses for each condition (over 11 possible correct).
[d] Percentage obtained over the total of possible commissions for each condition (over 58 possible commissions).
[e] In milliseconds.

existence of individual variability in gray matter volumes could increase the magnitude and size of the functional effect cluster, likely due to better modeling of anatomically related variance (Oakes et al., 2007). Cocaine addiction is related to spread reductions in gray matter density and volume in the frontal, parietal, temporal lobes (Matochik et al., 2003; Tanabe et al., 2009; Franklin et al., 2002), and the cerebellum (Sim et al., 2007), as well as frontal (Lim et al., 2002, 2008), insular (Lyoo et al., 2004), and callosal (Moeller et al., 2005) white matter. Gray and white matter changes may have important effects on functional brain activation. Thus, functional differences between groups may be affected by structural changes. Therefore, we apply BPM as a good instrument to voxel-by-voxel control for anatomically related variance effects such as GMV effects or misalignment after spatial transformations in our data set (e.g., normalization). In our study, the covariation of structural effects increased the magnitude and size of the functional contrast between groups.

Overall, the *n*-back task shows the activation in the frontoparietal networks in both patients and matched controls, which coincides with previous reports of this task (Forn et al., 2007a, 2007b; Owen et al., 2005; McMillan et al., 2007). This pattern of activation reflects the joint activity of the lateral and medial premotor cortex, the dorsal cingulate, the dorsolateral and ventrolateral prefrontal cortex, the frontal poles, and the medial and lateral posterior parietal cortex when performing *n*-back tasks. When we compare the task-related activation between groups regressing out structural effects and taking into account that groups did not differ in terms of task performance, a consistently reduced activation in the right inferior parietal cortex is seen in patients. This result is in agreement with a previous study, which revealed the reduced activation in the parietal areas of cocaine-addict patients during attentional switching in the course of a verbal working-memory task when task performance was equaled between subgroups of the studied sample (Kubler et al., 2005).

Table 2 – Coordinates of the main brain activation during the 2-back task in both groups separately ($p<0.0001$, uncorrected; activation cluster size threshold (k)=16).

Brain region	Brodmann area	Comparison group			Cocaine-dependent group		
		Coordinates global maxima	Activation cluster size	z score	Coordinates global maxima	Activation cluster size	z score
Left inferior frontal gyrus	44/45/47	–45, 10, 22	375	5.74			
Right inferior frontal gyrus	44/45/47	39, 7, 30	491	5.19	45,10,24	92	4.83
Left middle Frontal gyrus	9/10/46	–45, 27, 24	570	5.65	–53, 13, 30	594	5.17
Right middle frontal gyrus	9/10/46	36, 47, 17	1005	5.71	36, 8, 41	203	4.86
Left medial frontal gyrus	6/8	–6, 31, 40	363	5.16			
Right medial frontal gyrus	6/32/8				9, 20, 43	159	4.82
Left inferior parietal cortex	40/7	–42, –36, 38	627	4.94	–42, –41, 46	399	5.33
Right inferior parietal cortex	7/39/40	50, –39, 41	778	5.54	33, –50, 41	656	5.78
Left superior temporal gyrus	21/22	–53, –32, 7	113	4.67			
Right superior temporal gyrus	21/22	56, –26, 4	152	5.05			
Left thalamus/left caudate		–12, 0, 0	294	4.88			
Right caudate		12, 4, 16	213	4.52			
Left cerebellum		–42, –65, –19	1511	5.33	–36, –57, –27	239	4.68
Right cerebellum					33, –59, –22	114	4.85

Coordinates global maxima in Talairach coordinates; z score=standardized score.

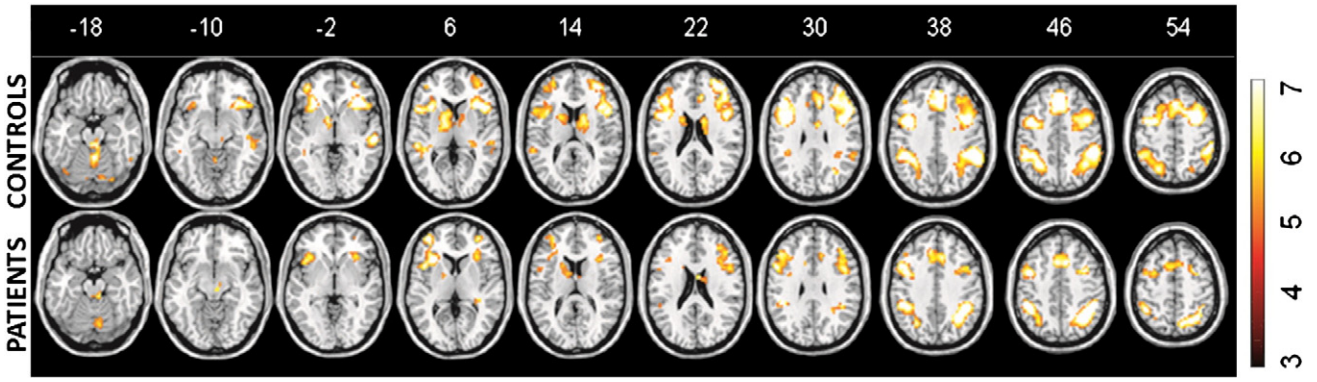


Fig. 1 – Main activation in the 2-back condition in both groups ($p<0.0001$, uncorrected; activation cluster size threshold (k)=16). Right is right. White labels (top) indicate the z-coordinate of each slice in the MNI frame of reference (0, 0, z). Bar plot represents z-values.

Our study replicates this previous result in a verbal working memory task without attentional switching contingencies, and moreover, it shows that gray matter volume variability can have an important effect on cognitive-related activations in a study that tests for functional deficits in cocaine-dependent patients.

Differential brain activation in a task can be interpreted in accordance with behavior, and it improves when recordings of brain activation and performance are done simultaneously. Cocaine dependence has been related to a wide range of cognitive and affective dysfunctions, and fMRI has proven to be an invaluable technique to study these drug-related changes (see Aron and Paulus, 2007, for a review). Abnormal functioning is usually associated with lower task performance in cocaine-dependent patients after long-term cocaine use. When assuming an actual executive functional deficit associated with cocaine dependence, the need for equal task performance in order to test for functional differences is proposed (Price et al., 2006). The results under these conditions may also help to better interpret functional differences when behavioral performance is not equaled. Thus, equal patient performance to a matched control group improves the interpretation of functional differences in the dysfunction sense. Furthermore, it reduces the caveat of an abnormal response or artifacts as a consequence of patients not being able to perform the task (Murphy and Garavan, 2004; Price and Friston, 1999; Price et al., 2006; Goldstein et al., 2009). Therefore, if patients are able to perform the task at the same level as controls, observed hypoactivation is not interpreted as a possible true or artifactual effect of task performance differences (e.g., are patients doing something different?), but as drug-related functional changes in the underlying neural circuitry affected after long-term drug consumption. Otherwise, the reduced activation in the patient group that equals the performance of a matched control group can be interpreted as more efficient neural processing, just as it has already been related to normal cognitive functioning (Mattay et al., 2003, 2006). However, it is difficult to be applied in this case since cocaine-dependent patients typically show cognitive deficits in executive tasks and reduced activations associated with a worse performance.

The right inferior parietal lobule maintains bidirectional connections to the right dorsolateral prefrontal cortex and anterior insular cortex and has been implicated in processes of

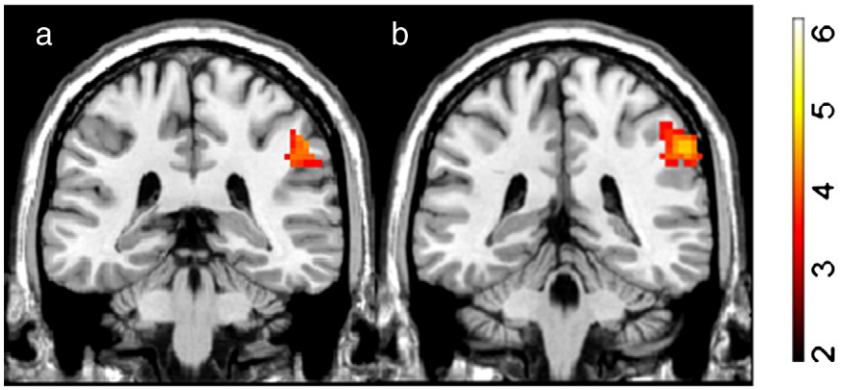


Fig. 2 – Comparison between groups in the 2-back condition ($p<0.001$, uncorrected; activation cluster size threshold (k)=20), see panel a, and comparison between groups in the 2-back condition when gray matter volume effects were regressed out ($p<0.05$, FWE corrected), see panel b. Right is right. Bar plot represents z-values.

sustained and selective attention, voluntary attentional control, inhibitory control, and switching (Corbetta and Shulman, 2002). Previous research with working memory tasks suggests that the dorsal part of the inferior parietal cortex may be part of a general executive attentional network (Chein et al., 2003; Corbetta et al., 2000; Wojciulik and Kanwisher, 1999). Specifically, Ravizza et al. (2004) proposed this role for this brain area in contraposition to the ventral part of the inferior parietal cortex that was more related to spatial processing. The different activation pattern at the right inferior parietal cortex in our study is consistent with previous fMRI results (Tomasi et al., 2007; Kubler et al., 2005), and it could be related with neuropsychological studies, showing the possibility that cocaine users perform poorly in measures of selective and sustained attention like other studies have shown (Simon et al., 2000; Verdejo-García et al., 2005; Pace-Schott et al., 2008). Notably, Tomasi et al. (2007) obtained inter-group performance differences and proposed that hyperactivation of the inferior parietal cortex within cocaine users reflects increased attention and control processes that compensate behavioral differences in a capacity-constrained response across the working memory load. A capacity-constrained load response in the parietal cortex (Linden et al., 2003) has been considered consistent with findings showing that this region is a key neural locus of capacity limitations in working memory (Todd and Marois, 2004), even at low-load conditions in normal participants with lower task performance (Nyberg et al., 2009) and in cocaine-dependent patients (Tomasi et al., 2007). Therefore, the interpretation of an executive attentional functioning and working memory-related involvement of the reduced parietal cortex activation in the cocaine-dependent patients of our study are not divorced, but neuroanatomically associated (Garavan et al., 2000). In our study, no significant area of increased activation is seen in patients when compared to controls, which excludes any of the hypothesized compensatory activation. We might consider that the lack of compensatory activation in the frontal lobes, as expected to be reflected by others (Tomasi et al., 2007), could be an effect of using a task that is not really challenging, which most of the patients and matched controls did not have problems to perform.

In short, our functional results suggest that chronic cocaine use may affect the attentional executive system in the right parietal lobe, making patients more prone to continued drug abuse. However, we should consider that although a reduced activation of the right inferior parietal region may be associated with an attentional executive deficit in working memory, its functionality might not be essential in verbal working memory processes when neither task performance is compromised nor other areas show a compensatory activation, at least at a level at which patients can perform the task.

It is important to notice the difficulty of obtaining a homogeneous sampling of the cocaine-dependent group in a study like this one, besides the recruitment of patients with a mono-addiction pattern to cocaine or without possible comorbidity with other psychiatric diseases (Sareen et al., 2006). Likewise, it is important to notice the limitation of our study related to the small size of the sample that could be conditioning our results. Nevertheless, several studies in cocaine dependence have used similar sample sizes given the difficulty in recruiting homogeneous groups. On the other hand, it would be interesting to test for the effects in functional results of the period of abstinence (Lim et al., 2008; Kosten et al., 1998), as well as withdrawal symptoms after a craving-induced state (Sinha et al., 2005; Duncan et al., 2007) in cognitive task performance of cocaine-dependent patients. However, it was not possible to study these effects in our sample given a low control on the patterns of relapses in the clinical history of each patient. In this sense, a variable that was not considered in detail in both groups was the screening of habits of consumption for alcohol, which have been shown to have an important effect on neuroadaptation changes after alcohol abstinence (Cosgrove et al., 2009). Future research will overcome the limitations of the present study and make the most of its results.

In conclusion, further studies on executive functioning in which a worse behavioral performance in cocaine-dependent patients compromises the right inferior parietal cortex will clarify its involvement in working memory and executive functioning by applying the present results to avoid the caveat of performance and anatomical effects on functional activation. This research could represent the first step toward a better understanding of different disrupted pattern activation in cocaine-dependent patients and its effects on attention processing to clarify the involvement of the parietal regions in patterns of cocaine use and abuse. Diverse studies have established the prefrontal cortex as the main neural substrate that holds the neurocognitive pattern and the addiction process in cocaine-dependent subjects. Nonetheless, new studies are required to provide more empirical data about the relevance of other brain areas like the parietal cortex.

4. Experimental procedures

4.1. *Participants*

The participants were 19 cocaine-dependent men and 19 comparison men. All the participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). General intellectual functioning was assessed with the Matrix Reasoning test from the WAIS-III (Wechsler, 2001). An initial study of their clinical history and a subsequent onsite evaluation by a neuropsychologist and a psychiatrist ensured that both groups were physically healthy with no major medical illnesses or DSM IV Axis I disorders, no current use of psychoactive medications, and no history of head injury with loss of consciousness or neurological illness. All the patients were recruited at the time they turned to the clinical service for cocaine addiction in which they had been going during a mean (±standard deviation, SD) of 15.58 months (12.64) before the scanning session. They were not under pharmacological treatment, and four of them had occasionally received a palliative treatment of anxiety/depressive symptoms. None of the participants were taking psychoactive medication at the time they were recruited for the experiment. The participants of the control group had no history of psychoactive substance dependence or abuse.

A urine toxicology test was done to rule out cocaine consumption, which ensured a minimum period of abstinence of over 4/5 days prior to the acquisition of fMRI data, as with any urine test done at the clinic during treatment. Two patients were excluded due to positive urine toxicology onsite fMRI context. Given the absence of a formal validation of the 2-back task, we included participants with a performance of over 70% and less than 6% of commission errors in the 2-back task during the fMRI scanning session. Furthermore, participants performed a similar version of the task prior to the scanning session in order to control for learning differences of the task procedure. One patient and one control were excluded because they did not meet the performance criteria of accuracy during the scanning session. One patient and three controls were excluded for excessive head movements (more than 2 mm of translation or 2 degrees of rotation) during fMRI acquisition.

The final sample was composed by 15 patients and 15 controls that were matched for age, level of education, and general intellectual functioning (see Table 1). Some patients reported precedents of depressive symptoms ($n=4$), anxiety symptoms ($n=3$), but they never constituted a DSM IV Axis I disorder, and these symptoms were all absent at the time the patients participated in the experiment. Two other subjects had a medical history of head injury without loss of consciousness ($n=2$). The cocaine-dependent participants reported a mean first-used-cocaine age and years of cocaine use at 20.07 (±6.79 SD) years old and for 11.67 (±5.89 SD) years, respectively. Moreover, twelve patients (80% of the final sample) and nine controls (57% of the final sample) were smokers. There were no distribution sample differences between groups in terms of smoking habits ($p>0.1$). On the other hand, nine patients (60%), four patients (26.7%), and one patient (6.7%) presented a consumption pattern without abuse of alcohol, cannabis, and amphetamine, respectively. Participants were informed of the nature of the research and were provided with a written informed consent prior to participating in this study.

4.2. *Paradigm*

The paradigm consisted of an auditory working memory task that had been previously used by our research group (Forn et al., 2007a, 2007b). The task sequentially presents alphabetical letters (a single-female speaker approach was used to record the stimuli) in random order, and participants were instructed to press a response button whenever they heard the letter "A" (0-back, control condition) or whenever they heard that the current letter was the same as the two before it (2-back, activation condition). The paradigm was based according to a block design (1 min/block) with 3 blocks for each condition. Each block contained 23 letters with a duration of 750 ms every 2.5 s. Each block was preceded by an auditory instruction of the condition. There were 11 possible correct responses for each condition during the task. Before scanning began, subjects were trained with a computerized practice version lasting 6 min in which they received feedback from the experimenter about their performance. Performance data were collected during the MRI session.

4.3. *fMRI acquisition*

Blood oxygenation level-dependent (BOLD) fMRI data were acquired on a 1.5-T Siemens Avanto (Erlangen, Germany). Subjects were placed in the MRI scanner in a supine position. Their heads were immobilized with cushions to reduce motion artifact. Auditory stimuli were presented through fMRI-compatible headphones (Resonance Technologies, Northridge, CA), which ensure a correct auditory presentation of the stimulus over the scanner noise level (Tomasi et al., 2005), and a response system was used to control performance during the scanning session (Responsegrips, NordicNeuroLab). Stimulus presentation was controlled by the Presentation® software (http://www.neurobs.com).

A gradient-echo T2*-weighted echo-planar MR sequence was used for fMRI (TE=50 ms, TR=3000 ms, flip angle =90º, matrix=64×64, voxel size =3.94×3.94 with 5 mm thickness and 0 mm gap). We acquired 29 interleaved axial slices parallel to the anterior–posterior commissure (AC–PC) plane covering the entire brain. Prior to the functional MR sequence, an anatomical 3D volume was acquired by using a T1-weighted gradient echo pulse sequence (TE=4.9 ms; TR=11 ms; FOV=24 cm; matrix=256×224×176; voxel size=1×1×1).

4.4. *Statistical analyses*

4.4.1. *Image preprocessing*

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM5). All the functional volumes were realigned for the former, corrected for motion artifacts, coregistered with the corresponding anatomical (T1-weighted) image, and normalized (voxels rescaled to 3 mm^3) with the normalization parameters obtained after anatomical segmentation within a standard stereotactic space (T1-weighted template from the Montreal Neurological Institute—MNI) to present functional images in coordinates of a standard stereotactic space. In addition, the time series of hemodynamic responses were high-pass filtered (256 s) to eliminate low-frequency components. To investigate the relationships between functional activation and the gray matter structure, we used Biological Parametric Mapping (BPM), a newly developed statistical toolbox that allows multimodal magnetic resonance imaging analysis (Casanova et al., 2007). Gray matter volume (GMV) maps were preprocessed using the voxel-based morphometry toolbox (VBM5.1; http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM5. The VBM preprocessing combined tissue segmentation, bias correction, and spatial normalization into a unified model. Otherwise, default parameters were used. GMV segmented images were modulated for nonlinear warping only removing global brain volume effects from the data to allow inferences on local GM changes. Functional and GMV maps were smoothed using an 8-mm Gaussian kernel to provide a similar smoothing to both image modalities.

4.4.2. *fMRI data analysis*

A statistical analysis was performed with the individual and group data using the General Linear Model (Friston et al., 1995). Serial autocorrelation caused by aliased cardiovascular and respiratory effects on functional time series was

corrected by a first-degree autoregressive (AR1) model. Group analyses were performed at the random-effects level. In a first level analysis, time series were modeled under the 2-back condition using a boxcar function convolved with the hemodynamic response function and its temporal derivative. Moreover, the movement parameters from motion correction were included for each subject as regressors of non interest. To identify the significantly activated brain areas during the 2-back task performance at the group level, statistical contrast images of the parameter estimates for each subject were created (2-back>0-back) at the fixed-effect level analysis and brought to random-effect analysis. The task-related activation in each group and between-group differences were studied with one- ($p<0.0001$, uncorrected) and two-sample t-tests ($p<0.001$, uncorrected), respectively. A corrected threshold of $p<0.05$ was applied at the cluster level to each contrast of interest to correct for family-wise errors (FWE). Furthermore, we did a regression analysis in the cocaine-dependent group between the first-used-cocaine age and years of cocaine use variables with functional activation separately to control for any possible related activation to these variables.

On the other hand, the Biological Parametric Mapping (BPM) statistical toolbox was used to analyze the possible brain-related activation during the 2-back task and gray matter volumes. The BPM toolbox produces statistical output images (e.g., T maps or F maps) in a massive voxel-by-voxel univariate analysis between two or more image modalities (and non-image data sets too) at random effects level based on the general linear model (see Casanova et al., 2007). First, we studied anatomical differences in GMV between groups, and possible relationships between GMV and the functional activation during the 2-back task within each group separately, restricting the analysis to the cluster of functional differences between groups. Formerly, we conducted a partial correlation between parameter estimate maps and gray matter volume maps and controlled for age effects. Furthermore, this analysis was repeated in a whole-brain voxelwise regression analysis between the parameter estimate maps and gray matter volume maps regressing out the age effects. Likewise, an ANCOVA analysis testing for GMV differences between groups was conducted as an exploratory analysis to test at which statistical level anatomical differences were present at the region of functional differences between groups. However, it is important to notice that in the GMV contrast between groups, subthreshold voxels are as important as those that show a significant effect for a predefined threshold, since one of the objectives of this study was to test for the possible role of GMV variability as a source of variability in functional activation related to cognitive tasks. Therefore, we included each subject's gray matter volume maps and age as covariates in a whole-brain voxelwise ANCOVA analysis. This last analysis tested for between groups' functional differences after controlling for individual differences in age and voxel-by-voxel GMV effects.

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Authors' contribution

Juan Carlos Bustamante was responsible for sample recruitment, acquisition of the data, data analysis, interpretation of findings, and manuscript preparation.

Alfonso Barrós-Loscertales was responsible for the study design, sample recruitment, data analysis, interpretation of findings, and manuscript preparation.

Noelia Ventura-Campos was responsible for the data analysis and interpretation.

Ana Sanjuán was responsible for the acquisition of the data and data analysis.

Juan Jose Llopis was responsible for sample recruitment, data acquisition, and critical review of the article.

Maria Antonia Parcet provided a critical revision of the manuscript for important intellectual contents and designed the neuropsychological assessment.

Cesar Avila was responsible for the study design, analysis, interpretation of findings, and the critical revision of the manuscript.

Acknowledgments

We thank the professional group at the Addictive Behaviors Unit San Agustín of Castellón (UCA, Unidad de Conductas Adictivas San Agustín de Castellón) for their collaboration. This study was supported by grants from FEPAD (Fundación para el Estudio, Prevención y Asistencias a la Drogodependencia), from the "National Plan of Drugs" (Plan Nacional de Drogas), and from the BRAINGLOT, a Spanish Research Network on Bilingualism and Cognitive Neuroscience (Consolider-Ingenio 2010 Programme, Spanish Ministry of Science and Education, CSD2007-00012). Moreover, the study was supported by a Ph.D. fellowship from "Universitat Jaume I" of Castellón (PREDOC/2007/13).

REFERENCES

Aron, J.L., Paulus, M.P., 2007. Location, location: using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. Addiction 102 (Suppl.1), 33–43.

Barrós-Loscertales, A., Belloch-Ugarte, V., Mallol, R., Martínez-Lozano, M.D., Forn, C., Parcet, M.A., Campos, S., Ávila, C., 2008. Volumetric differences in hippocampal volume affect fMRI differences in the brain functional activation for Alzheimer's disease during memory encoding. In: Chan, A.P. (Ed.), Alzheimer's Disease Research Trends. Nova Science Publishers, New York, pp. 147–173.

Beatty, W.W., Katzung, V.M., Moreland, V.J., Nixon, S.J., 1995. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. Drug Alcohol Depend. 37, 247–253.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12, 1–47.

Casanova, R., Srikanth, R., Baer, A., Laurienti, P.J., Burdette, J.H., Hayasaka, S., Flowers, L., Wood, F., Maldjian, J.A., 2007. Biological parametric mapping: a statistical toolbox for multimodality brain image analysis. Neuroimage 34, 137–143.

Chein, J.M., Ravizza, S.M., Fiez, J.A., 2003. Using neuroimaging to evaluate models of working memory and their implications for language processing. J. Neurolinguist 16, 315–339.
Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.
Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., Shulman, G.L., 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3, 292–297.
Cosgrove, K.P., Krantzler, E., Frohlich, E.B., Stiklus, S., Pittman, B., Tamangnan, G.D., Baldwin, R.M., Bois, F., Seibyl, J.P., Krystal, J.H., O'Malley, S.S., Staley, J.K., 2009. Dopamine and serotonin transporter availability during acute alcohol withdrawal: effects of comorbid tobacco smoking. Nueropsychopharmacology 34, 2218–2226.
Duncan, E., Boshoven, W., Harenski, K., Fiallos, A., Tracy, H., Jovanovic, T., Hu, X., Drexler, K., Kilts, C., 2007. An fMRI study of the interaction of stress and cocaine cues on cocaine craving in cocaine-dependent men. Am. J. Addict. 16, 174–182.
Fein, G., Di Sclafani, V., Meyerhoff, D.J., 2002. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug Alcohol Depend. 68, 87–93.
Forn, C., Barrós-Loscertales, A., Escudero, J., Belloch, V., Campos, S., Parcet, M.A., 2007a. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-BACK task. Hum. Brain Mapp. 28, 424–430.
Forn, C., Barrós-Loscertales, A., Escudero, J., Campos, S., Parcet, M.A., Ávila, C., 2007b. Compensatory activation in patients with multiple sclerosis during preserved performance on the auditory N-back task. Hum. Brain Mapp. 28, 424–430.
Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., O'Brien, C.P., Childress, A.R., 2002. Decreased gray matter concentration in the insular, orbitofrontal, cingulated and temporal cortices of cocaine patients. Biol. Psychiatry 51, 134–142.
Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiack, S.R., Turner, R., 1995. Analysis of fMRI time-series revisited. Neuroimage 2, 45–53.
Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.K., Sperry, L., Ross, T.J., 2000. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimulus. Am. J. Psychiatry 157, 1789–1798.
Goldstein, R.Z., Alia-Klein, N., Tomasi, D., Carrillo, J.H., Maloney, T., Woicik, P.A., Wang, R., Telang, F., Volkow, N.D., 2009. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. Proc. Natl Acad. Sci. USA 106, 9453–9458.
Hester, R., Garavan, H., 2004. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate and cerebellar activity. J. Neurosci. 24, 11017–11022.
Iwanami, A., Kuroki, N., Iritani, S., Isono, H., Okajima, Y., Kamijima, K., 1998. P3a of event-related potential in chronic methamphetamine dependence. J. Nerv. Ment. Dis. 186, 746–751.
Jovanovski, D., Erb, S., Zakzanis, K.K., 2005. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. J. Clin. Exp. Neuropsychol. 27, 189–204.
Kosten, T.R., Cheeves, C., Palumbo, J., Seibyl, J.P., Price, L.H., Woods, S.W., 1998. Regional cerebral blood flow during acute and chronic abstinence from combined cocaine–alcohol abuse. Drug Alcohol Depend. 50, 187–195.
Kubler, A., Murphy, K., Garavan, H., 2005. Cocaine dependence and attention switching within and between verbal and visuospatial working memory. Eur. J. Neurosci. 21, 1984–1992.
Lim, K.O., Choi, S.J., Pomara, N., Wolkin, A., Rotrosen, J.P., 2002. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. Biol Psychiatry 51, 890–895.
Lim, K.O., Wozniak, J.R., Mueller, B.A., Franc, D.T., Specker, S.M., Rodriguez, C.P., Silverman, A.B., Rotrosen, J.P., 2008. Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug Alcohol Depend. 92, 164–172.
Linden, D.E., Bittner, R.A., Muckli, L., Waltz, J.A., Kriegeskorte, N., Goebel, R., Singer, W., Munk, M.H., 2003. Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. Neuroimage 20, 1518–1530.
Lyoo, I.K., Streeter, C.C., Ahn, K.H., Lee, H.K., Pollack, M.H., Silveri, M.M., Nassar, L., Levin, J.M., Sarid-Segal, O., Ciraulo, D.A., Renshaw, P.F., Kaufman, M.J., 2004. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. Psychiatry Res. 131, 135–145.
Matochik, J.A., London, E.D., Eldreth, D.A., Cadet, J.L., Bolla, K.I., 2003. Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study. Neuroimage 19, 1095–1102.
Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., Weinberger, D.R., 2003. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc. Natl Sci. USA 100, 6186–6191.
Mattay, V.S., Fera, F., Tessitore, A., Hariri, A.R., Berman, K.F., Das, S., Meyer-Lindenberg, A., Goldberg, T.E., Callicott, J.H., Weinberger, D.R., 2006. Neurophysiological correlates of age-related changes in working memory capacity. Neurosci. Lett. 392, 32–37.
Mcketin, R., Mattick, R.P., 1997. Attention and memory in illicit amphetamine users. Drug Alcohol Depend. 48, 235–242.
McMillan, K.M., Laird, A.R., Witt, S.T., Meyerand, M.E., 2007. Self-paced working memory: validation of verbal variations of the n-back paradigm. Brain Res. 1139, 133–142.
Moeller, F.G., Hasan, K.M., Steinberg, J.L., Kramer, L.A., Dougherty, D.M., Santos, R.M., Valdes, I., Swann, A.C., Barratt, E.S., Narayana, P.A., 2005. Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. Neuropsychopharmacology 30, 610–617.
Morgan, P.T., Pace-Schott, E.F., Sahul, Z.H., Coric, V., Stickgold, R., Malison, R.T., 2006. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: evidence for occult insomnia. Drug Alcohol Depend. 82, 238–249.
Murphy, K., Garavan, H., 2004. Artifactual fMRI group and condition differences driven by performance confounds. Neuroimage 21, 219–228.
Nyberg, L., Dahlin, E., Neely, S., Bäckman, L., 2009. Neural correlates of variable working memory load across adult age and skill: dissociative patterns within the fronto-parietal network. Scand. J. Psychol. 50, 41–46.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Oakes, T.R., Fox, A.S., Johnstone, T., Chung, M.K., Kalin, N., Davidson, R.J., 2007. Integrating VBM into the General Linear Model with voxelwise anatomical covariates. Neuroimage 34, 500–508.
Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E.D., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59.
Pace-Schott, E.F., Morgan, P.T., Malison, R.T., Hart, C.L., Edgar, C., Walker, M., Stickgold, R., 2008. Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. Am. J. Drug Alcohol Abuse 34, 109–121.
Price, C.J., Friston, K.J., 1999. Scanning patients with tasks they can perform. Hum. Brain Mapp. 8, 102–108.
Price, C.J., Crinion, J., Friston, K.J., 2006. Design and analysis of fMRI studies with neurologically impaired patients. J. Magn. Reson. Imaging 23, 816–826.
Ravizza, S.M., Delgado, M.R., Chein, J.M., Becker, J.T., Fiez, J.A., 2004. Functional dissociations within the inferior parietal cortex in verbal working memory. Neuroimage 22, 562–573.

Sareen, J., Chartier, M., Paulus, M.P., Stein, M.B., 2006. Illicit drug use and anxiety disorders: findings from two community surveys. Psychiatry Res. 142, 11–17.

Sim, M.E., Lyoo, I.K., Streeter, C.C., Covell, J., Sarid-Segal, O., Ciraulo, D.A., Kim, M.J., Kaufman, M.J., Yurgelun-Todd, D.A., Renshaw, P.F., 2007. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology 32, 2229–2237.

Simon, S.L., Domier, C., Carnell, J., Brethen, P., Rawson, R., Ling, W., 2000. Cognitive impairment in individuals currently using methamphetamine. Am. J. Addict. 9, 222–231.

Sinha, R., Lacadie, C., Skudlarski, P., Fulbright, R.K., Rounsaville, B.J., Kosten, T.R., Wexler, B.E., 2005. Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. Psychopharmacology 183, 171–180.

Tanabe, J., Tregellas, J.R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., Banich, M., 2009. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. Biol. Psychiatry 65, 160–164.

Todd, J.J., Marois, R., 2004. Capacity limit of visual short term memory in human posterior parietal cortex. Nature 428, 751–754.

Tomasi, D., Caparelli, E.C., Chang, L., Ernst, T., 2005. fMRI-acoustic noise alters brain activation during working memory tasks. Neuroimage 27, 377–386.

Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., Volkow, N.D., 2007. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. Brain Res. 1171, 83–92.

Verdejo-García, A., Rivas-Pérez, C., Lopez-Torrecillas, F., Perez-García, M., 2005. Differential impact of severity of drug use on frontal behavioral symptoms. Addict. Behav. 31, 1373–1382.

Wechsler, D., 2001. Escala de inteligencia de Wechsler para adultos-III (Intelligence Scale Weschler, WAIS-III). TEA Ediciones, Madrid.

Wojciulik, E., Kanwisher, N., 1999. The generality of parietal involvement in visual attention. Neuron 23, 747–764.

Section 2.4. Barrós-Loscertales A., Bustamante J.C., Ventura-Campos N., Llopis J.J., Parcet M.A., Ávila C. (2011). Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group. 'Psychiatry Research', 194, 111-118.

Psychiatry Research: Neuroimaging 194 (2011) 111–118

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group

Alfonso Barrós-Loscertales *[,1], Juan-Carlos Bustamante [1], Noelia Ventura-Campos, Juan-José Llopis, María-Antonia Parcet, César Ávila

Avd. Vicente Sos Baynat s/n, Dpto. Psicología Básica, Universitat Jaume I., 12080 Castellón de la Plana., Spain

ARTICLE INFO

Article history:
Received 31 March 2010
Received in revised form 30 March 2011
Accepted 3 May 2011

Keywords:
Addiction
Cocaine
Interference control
Attention
Prefrontal cortex
Parietal cortex

ABSTRACT

Dysregulation in cognitive control networks may mediate core characteristics of drug addiction. Cocaine dependence has been particularly associated with low activation in the frontoparietal regions during conditions requiring decision making and cognitive control. This functional magnetic resonance imaging (fMRI) study aimed to examine differential brain-related activation to cocaine addiction during an inhibitory control paradigm, the "Counting" Stroop task, given the uncertainties of previous studies using positron emission tomography. Sixteen comparison men and 16 cocaine-dependent men performed a cognitive "Counting" Stroop task in a 1.5 T Siemens Avanto. The cocaine-dependent patient group and the control group were matched for age, level of education and general intellectual functioning. Groups did not differ in terms of the interference measures deriving from the counting Stroop task. Moreover, the cocaine-dependent group showed lower activation in the right inferior frontal gyrus, the right inferior parietal gyrus and the right superior temporal gyrus than the control group. Cocaine patients did not show any brain area with increased activation when compared with controls. In short, Stroop-interference was accompanied by lower activation in the right frontoparietal network in cocaine-dependent patients, even in the absence of inter-group behavioral differences. Our study is the first application of a counting Stroop task using fMRI to study cocaine dependence and yields results that corroborate the involvement of a frontoparietal network in the neural changes associated with attentional interference deficits in cocaine-dependent men.

1. Introduction

It is generally agreed that drug dependence may be a result of the compromise of the executive processes that control behavior (Moeller et al., 2001; Garavan et al., 2008). Long-term cocaine use produces changes in brain structure and function in the frontal lobe (Fein et al., 2002; Matochik et al., 2003; Lim et al., 2008; Tanabe et al., 2009). Previous studies have shown deficits in the frontal lobe functioning and executive functions related to it in cocaine-dependent patients (Aron and Paulus, 2007). Among the frontal executive functions, the study of interference control in cocaine dependence can reveal the functional and anatomical changes responsible for a cocaine addiction diagnosis criterion in relation to behavioral patterns of diminished control.

Cognitive control has been defined as the processes that allow information processing and behavior to vary adaptively from one time to another in accordance with current goals rather than remaining rigid and inflexible. Cognitive control processes include a broad class of mental operations, including goal or context representation and maintenance, as well as strategic processes such as attention allocation and stimulus–response mapping. Prefrontal networks involving the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) are important for the executive cognitive functions governing cognitive control such as response inhibition and error monitoring (Kerns et al., 2004).

The Stroop effect can serve as a paradigmatic task for studying the interference control-function (Nigg, 2000). The Stroop task demands a number of different cognitive subprocesses like error monitoring, response selection and suppression of inadequate responses. Moreover, the prototypical Stroop interference task is able to provide us much information about attention and cognition mechanisms in normal humans and clinical patients (McLeod, 1991), and also provides information about the frontal lobe's executive functioning and integrity. In the context of functional magnetic resonance imaging (fMRI), the Stroop paradigm has shown the involvement of a frontoparietal network that includes regions of the frontal lobe (e.g., lateral prefrontal cortex, frontopolar regions, anterior cingulate cortex), as well as the parietal cortex (Pardo et al., 1990; Bush et al., 1998; Leung et al., 2000; Zysset et al., 2001; Laird et al., 2005).

Dysregulation in cognitive control networks may mediate core characteristics of drug addiction (Goldstein and Volkow, 2002) as cocaine abusers have shown dysfunction in decision-making and cognitive control tasks (Bechara and Damasio, 2002). In the specific

* Corresponding author. Tel.: +36 964729709; fax: +34 964729267.
E-mail address: barros@psb.uji.es (A. Barrós-Loscertales).
[1] These two authors contributed equally to this work.

0925-4927/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2011.05.001

case of the Stroop task, some neuropsychological studies have reported severe effects of cocaine to be related to worsened performance (Roselli et al., 2001; Verdejo-García et al., 2004), which is consistent with the hypothesis that stimulant use alters an individual's ability to selectively attend stimuli or to inhibit pre-potent responses (Simon et al., 2000; Verdejo-García et al., 2005). However, other studies have not found differences in performance between patients and controls (Hoff et al., 1996; Selby and Azrin, 1998; Bolla et al., 1999), indicating that neuropsychological results are inconsistent and that those variations in both task and sample characteristics should be taken into account when interpreting results.

Frontoparietal dysfunction has been identified for a wide range of executive functions in cocaine-dependent patients (Kaufman et al., 2003; Aron and Paulus, 2007; Tomasi et al., 2007; Garavan et al., 2008). Previous neuroimaging studies in cognitive functioning have shown a frontal deficit in cocaine addicts in the absence of cognitive deficits (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008) or when concomitant behavioral deficits were present (Kaufman et al., 2003; Hester and Garavan, 2004; Kübler et al., 2005). Moreover, recent studies have shown functional deficits in the parietal lobe in cocaine-dependent patients during working memory (Bustamante et al., 2011) and cognitive control tasks (Garavan et al., 2008). Previous research that compared patients and controls using the Stroop task has found differences in several frontal and cingulate areas. Using a manual version of the Stroop task and positron emission tomography (PET), Bolla et al. (2004) revealed how the anterior cingulate cortex (ACC) and the right lateral prefrontal cortex (rLPFC) were less active in a group of abstinent cocaine-dependent individuals. Goldstein et al. (2001) did not find brain functional differences using PET between cocaine-dependent patients and a group of matched controls during an event-related color-word Stroop task. However, their results revealed increased activation in the orbitofrontal cortex associated with lower and higher conflict in controls and patients, respectively, while groups did not differ in terms of task performance. Otherwise, Brewer et al. (2008) found that activations in the frontal and parietal regions during performance of the Stroop task were related to treatment outcomes. These studies documented the different underlying brain regions associated with the ability to inhibit prepotent response tendencies in cocaine-dependent patients by comparing them to controls. These differences can be attributed to neither disparities in education and general intellectual functioning nor observable behavioral changes in standard neuropsychological measures.

In view of the variability in the PET-obtained results (Goldstein et al., 2001; Bolla et al., 2004) and the relevance of deficits on the Stroop task to the treatment of these patients (Brewer et al., 2008), the objective of the present research work was to study interference-control functioning in cocaine-dependent patients using fMRI, which offers better spatial and temporal resolution than PET. As far as we know, this is the first study to compare cocaine-dependent patients and controls during Stroop performance using fMRI. We selected the counting Stroop task (Bush et al., 1998) as it is better suited for the fMRI environment (Bush et al., 2006). The advantages of this version of the task are the possibility of registering manual on-line response time measurements while obviating speech and increased stimulus–response compatibility. Therefore, the final objective of this study was to identify the brain regions that are differently involved in a counting Stroop task for a cocaine group and a comparison group. We hypothesize that the cocaine-dependent group will show lower activation in the frontoparietal areas that are involved in the Stroop effect and which are affected by cocaine dependence when compared with controls.

2. Methods

2.1. Participants

Eighteen cocaine-dependent men and 20 matched healthy men participated in this study. All the participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). An initial study of their clinical history and a subsequent onsite assessment by a neuropsychologist and a psychiatrist ensured that both groups were physically healthy with no major medical illnesses or DSM-IV Axis-I disorders, had no current use of psychoactive medications, and had no history of head injury with loss of consciousness or neurological illness. All the patients were recruited at the time they came to a clinical service to seek treatment for cocaine addiction. Patients were scanned over a maximum period of 2 months since they were recruited for the study. During this time, they were evaluated and diagnosed, and they could voluntary attend the counseling group sessions offered by the clinic.

Prior to participation in the study, subjects completed the color-word Stroop test according to the normative Spanish version (1994). We established a minimum performance criterion based on a corrected standard T value of the interference score as described by Golden (1978). We involved those participants who displayed an accuracy performance with a score of over 36 in terms of the standard T value corresponding to their interference score in accordance with the normative Spanish data (see Manual of the Spanish version of the Stroop Color and Word Test, 1994. TEA Ediciones, Madrid). On the basis of these performance criteria, one participant from the control group was not included in the final sample. A urine toxicology test was done to rule out cocaine consumption, which ensured a minimum period of abstinence of over 2/4 days (Vearrier et al., 2010) prior to fMRI data acquisition, as with any urine test done at the clinic before patients participated in the scanning session.

Three and two subjects were excluded from the control group and the cocaine group, respectively, as they had a positive urine test (one patient), MRI technical issues (one control) and excessive movement during fMRI acquisition (one patient and two controls; more than 2 mm of translation or 2° of rotation). The final sample (16 cocaine-dependent men and 16 comparison men) who took part in the study were matched for age, level of education, and general intellectual functioning (see Table 1). General intellectual functioning was assessed with the Matrix Reasoning test from the Wechsler Adult Intelligence Scale-III (Wechsler, 2001). Some patients reported histories of depressive symptoms ($n=3$) or anxiety symptoms ($n=3$), but never of sufficient severity to constitute a DSM-IV Axis-I disorder, and these symptoms were all absent at the time the patients participated in the experiment. The cocaine-dependent participants reported an average (±S.D.) of 19.85 (6.25) and 13.94 (5.85) as first-used cocaine age and years of cocaine use, respectively. Moreover, 10 patients (62.5% of the final sample) compared to nine controls (56.25% of the final sample) were smokers. There were no inter-group distribution sample differences in this variable ($p>0.1$). On the other hand, eight patients (50%), two patients (12.5%), one patient (6.3%) and one patient (6.3%) reported a sporadic consumption pattern without abuse of alcohol, cannabis, amphetamines and other types of

Table 1
Means (and standard deviations) of the main demographic characteristics, and the behavioral results on percentage of correct responses, interference effect and response time (RT) of the cocaine-dependent and the comparison groups (n.s., non-significant).

	Comparison group $n=16$	Cocaine dependent group $n=16$	Statistical difference
Age	34.20 (8.86)	34.38 (7.15)	n.s
Years of education	8.53 (1.46)	9.25 (1.69)	n.s
General intellectual functioning (Matrix Reasoning test)	10.87 (2.59)	9.94 (2.41)	n.s
Word test in color-word Stroop version	49.33 (6.32)	48 (7.04)	n.s
Color test in color-word Stroop version	45.27 (6.76)	44.77 (9.12)	n.s
Word/color test in color-word Stroop version	52.40 (8.93)	53.69 (10.68)	n.s
Interference scores in color-word Stroop version	54.27 (6.43)	56.31 (8.95)	n.s

psychoactive drugs, respectively. These 12 patients did not meet the criteria for either current dependence on or abuse of these substances. Participants were informed of the nature of the research and were provided a written informed consent prior to participation in this study. This research work was approved by the institutional review board of the Universitat Jaume I of Castellón (E. Spain).

2.2. Paradigm

Participants viewed sets of one to four identical words presented on the screen for each trial during the whole paradigm. They were instructed to respond as quickly as possible via button pressing using a keypad with two buttons for each hand (Response Grips, NordicNeuroLab, Norway) to the number of words in each set, regardless of what the words were. During the Stroop or conflict blocks, the words were number words: "one", "two", "three" and "four" ("uno", "dos", "tres" "cuatro" in Spanish), which were always discordant with the number of words presented. During the control or no-conflict blocks, words were common names from different categories (balanced by frequency and length). Subjects were trained during a 4-min computerized practice version without interference trials, in which they received feedback from the experimenter about their performance. The paradigm within the scanner lasted 4 min and was divided into blocks of 30 s for each condition (Stroop condition or control condition), starting with a no-conflict condition. Thus, each condition was repeated during four alternated blocks. Words were presented for 800 ms in each trial with a fixed ISI (interstimuli interval) of 866 ms. Reaction time (RT) and accuracy data were collected across all the trials during task performance in the scanner.

2.3. FMRI data acquisition

Blood oxygenation level dependent (BOLD) fMRI data were acquired in a 1.5T Siemens Avanto (Erlangen, Germany). Subjects were placed in a supine position in the MRI scanner. Their heads were immobilized with cushions to reduce motion artifact. Stimuli were directly presented using Visuastim XGA goggles with a resolution of 800×600 (Resonance Technologies, Inc., CA, USA), and a response system was used to control performance during the scanner session (Responsegrips, NordicNeuroLab, Norway). Stimulus presentation was controlled by means of the Presentation® software (http://www.neurobs.com). Vision correction was used whenever necessary.

A gradient-echo T2*-weighted echo-planar MR sequence was used for fMRI (TE = 50 ms, TR = 3000 ms, flip angle = 90°, matrix = 64×64, voxel size = 3.94×3.94 with 5 mm thickness and 0 mm gap). We acquired 29 interleaved axial slices parallel to the anterior–posterior commissure (AC–PC) plane covering the entire brain. Prior to the functional MR sequence, an anatomical 3D volume was acquired by using a T1-weighted gradient echo pulse sequence (TE = 4.9 ms; TR = 11 ms; FOV = 24 cm; matrix = 256×224×176; voxel size = 1×1×1).

2.4. Statistical analysis

2.4.1. Image preprocessing

Image processing and statistical analyses were carried out using SPM5. All the functional volumes were realigned to the first one, corrected for motion artifacts, coregistered with the corresponding anatomical (T1-weighted) image, and normalized (voxels were rescaled to 3 mm^3) with the normalization parameters obtained after the anatomical segmentation within a standard stereotactic space (T1-weighted template from the Montreal Neurological Institute — MNI) to present functional images in coordinates of a standard space. Finally, functional maps were smoothed using a 9-mm Gaussian kernel.

2.4.2. FMRI data analysis

Statistical analysis was performed with the individual and group data using the General Linear Model (Friston et al., 1995). Serial autocorrelation caused by aliased cardiovascular and respiratory effects on functional time series was corrected by a first-degree autoregressive (AR1) model. Group analyses were performed at the random-effects level. In a first level analysis, time series were modeled under the Stroop condition using a boxcar function convolved with the hemodynamic response function and its temporal derivative. Moreover, the movement parameters from motion correction were included for each subject as regressors of non-interest. The time series of the hemodynamic responses were high-pass filtered (128 s) to eliminate low-frequency components. To identify the significantly activated brain areas, statistical contrasts to the parameter estimates for each subject were created to the Stroop condition compared to the implicitly modeled control condition. Both the task-related activation in each group and the inter-group differences were studied with a one-sample t-test ($p<0.001$, corrected for multiple comparisons at the cluster level $p<0.05$; the equivalent to a k-threshold = 37); and a two-sample t-test ($p<0.005$), corrected for multiple comparisons at the cluster level ($p<0.05$, the equivalent to a k-threshold = 125).

3. Results

3.1. Behavioral results

Table 2 shows the behavioral results obtained during the fMRI scanning session. Two 2×2 mixed-model analyses of variance (ANOVAs) were conducted using Condition (Conflict vs. Neutral) as a within-subjects factor and Group (Patients vs. Controls) as a between-subjects factor to analyze RTs and correct responses. The analysis of RTs revealed a main effect of condition ($F(1,30) = 68,96$, $p<0.05$), showing faster RTs in the Neutral than in the Conflict condition for both groups. Thus, there were significant differences between the conditions in the control group ($t(15) = 5.54$, $p<0.001$) and the patient group ($t(15) = 6.35$, $p<0.001$). There was also an unexpected group effect ($F(1,30) = 4.36$, $p<0.05$), indicating faster responses in controls than in patients in the Neutral condition ($t(30) = 2.29$, $p<0.05$; $p = 0.029$) and a trend to this effect in the Conflict condition ($t(30) = 1.85$, $p>0.05$; $p = 0.074$). The same analysis for errors did not yield any significant effect ($p>0.1$).

3.2. fMRI results

The comparison group and the cocaine-dependent group showed an activation pattern in the counting Stroop task in a frontoparietal network implicated in this type of manual Stroop task. For both groups, it principally included the right inferior frontal gyrus (BA 9/44/45/47), the left inferior frontal gyrus (BA 9/46), the right middle frontal gyrus (BA 6/9), the left middle frontal gyrus (BA 9), the right inferior parietal lobule (BA 40), the left inferior parietal lobule (BA 39/40) and the left superior parietal lobule (BA 7) (see Table 3, Fig. 1).

Table 2
Means (and standard deviations) of the behavioral results on percentage of correct responses, interference effect and reaction time (RT) of the cocaine-dependent and the comparison groups during the counting Stroop task (n.s., non-significant).

	Comparison group $n = 16$	Cocaine-dependent group $n = 16$	Statistical difference between conditions/groups
Correct responses neutral condition	94.79% (2.66)	93.75% (2.73)	n.s./n.s.
Correct responses conflict condition	95.14% (4.15)	94.71% (5.00)	n.s/n.s.
Interference effect	55.12 (39.79)	51.43 (32.41)	n.s./n.s.
RT neutral condition	611.44 (45.40)	678.36 (107.79)	$p<0.05/p<0.05$
RT conflict condition	666.56 (71.48)	729.79 (116.48)	$p<0.05/p = 0.76$

The functional contrast between groups (two-sample *t*-test; $p<0.005$, corrected for multiple comparisons at the cluster level, $k=125$) showed less activation in the cocaine-dependent group for the right inferior frontal gyrus (BA 47; 45,17,−8; $Z=3.55$; $k=329$), the right inferior parietal gyrus (BA 40; 53,−39,38; $Z=3.93$; $k=261$) and the right superior temporal gyrus (BA 22; 53,−41,2; $Z=3.66$; $k=189$) if compared with the control group (see Fig. 2). As the groups differed in RTs in each condition, inter-group brain activation differences were also studied using two separate analyses of covariance, including the RTs in the conflict and control conditions as covariates separately. The inter-group functional differences remained significant after controlling for the RT in either condition. Likewise, no brain region showed greater activation in the cocaine-dependent group if compared to the control group for any previous inter-group contrast. Lastly, a limited set of exploratory correlations was performed among drug use (years of cocaine use, age of first use), fMRI task behavioral performance (RT difference between conditions) and functional brain activation. These analyses did not report any significant correlation. The coordinates for peak significant activation in each significant cluster of activation were localized using the xjView toolbox (http://www.alivelearn.net/xjview/) based on the MNI Space utility (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html) and the WFU-Pickatlas (Maldjian et al., 2003).

4. Discussion

The comparison made between cocaine-dependent patients and matched controls showed lower cerebral activation in the right inferior frontal cortex for the cocaine-dependent group during the counting Stroop task. We also noted lower activation in the patient group for the right inferior parietal and the superior temporal cortex. These inter-group differences in brain activation were obtained in the absence of other differences like RT interference effects or response accuracy during task performance. Moreover, patients showed no significant area of increased activation when compared to controls, which excluded any compensatory activation.

Both the cocaine and control groups displayed a prototypical pattern of brain activation during the counting Stroop task, which is in agreement with previous studies (Pardo et al., 1990; Bush et al., 1998; Leung et al., 2000; Laird et al., 2005) and supports the validity of applying the counting Stroop fMRI paradigm to our samples. This activation pattern reflects the joint activity of the bilateral frontoparietal networks during Stroop task performance, principally in the manual versions of the task. These results are consistent with those reported in the study of Bush et al. (1998) where the bilateral DLPFC and the anterior cingulate were activated (including areas of the SMA as reported in the manual versions of the Stroop paradigm; see Laird et al., 2005).

The current findings also indicate that the interference score overlaps significantly between cocaine-dependent patients and controls. This interference score in the Stroop task can be influenced by multiple sensory and motor conditions, and by other mental processes (such as effort) which are not directly related to the measure of interest. Moreover, we cannot rule out that the selection criteria in the word-color Stroop test may equate performance. Thus the interference score, as a behavioral measure within the adaption of the counting Stroop to fMRI environment, may not capture the inter-group differences in the cognitive control processes. However, this study reveals that neuroimaging is an additional tool to explore the neural processes associated with impaired cognitive control in cocaine-dependent patients. In fact, the differences observed in regional brain activation, despite similar behavioral performance, are reminiscent of other imaging studies into drug addiction (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008; Hester et al., 2009; Bustamante et al., 2011). Previous authors have highlighted that this scenario has the advantage of restricting the number of interpretations of results since inter-group performance differences or engagement may not explain neural differences (Price et al., 2006; Goldstein et al., 2009). The fact that our results indicate lower activation in brain areas similarly to those of previous research works, which studied executive dysfunctions as an effect of cocaine dependence, validates our interpretation of the neural results in the absence of behavioral differences.

How do we interpret these differences between groups? The joint effects of reduced brain activation in the cocaine group when compared with the control group, plus the absence of differences in the interference effect between these same groups, may be interpreted in several ways. One way is to consider that cocaine patients recruit less neural resources to perform the task than controls do, as usually interpreted in studies with healthy participants (Mattay et al., 2003, 2006). Likewise, another consideration may be that the areas of lower activation, although typically active during task completion, are not essential to perform the task since patients' performance is not worse than that of controls (Price and Friston, 1999). However, these two interpretations are difficult to apply in cocaine dependence since cocaine-dependent patients typically show lower accuracy in executive tasks and lower activations associated with worse performance in these regions. Having said that, the cocaine group may have a higher baseline metabolism, which would give rise to a lower contrast effect of the conflict condition vs. the control condition in those regions of functional differences between groups. However, previous studies have not

Table 3
Coordinates of the main brain activations during the "Counting" Stroop task for each group ($p<0.001$, corrected for multiple comparisons at cluster level $p<0.05$). Coordinates of global maxima in MNI coordinates.

Brain region	Brodmann area	Comparison group			Cocaine dependent group		
		Coordinates	Activation cluster size	*Z* score	Coordinates global maxima	Activation cluster size	*Z* score
Right superior frontal gyrus	6	15,14,52	304	5.38			
Right medial frontal gyrus/SMA	6	15,9,55	347	5.47			
Left middle frontal gyrus	9	−45,22,32	686	4.98	−42,25,29	186	4.14
Right middle frontal gyrus	6,9	42,−1,36	772	5.01	42,2,47	48	4.86
Right inferior frontal gyrus	9,44,45,47	59,21,7	605	4.51	53,10,24	58	3.68
Left inferior frontal gyrus	9,46	−45,22,29	555	4.76	−48,12,27	93	4.85
Right superior temporal gyrus	21,22	53,−26,−1	170	4.78	45,−48,27	398	4.17
Right inferior temporal gyrus	37	45,−64,−2	215	5.17			
Right superior parietal lobule	7	33,−53,52	172	4.56			
Left superior parietal lobule	7	−30,−64,53	310	5.15	−15,−35,54	573	4.43
Right inferior parietal lobule	40	50,−42,38	317	4.85	50,−53,41	62	3.87
Left inferior parietal lobule	39,40	−36,−45,38	576	4.83	−36,−48,38	398	4.16
Left thalamus		−15,−11,6	40	3.94			
Right thalamus		15,−5,11	566	5.41			

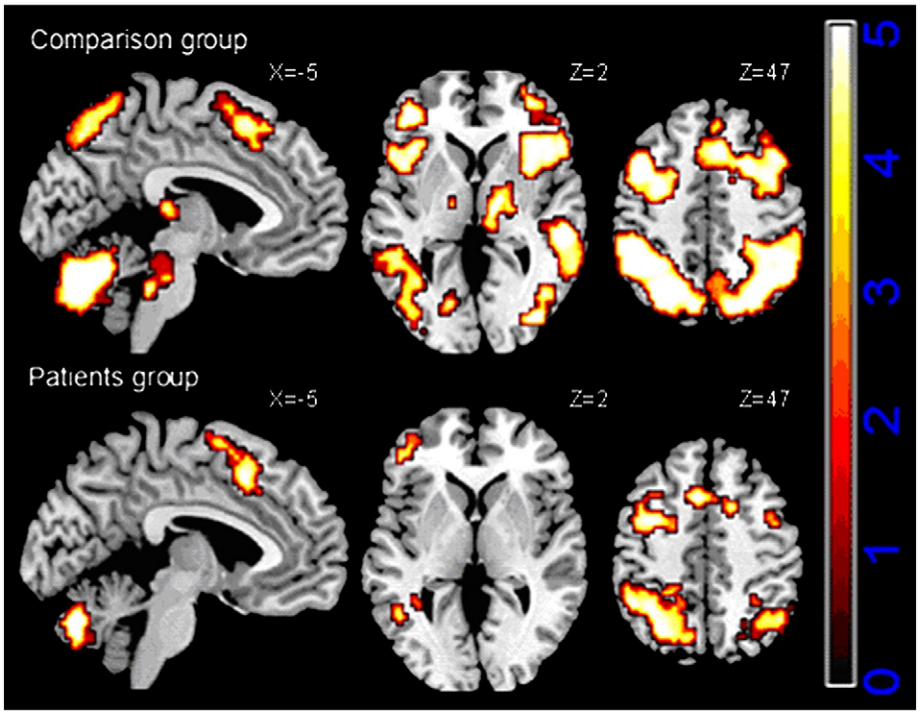


Fig. 1. Main activations in the "Counting" Stroop task for each group. Right is right. White labels (top) indicate the coordinate of each slice in the MNI frame of reference (*x,y,z*). Bar plot represents *Z*-values.

reported a homogeneous brain pattern of basal metabolism in relation to cocaine dependence (Goldstein et al., 2001; Tomasi et al., 2007); moreover, the lack of a resting condition to test the baseline effects in our design makes it difficult to conclude a basal metabolic effect from our results. On the other hand, cognitive-behavioral impairments in cocaine addiction have been suggested to be associated with compromised habituation or practice effects (Goldstein et al., 2007). As an effect of cocaine addiction, a signal change activation and deactivation toward the baseline has been shown to be an effect of neural habituation in an incentive-sustained attention task associated with more severe cocaine use (Goldstein et al., 2007). However, talking about the habituation or basal metabolism effect in our results may be rather speculative given that these effects are subject to a wide range of factors (Petersen et al., 1998; Garavan et al., 2000; Kelly and Garavan, 2005). In summary, a plausible interpretation of these results would be to relate patients' neural lower activation as a vulnerability index toward the cognitive dysfunction underlying the neuronal changes associated with lengthy drug use. This interpretation is the most frequent one in drug addiction research to refine neuropsychological investigations (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008; Hester et al., 2009), and would probably imply a more cognitively demanding Stroop task to be able to translate neural differences into behavioral deficits. Further research will be necessary to clarify the conditions under which a behavioral deficit is sensitive to a cognitive change in order to reflect a concomitant reduced functional activation, or vice versa.

Cocaine consumption is principally related to orbitofrontal cognitive deficits (Winstanley, 2007) and subtle dorsolateral prefrontal deficits, whose standard neuropsychological test might not be sensitive enough for detection (Goldstein et al., 2001), or can be detected at different degrees (Fernandez-Serrano et al., 2010). As our results suggest, fMRI can detect these deficits in the absence of executive deficits in neuropsychological tasks (Goldstein et al., 2001). Thus, the results of our study are consistent with previous reports showing lower frontoparietal activations during executive tasks in cocaine-addicted patients in the absence of behavioral deficits (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008) or are concomitant with behavioral

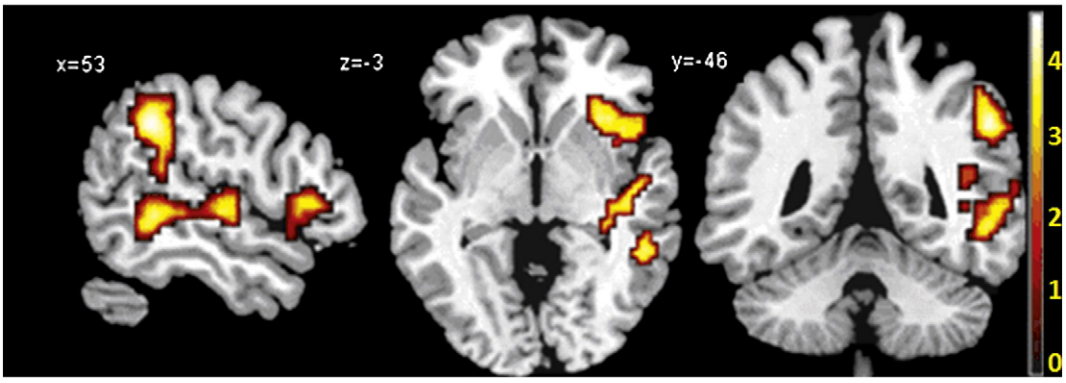


Fig. 2. Functional differences between groups in the "Counting" Stroop task. Right is right. White labels (top) indicate the coordinate of each slice in the MNI frame of reference (*x,y,z*). Bar plot represents *Z*-values.

differences (Kaufman et al., 2003; Hester and Garavan, 2004; Kübler et al., 2005).

The lower activation observed while patients performed the counting Stroop task may be considered an indicator of their proneness toward executive deficits. Specifically, the differences in activation of the right inferior frontal gyrus are relevant to and coincident with the previous literature. This brain area has been repeatedly associated with inhibitory processing and stimulus reconfiguration after using different paradigms such as the stop-signal task, switching tasks, go/no go tasks, the Wisconsin Card Sorting Test (WCST) or Stroop tasks (Aron et al., 2007; Robbins, 2007). With Stroop tasks, a series of recent neuroimaging studies has detected activity in the dorsal cingulate and the dorsomedial prefrontal cortex, which is associated with conflict monitoring, whereas activity in the lateral inferior prefrontal cortices is associated with conflict resolution (Botvinick et al., 1999; Kerns et al., 2004; Egner and Hirsch, 2005). In studies conducted with cocaine-addicted patients, this area has repeatedly yielded reduced activation during the Stroop task in patients when compared with controls (Bolla et al., 2004), and when performing other inhibitory control tasks (Kaufman et al., 2003; Hester and Garavan, 2004). Furthermore, a recent report has shown that the lower activation observed in the right lateral prefrontal cortex during inhibitory tasks was reversed with an intravenous administration of cocaine (Garavan et al., 2008). Therefore, this study corroborates previous results of dysfunction in the right inferior frontal cortex associated with cognitive control in cocaine-dependent patients.

The inferior parietal cortex has been seen to be implicated in tasks involving resolution interference processes such as the Stroop task (Derrfuss et al., 2004; Nee et al., 2007). Several studies have implicated the parietal lobes in supporting a notation-independent semantic representation of quantities (see Dehaene and Cohen, 1995, for a review). More specifically in a numeric Stroop task, the intraparietal sulcus and the precuneus have been found to be implicated in the comparison process of numbers, and the activity of these regions is modulated by the numerical distance effect: smaller numerical distances associated with high activation levels (Pinel et al., 2001). This area has been proposed to be altered in cocaine addiction as an effect of an attentional deficit (Tomasi et al., 2007; Bustamante et al., 2011). The right inferior parietal cortex maintains bidirectional connections with the right dorsolateral prefrontal cortex and the anterior insular cortex, and has been implicated in processes of sustained and selective attention, voluntary attentional control, inhibitory control and switching (Corbetta and Shulman, 2002). The altered activation pattern of the right inferior parietal cortex is consistent with not only previous fMRI results (Kübler et al., 2005; Tomasi et al., 2007), but also with neuropsychological studies showing how cocaine users perform poorly in the measures of selective (Simon et al., 2000; Verdejo-García et al., 2005) and sustained attention (Pace-Schott et al., 2008), these being the brain functions related to this brain area. Thus, the attentional control processes affected in cocaine-dependent patients may explain this lower activation in the right inferior parietal cortex during cognitive control.

The superior temporal gyrus displayed lower activation in cocaine-dependent patients compared to matched controls while performing the counting Stroop task. Task-related activation indicates that this area is involved in the execution of the counting Stroop task in both groups (see Table 3). This activation has also been shown when other inhibitory control paradigms were applied (Garavan et al., 1999; Braver et al., 2001; Kiehl and Liddle, 2001; Menon et al., 2001; Garavan et al., 2002). Furthermore, this region reveals a lower gray matter density in cocaine-dependent patients in early studies applying voxel-based morphometry (Franklin et al., 2002; Sim et al., 2007). Thus, its decreased activation in the patient's group might be associated with inhibitory control dysfunction as an effect of the neuropathology underlying cocaine dependence. However, its role in inhibitory control processes has not been defined in functional studies and further research will be necessary to clarify this result.

One of the unexpected results of this research is that both groups differed in terms of the overall response speed in the absence of both differences in speed of reading and the magnitude of the interference in both the paper and fMRI versions of the task. These differences, however, may not be responsible for the observed functional results since covarying out these effects did not change the functional differences between groups. Otherwise, it may be unclear whether reaction time differences might be captured by individual differences in the temporal characteristics of the hemodynamic response. Future event-related designs could better test the possible effect of variability in the reaction time on cocaine-dependent patients' hemodynamic response. The fact that patients displayed slower reaction times than comparison subjects for general task performance could be related to the fact that cocaine use has been shown to lead to general psychomotor slowing in cognitive processing, principally in the Stroop task (Vassileva et al., 2007), as others have shown during working memory tasks (Tomasi et al., 2007). This slowing in cognitive processing could be associated with the disrupted integrity of white matter and fiber tracts in cocaine dependence (Lim et al., 2002; Schlaepfer et al., 2006; Liu et al., 2008), which has an effect on ongoing task performance.

To our knowledge, this is the first study to report lower activation in the right frontoparietal network of treatment-seeking cocaine-dependent patients while performing a Stroop task in an fMRI block design. The Stroop test, when compared to others (e.g., Five Digit test, Go/no Go task), has proved to be a good discriminating interference task between the controls and polysubstance abusers enrolled in therapeutic communities (Fernandez-Serrano et al., 2010), and as a tool to identify cocaine-dependent patients at risk for treatment dropout (Streeter et al., 2008). In a similar sample, a previous event-related fMRI study (Brewer et al., 2008) analyzed the relationship between brain activation during the color-word Stroop task and treatment outcomes for a sample of 20 treatment-seeking cocaine-dependent subjects, without involving healthy control subjects. Their study (Brewer et al., 2008) strictly controlled the variables related to treatment outcomes which, although related to brain activation, questioned possible inter-group functional differences during Stroop performance since no group of controls was involved. Although we could not strictly control the treatment outcome-related variables in this study, we involved a group of cocaine-dependent patients and a matched control group to allow for group comparisons in terms of task performance and brain activation. Furthermore, and as reported before, the Stroop-related activations we obtained were studied under blocked-performance conditions. Therefore, brain functional differences should be interpreted by considering the possible effect of sustained rather than transient activations in the observed functional differences if compared to more common event-related paradigms which do a detailed analysis of brain transient activation to cognitive and response interference to a stimulus (Laird et al., 2005).

Study limitations include a relatively small sample size within which there is a pattern of concurrent substance use in the patient group other than cocaine. A limited assessment ignored the effect of the variables that have already shown their association with brain activation in cocaine dependence such as craving (Li et al., 2010), drug compulsivity abuse (Ersche et al., 2010) or treatment outcome (Brewer et al., 2008). Likewise, a variable that was not considered in detail in both groups was the screening of consumption habits for alcohol, which have been shown to have an important effect on neuroadaptation changes (Cosgrove et al., 2009). Otherwise, the sample is restricted to male participants and involves limitation and strength at the same time. Although restricting the present study to males offers the advantage of maximizing the patient group's homogeneity, this selection limits the scope of the present results. Furthermore, it would be useful to know the structural correlates of these functional differences in the patients. In a previous report by our research group (Bustamante et al., 2011), individual structural variability was seen to

affect inter-group functional differences. However, the individual variability in structural changes did not have a significant effect on the inter-group functional differences during the counting Stroop task analyzed in this study (data not shown; see Bustamante et al., 2011, for a description of the procedure). Finally, the present study does not include another psychometric psychological assessment to test whether lower functional activations are plausibly related to the known behavioral deficits in cocaine addicts, such as impulsivity or compulsivity. Future investigations will overcome the limitations of the present study by considering the difficulties of controlling the wide range of variables involved in cocaine dependence.

In conclusion, our study is the first application of a counting Stroop task in the study of cocaine dependence, and provides more empirical data on the involvement of a frontoparietal network in the neural changes associated with attentional-interference deficits in cocaine-dependent men. All these results indicate the existence of a network of the prefrontal, parietal and temporal regions mediating attentional cognitive control in tasks of cognitive coordination, inhibitory processes and interference control, such as the Stroop task (Egner and Hirsch, 2005). These processes may be associated with the cocaine-related cognitive deficits that have been linked to the relationship between drug cues and compulsive drug self-administration in drug dependence (Goldstein et al., 2001; Carpenter et al., 2006).

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Authors' contribution

Alfonso Barrós-Loscertales was responsible for the study concept, design, sample recruitment, analysis, interpretation of findings and manuscript preparation.

Juan Carlos Bustamante was responsible for data acquisition, data analysis, interpreting the results and preparing the manuscript.

Noelia Ventura-Campos was responsible for data analysis and interpretation.

Juan José Llopis was responsible for sample recruitment, data acquisition and critically reviewing the article.

María Antonia Parcet critically revised the manuscript for important intellectual content and designed the neuropsychological assessment.

Cesar Ávila was responsible for the study design, analysis, interpreting the findings and for critically revising the manuscript.

Acknowledgments

We thank the professional group at the Addictive Behaviors Unit San Agustín of Castellón (UCA, Unidad de Conductas Adictivas San Agustín de Castellón) for their collaboration. This study has been supported by grants from FEPAD (Fundación para el Estudio, Prevención and Asistencias a la Drogodependencia), from the "National Plan of Drugs" (Plan Nacional de Drogas), from the BRAINGLOT, a Spanish Research Network on Bilingualism and Cognitive Neuroscience (Consolider-Ingenio 2010 Scheme, Spanish Ministry of Science and Education), and by other grants (SEJ2007-65929/PSIC, P1·1B2008-35, P1-1A2010-01 and PSI2010-20168). The second author was awarded a Universitat Jaume I research grant (PREDOC/2007/13).

References

Aron, J.L., Paulus, M.P., 2007. Location, location: using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. Addiction 102 (Suppl. 1), 33–43.

Aron, A.R., Behrens, T.E., Smith, S., Frank, M.J., Poldrack, R.A., 2007. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. The Journal of Neuroscience 27, 3743–3752.

Bechara, A., Damasio, H., 2002. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia 40, 1675–1689.

Bolla, K.I., Rothman, R., Cadet, J.L., 1999. Dose-related neurobehavioral effects of chronic cocaine use. The Journal of Neuropsychiatry and Clinical Neurosciences 11, 361–369.

Bolla, K., Ernst, M., Kiehl, K., Mouratidis, M., Eldreth, D., Contoreggi, C., Matochik, J., Kurian, V., Cadet, J., Kimes, A., Funderburk, F., London, E., 2004. Prefrontal cortical dysfunction in abstinent cocaine abusers. The Journal of Neuropsychiatry and Clinical Neurosciences 16, 456–464.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., Cohen, J.D., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179–181.

Braver, T.S., Barch, D.M., Gray, J.R., Molfese, D.L., Snyder, A., 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition, and errors. Cerebral Cortex 11, 825–836.

Brewer, J.A., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Potenza, M.N., 2008. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. Biological Psychiatry 64, 998–1004.

Bush, G., Whalen, P.J., Rosen, B.T.R., Jenike, M.A., McInerney, S.C., Rauch, S.L., 1998. The counting Stroop: an interference task specialized for functional neuroimaging — validation study with functional MRI. Human Brain Mapping 6, 270–282.

Bush, G., Whalen, P.J., Shin, L.M., Rauch, S.L., 2006. The counting Stroop: a cognitive interference task. Nature Protocols 1, 230–233.

Bustamante, J.C., Barrós-Loscertales, A., Ventura-Campos, N., Sanjuán, A., Llopis, J.J., Parcet, M.A., Avila, C., 2011. Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task. Brain Research 1375, 111–119.

Carpenter, K.M., Schreiber, E., Church, S., McDowell, D., 2006. Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. Addictive Behaviours 31, 174–181.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews 3, 201–215.

Cosgrove, K.P., Krantzler, E., Frohlich, E.B., Stiklus, S., Pittman, B., Tamangnan, G.D., Baldwin, R.M., Bois, F., Seibyl, J.P., Krystal, J.H., O'Malley, S.S., Staley, J.K., 2009. Dopamine and serotonin transporter availability during acute alcohol withdrawal: effects of comorbid tobacco smoking. Neuropsychopharmacology 34, 2218–2226.

Dehaene, S., Cohen, L., 1995. Towards an anatomical and functional model of number processing. Mathematical Cognition 1, 83–120.

Derrfuss, J., Brass, M., Von Cramos, D.Y., 2004. Cognitive control in the posterior fronto lateral cortex: evidence from common activations in task coordination, interference control, and working memory. NeuroImage 23, 604–612.

Egner, T., Hirsch, J., 2005. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. Nature Neuroscience 8, 1784–1790.

Ersche, K.D., Bullmore, E.T., Craig, K.J., Shabbir, S.S., Abbott, S., Müller, U., Ooi, C., Suckling, J., Barnes, A., Sahakian, B.J., Merlo-Pich, E.V., Robbins, T.W., 2010. Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. Archives of General Psychiatry 67, 632–644.

Fein, G., Di Sclafani, V., Meyerhoff, D.J., 2002. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug and Alcohol Dependence 68, 87–93.

Fernandez-Serrano, M.J., Pérez-Garcia, M., Perales, J.C., Verdejo-Garcia, A., 2010. Prevalence of executive dysfunction in cocaine, heroin alcohol users enrolled in therapeutic communities. European Journal of Pharmacology 626, 104–112.

Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., O'Brien, C.P., Childress, A.R., 2002. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biological Psychiatry 51, 134–142.

Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiack, S.R., Turner, R., 1995. Analysis of fMRI time-series revisited. NeuroImage 2, 45–53.

Garavan, H., Ross, T.J., Stein, E.A., 1999. Right hemispheric dominance of inhibitory control: an event-related fMRI study. Proceedings of the National Academy of Sciences of the United States of America 96, 8301–8306.

Garavan, H., Kelley, D., Rosen, A., Rao, S.M., Stein, E.A., 2000. Practice-related functional activation changes in a working memory task. Microscopy Research and Technique 51, 54–63.

Garavan, H., Ross, T.J., Murphy, K., Roche, R.A.P., Stein, E.A., 2002. Dissociable executive functions in the dynamic control of behaviour: inhibition, error detection and correction. NeuroImage 17, 1820–1829.

Garavan, H., Kaufman, J.N., Hester, R., 2008. Acute effect of cocaine in the neurobiology of cognitive control. Philosophical Transactions of the Royal Society London B: Biological Sciences 362, 3267–3276.

Golden, C.J., 1978. The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Stoelting, Wood Dale, IL.

Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. The American Journal of Psychiatry 159, 1642–1652.

Goldstein, R.Z., Volkow, N.D., Wang, G.J., Fowler, J.S., Rajaram, S., 2001. Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport 12, 2595–2599.

Goldstein, R.Z., Tomasi, D., Alia-Klein, N., Zhang, L., Telang, F., Volkow, N.D., 2007. The effect of practice on a sustained attention task in cocaine abusers. Neuroimage 35, 194–206.

Goldstein, R.Z., Volkow, N.D., Wang, G.J., Fowler, J.S., Rajaram, S., 2009. Anterior cingulate cortex hypoactivation to an emotionally salient task in cocaine addiction. Proceedings of the National Academy of Sciences of the United States of America 106, 9453–9458.

Hester, R., Garavan, H., 2004. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. The Journal of Neuroscience 24, 11017–11022.
Hester, R., Nestor, L., Garavan, H., 2009. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. Neuropsychopharmacology 34, 2450–2458.
Hoff, A.L., Riordan, H., Morris, L., Cestaro, V., Wieneke, M., Alpert, R., Wang, G.J., Volkow, N., 1996. Effects of crack cocaine on neurocognitive function. Psychiatry Research 60, 167–176.
Kaufman, J.N., Ross, T.J., Stein, E.A., Garavan, H., 2003. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. The Journal of Neuroscience 23, 7839–7843.
Kelly, A.M., Garavan, H., 2005. Human functional neuroimaging of brain changes associated with practice. Cerebral Cortex 15, 1089–1102.
Kerns, J.G., Cohen, J.D., MacDonald III, A.W., Cho, R.Y., Stenger, V.A., Carter, S.C., 2004. Anterior cingulate conflict monitoring and adjustments in control. Science 303, 1023–1026.
Kiehl, K.A., Liddle, P.F., 2001. An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia. Schizophrenia Research 30, 159–171.
Kübler, A., Murphy, K., Garavan, H., 2005. Cocaine dependence and attention switching within and between verbal and visuospatial working memory. The European Journal of Neuroscience 21, 1984–1992.
Laird, A.R., McMillan, K.M., Lancaster, J.L., Kochunov, P., Turkeltaub, P.E., Pardo, J.V., Fox, P.T., 2005. A comparison of label-based review and ALE meta-analysis in the Stroop task. Human Brain Mapping 25, 6–21.
Leung, H.C., Skudlarski, P., Gatenby, J.C., Peterson, B.S., Gore, J.C., 2000. An event-related functional MRI study of the Stroop Color Word Interference task. Cerebral Cortex 10, 552–560.
Li, C.-S.R., Huang, C., Yan, P., Baghwagar, Z., Milivojevic, V., Sinha, R., 2008. Neural correlates of impulse control during Stop signal inhibition in cocaine-dependent men. Neuropsychopharmacology 33, 1798–1806.
Li, C.-S.R., Luo, X., Sinha, R., Roundsville, B.J., Carroll, K.M., Malison, R.T., Ding, Y.-S., Zhang, S., Ide, J.S., 2010. Increased error-related thalamic activity during early compared to late cocaine abstinence. Drug and Alcohol Dependence 109, 181–189.
Lim, K.O., Choi, S.J., Pomara, N., Wolkin, A., Rotrosen, J.P., 2002. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. Biological Psychiatry 51, 890–895.
Lim, K.O., Wozniak, J.R., Mueller, B.A., Franc, D.T., Specker, S.M., Rodriguez, C.P., Silverman, A.B., Rotrosen, J.P., 2008. Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug and Alcohol Dependence 92, 164–172.
Liu, H., Li, L., Hao, Y., Cao, D., Xu, L., Rohrbaugh, R., Xue, Z., Hao, W., Shan, B., Liu, Z., 2008. Disrupted white matter integrity in heroin dependence: a controlled study utilizing diffusion tensor imaging. The American Journal of Drug and Alcohol Abuse 34, 562–575.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19, 1233–1239.
Matochik, J.A., London, E.D., Eldreth, D.A., Cadet, J.L., Bolla, K.I., 2003. Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study. NeuroImage 19, 1095–1102.
Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., Weinberger, D.R., 2003. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proceedings of the National Academy of Sciences of the United States of America 100, 6186–6191.
Mattay, V.S., Fera, F., Tessitore, A., Hariri, A.R., Berman, K.F., Das, S., Meyer-Lindenberg, A., Goldberg, T.E., Callicott, J.H., Weinberger, D.R., 2006. Neurophysiological correlates of age-related changes in working memory capacity. Neuroscience Letters 392, 32–37.
McLeod, C.M., 1991. Half a century of research on the Stroop effect: an integrative review. Psychological Bulletin 109, 163–203.
Menon, V., Adleman, N.E., White, C.D., Glover, G.H., Reiss, A.L., 2001. Error-related brain activation during a Go/NoGo response inhibition task. Human Brain Mapping 12, 131–143.
Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C., 2001. Psychiatric aspects of impulsivity. The American Journal of Psychiatry 158, 1783–1793.
Nee, D.E., Wager, T.D., Jonides, J., 2007. Interference resolution: insight from a meta-analysis of neuroimaging task. Cognitive, Affective and Behavioural Neuroscience 7, 1–17.
Nigg, J.T., 2000. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychological Bulletin 126, 220–246.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Pace-Schott, E.F., Morgan, P.T., Malison, R.T., Hart, C.L., Edgar, C., Walker, M., Stickgold, R., 2008. Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. The American Journal of Drug and Alcohol Abuse 34, 109–121.
Pardo, J.V., Pardo, P.J., Janer, K.W., Raichle, M.E., 1990. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proceedings of the National Academy of Sciences of the United States of America 87, 256–259.
Petersen, S.E., Van Mier, H., Fiez, J.A., Raichle, M.E., 1998. The effects of practice on the functional anatomy of task performance. Proceedings of the National Academy of Sciences of the United States of America 95, 853–860.
Pinel, P., Dehaene, S., Rivière, D., Le Bihan, D., 2001. Modulation of parietal activation by semantic distance in a number comparison task. NeuroImage 14, 1013–1026.
Price, C.J., Friston, K.J., 1999. Scanning patients with tasks they can perform. Human Brain Mapping 8, 102–108.
Price, C.J., Crinion, J., Friston, K.J., 2006. Design and analysis of fMRI studies with neurologically impaired patients. Journal of Magnetic Resonance Imaging 23, 816–826.
Robbins, T.W., 2007. Shifting and stopping: fronto-striatal substrates, neurochemical modulations and clinical implications. Philosophical Transactions of the Royal Society London B: Biological Sciences 362, 917–932.
Roselli, M., Ardila, A., Lubomski, M., Murray, S., King, K., 2001. Personality profile and neuropsychological test performance in chronic cocaine-abusers. The International Journal of Neuroscience 110, 55–72.
Schlaepfer, T.E., Lancaster, E., Heidbreder, R., Strain, E.C., Kosel, M., Fisch, H.U., Pearlson, G.D., 2006. Decreased frontal white-matter volume in chronic substance abuse. The International Journal of Neuropsychopharmacology 9, 147–153.
Selby, M.J., Azrin, L.R., 1998. Neuropsychological functioning in drug abusers. Drug and Alcohol Dependence 50, 39–45.
Sim, M.E., Lyoo, I.K., Streeter, C.C., Covell, J., Sarid-Segal, O., Ciraulo, D.A., Kim, M.J., Kaufman, M.J., Yurgelun-Todd, D.A., Renshaw, P.F., 2007. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology 32, 2229–2237.
Simon, S.L., Domier, C., Carnell, J., Brethen, P., Rawson, R., Ling, W., 2000. Cognitive impairment in individuals currently using methamphetamine. The American Journal on Addictions 9, 222–231.
Streeter, C.C., Terhune, D.B., Whitfield, T.H., Gruber, S., Sarid-Segal, O., Silveri, M.M., Tzilos, G., Afshar, M., Rouse, E.D., Tian, H., Renshaw, P.F., Ciraulo, D.A., Yurgelun-Todd, D.A., 2008. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. Neuropsychopharmacology 33, 827–836.
Tanabe, J., Tregellas, J.R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., Banich, M., 2009. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. Biological Psychiatry 65, 160–164.
Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., Volkow, N.D., 2007. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. Brain Research 1171, 83–92.
Vassileva, J., Gonzalez, R., Bechara, A., Martin, E.M., 2007. Are all drug addicts impulsive? Effects of antisociality and extent of multidrug use on cognitive and motor impulsivity. Addictive Behaviours 32, 3071–3076.
Vearrier, D., Curtis, J.A., Greenberg, M.I., 2010. Biological testing for drugs of abuse. EXS 100, 489–517.
Verdejo-García, A., López-Torrecillas, F., Orozco, C., Pérez-García, M., 2004. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant and opioid abuse. Neuropsychology Review 14, 1–41.
Verdejo-García, A., Rivas-Pérez, C., Lopez-Torrecillas, F., Perez-García, M., 2005. Differential impact of severity of drug use on frontal behavioral symptoms. Addictive Behaviours 31, 1373–1382.
Wechsler, D., 2001. Escala de inteligencia de Wechsler para adultos-III (WAIS-III). TEA Ediciones, Madrid.
Winstanley, C.A., 2007. The orbitofrontal cortex, impulsivity, and addiction: probing orbitofrontal dysfunction at the neural, neurochemical and molecular level. Annals of the New York Academy of Sciences 1121, 639–655.
Zysset, S., Müller, K., Lohmann, G., von Cramon, D.Y., 2001. Color-word matching stroop task: separating interference and response conflict. NeuroImage 13, 29–36.

Section 2.5. Bustamante J.C., Barrós-Loscertales A., Costumero V., Fuentes-Claramonte P., Rosell P., Ventura-Campos N., Llopis J.J., Ávila C. (Submitted). Modulation of abstinence duration on striatal functioning during monetary reward processing in cocaine patients.

Number of words: 4.589

Number of tables: 2

Number of figures: 2

Title : Modulation of Abstinence duration on striatal functioning during monetary reward processing in cocaine patients.

Authors: J.C. Bustamante, MSc; A. Barrós-Loscertales, PhD; V. Costumero, MSc; P. Fuentes-Claramonte, MSc; P. Rosell, MSc; N. Ventura-Campos, MSc; J.J. Llopis, MD; C. Ávila, PhD.

Location of work: Department of Basic Psychology, Clinical Psychology and Psychobiology; Universitat Jaume I, Castellón (Spain).

Full Address for correspondence: J.C. Bustamante; Departamento de Psicología Básica, Clínica y Psicobiología; Edificio de Investigación 2, Universitat Jaume I de Castellón; Avda. Sos Baynat s/n, 12071, Castellón de la Plana (Spain).

Abstract

Objective:

Preclinical and clinical studies in cocaine addiction highlight alterations in the striatal dopaminergic reward system that subserve the maintenance of cocaine use. Using an instrumental conditioning paradigm with monetary reinforcement, we studied striatal functional alterations in long-term abstinent cocaine-dependent patients and striatal functioning as a function of abstinence and treatment duration.

Method:

Eighteen patients and twenty controls underwent fMRI during a Monetary Incentive Delay task. ROIs analyses based on two masks of the striatum (including caudate, accumbens and putamen) were conducted for testing between-group differences and the functional effects of time on treatment and protracted abstinence in the cocaine group. We applied a voxel-wise and a cluster-wise FWE-corrected level (pFWE) at a threshold of $p<.05$.

Results:

The patient group showed lower activation in the right caudate during reward anticipation than the control group. The regression analyses in the patients group revealed a positive correlation between time on treatment and brain activity in the left caudate during reward anticipation. Likewise, time of abstinence negatively correlated with brain activity in the bilateral nucleus accumbens during reward outcome.

Conclusions:

Caudate and nucleus accumbens showed a different brain response pattern to non-drug rewards during cocaine addiction, which could be modulated by treatment success. Reduced response to cues that anticipate reward was observed in the caudate, but this response was recovered as time on treatment prolonged. In contrast, the nucleus accumbens response to outcomes seemed to increase the shorter the time of abstinence was.

Introduction

The enhanced motivation to procure drugs is a hallmark in addiction (1). The alteration of the brain reward system in cocaine addiction is the core of compulsive drug taking and is thought to mediate intense drug craving and relapse (2,3). These brain alterations lead to an excessive attribution of incentive salience to drug-related stimuli, causing a "pathological wanting" to take drugs (1,3), paralleling altered incentive salience, motivation and reward sensitivity to other natural reinforcers of addicted subjects.

Dopamine (DA) is highly concentrated in the striatum as a part of the brain's reward system altered by drugs of abuse (4). Chronic cocaine use among human addicts has been associated with neuroadaptations in the dopaminergic reward system, especially in the striatum (5,6,7). Consequences of long-term cocaine use have been related to changes in the mesocorticolimbic dopamine system innervating the ventral striatum (VS) and the dorsal striatum (DS) (1,8,9,10,11). Dopaminergic innervation of the VS has been widely implicated in the reinforcing properties of cocaine (12,13), while the DS is known to mediate stimulus-response habit learning (14). Thus, the transition from voluntary drug use to habitual and progressively compulsive drug abuse is associated with a shift from ventral to dorsal striatal control over drug-response behavior (15).

Experimental paradigms using monetary incentives as reinforcers have been applied to study brain changes in reward-related areas due to cocaine addiction (11,16). The use of reinforcers other than the drug, such as money in instrumental conditioning, may also serve as an indirect measure of the brain function in reward target regions affected by the drug, thus avoiding ethical issues of using drugs as reinforcers in humans. Neuroimaging studies show that monetary reward processing tasks activate the striatum (DS and VS) not only in response to cues signaling an imminent opportunity to respond for monetary rewards (17), but also during the notification of monetary outcome (18). While individuals with cocaine addiction display striatal hypersensitivity in response to drug-related cues, evidence for striatal sensitivity to other rewards is mixed in the literature (11,19,20). Likely, the contradictions among the results depend on methodological issues and the characteristics of samples.

Cocaine exposure may produce non permanent alterations in the DA system, which recover with prolonged abstinence from drug use (21). In animal studies, regulation of the DA system is highly labile during the period immediately following cessation of cocaine self-administration, but is followed by a re-regulation of the system to approach a more normal distribution of DA receptors and transporters after more protracted abstinence (21). In humans, Volkow et al. (22) showed a recovery of the DA system in DS in stimulant substance users after protracted abstinence. Therefore, it is suggested that DA system recovery after long-term cocaine abstinence may regularize the functionality of the reward processing circuitry in cocaine addiction.

Functional and structural changes in cocaine addiction have been widely studied, although one of the less explored issues in human cocaine addiction is the neurobiological basis of cocaine abstinence and relapse (23). In the cognitive domain, there are two studies demonstrating a functional enhancement of dopaminergically innervated brain regions after long periods of abstinence (24,25). Only one study has investigated reward system functioning in cocaine patients with a motivational-related task, but it used a shorter period of abstinence (11). The aim of our study is to show the neurofunctional changes of cocaine protracted abstinence on striatum activation related with anticipation and reactivity to monetary outcomes in a cross-sectional study by adapting the Monetary Incentive Delay Task (MIDT; 17). The task was modified in order to enhance DS activity in reward-response processing (26). We expected striatal functional differences between our research groups and a regulation of striatum functionality during monetary reward processing associated with abstinence and time on treatment.

Method

Participants

Eighteen abstinent cocaine-dependent men and twenty matched healthy men participated in this study. All the participants were right-handed according to the Edinburgh Handedness Inventory (27). An initial study of their clinical history and a subsequent onsite assessment by a neuropsychologist and a psychiatrist ensured that both groups were physically healthy with no major medical illnesses or DSM IV Axis I

disorders, under no current use of psychoactive medications, and had no history of head injury with loss of consciousness or neurological illness.

An interview that included the Structured Clinical Interview for DSM-IV Axis I Disorders ensured that all the patients met the DSM-IV criteria for cocaine dependence. Cocaine-dependent volunteers were recruited at the Addictive Behaviors Unit of Castellón (Spain) from among those who regularly visit to manage their abstinence. Besides behavioral and/or pharmacological treatment, patients were monitored for continued abstinence with random urine toxicology testing or by clinical interviews with a psychiatrist who supervised treatment. According to clinical records, two variables were obtained to quantify time on treatment. Time of Abstinence was the number of months without lapses or relapses at the time of the scanning session (mean of 22.65 months, SD=20; range: 3-72 months). The second variable was Time on Treatment; that is, time (in months) from their first time they visited the clinical service to seek treatment at the time of scanning (mean of 26.47 months, SD=25.04; range: 2-99 months). In this case, patients were not included in the study if they had more than two lapses during this period. Both variables were inspected with the respective non parametric tests (Kolmogorov-Smirnov (K-S) for Time of Abstinence, $Z=0.74$, $p>0.1$; K-S for time on treatment, $Z=0.94$, $p>0.1$), thus ensuring normality in the distributions.

A urine toxicology test was done to rule out cocaine consumption, which ensured a minimum period of abstinence of over 2/4 days prior to fMRI data acquisition, as with any urine test done at the clinic before patients were appointed to the scanning session. One patient and one control were excluded because of technical issues affecting task performance during the scanning session. Moreover, one control was excluded for excessive head movements (more than 2 mm of translation or 2 degrees of rotation) during fMRI acquisition.

The final sample (17 cocaine-dependent men and 18 comparison men) who took part in the study were matched for age, number of years of education, and general intellectual functioning (see Table 1). General intellectual functioning was assessed with the Matrix Reasoning test from WAIS-III (28). The cocaine-dependent participants reported an average (±S.D.) of 22.24 (6.92) and 13.35 (7.01) years as first-used cocaine age and years of cocaine use, respectively. Ten of these patients (58.8%) and the other seven

(41.2%) reported daily and weekly frequency of cocaine consumption, respectively. Participants were informed of the nature of the research and were provided a written informed consent prior to participation in this study. This research work was approved by the institutional Review Board of the Universitat Jaume I of Castellón.

Table 1. Mean scores (standard deviations in parentheses) of the main demographic characteristics and the behavioral results of the percentage of correct responses and reaction time (RT) of the patients group and comparison group for both conditions of interest (LRC, low reward condition; HRC, high reward condition).

Sociodemographic variables			
	Comparison group (n=18)	**Patients group (n=17)**	**Difference (p>0.05)[a]**
Age (SD)	37.44 (8.15)	37.47 (5.90)	n.s.
Years of education (SD)	9.56 (2.20)	9.59 (2.53)	n.s.
Intellectual functioning (SD)[b]	8.94 (2.07)	9.53 (3.22)	n.s.
MIDT performance			
	Comparison group (n=18)	**Patients group (n=17)**	**Difference (p>0.05)[a]**
LRC			
Hit rate: % (SD)[c]	77.32 (15.07)	75.54 (19.69)	n.s.
RT (SD)[d]	192.96 (29.01)	194.32 (42.11)	n.s.
HRC			
Hit rate: % (SD)[c]	79.63 (13.63)	77.45 (18.98)	n.s.
RT (SD)[d]	189.96 (27.24)	189.28 (37.30)	n.s.

n, number of participants.
[a] Differences between groups (n.s.= no significance).
[b] Standard score in the Matrix Reasoning test (WAIS-III).
[c] Percentage of correct responses in the specific reward condition.
[d] RT in milliseconds.

Paradigm

We used an adaptation of the MID task described by Knutson et al. (17) to elicit neural responses to monetary incentive anticipation and outcomes. Before entering the scanner, all subjects were instructed in the task and completed a practice version for 13 min to minimize later learning effects and to provide an estimate of each individual's reaction time for standardizing task difficulty in the scanner. All the subjects started the task with € 20 and were made aware that they would receive cumulative money throughout the scanning task without including the practice period.

Inside the scanner, subjects performed two 8-min runs of the MID task. Each session consisted of 60 trials, yielding a total of 120 trials. There were two kinds of trials: incentive and non incentive. Each incentive trial consisted of a cue presented for 500 ms, followed by a black screen of variable duration (2000-2250 ms), and then by a white target square that appeared for 100 ms on which subjects had to respond with a response button as quickly as possible. After the subject's response, a black screen with a variable duration of 2000-4000 ms was presented, followed by a feedback (1500 ms) which notified participants whether they had won or lost money during that trial, and which indicated their cumulative total win up until that time. Four kinds of cues could appear at the beginning of incentive trials; a circle with two horizontal lines, indicating the possibility of winning 3 euros (n=24); a circle with one horizontal line indicating the possibility of winning 0.20 euros (n=24); a square with two horizontal lines indicating the possibility of avoiding losing 3 euros (n=24); a square with one horizontal line indicating the possibility of avoiding losing 0.20 euros (n=24). Finally, a triangle (n=24) was the cue for non incentive trials in which volunteers could not win or lose money. Trial types were pseudo-randomly ordered within each session. The inter-trials interval was randomized between 2000 and 4000 ms.

fMRI acquisition

Imaging was performed using a 1.5-T Siemens Avanto (Erlanger, Germany) MRI scanner. Functional images were acquired using a T2 * gradient (TR/TE =2000/30ms, flip angle= 90°, number of volumes= 251 per run). Thirty 3.5-mm-thick slices centered parallel to the hippocampus were axially acquired with a 0.5-mm interslice gap.

Structural images were acquired using a T1-weighted sequence with TR / TE = 11 / 4.9 ms, flip angle= 90 °, voxel size = 1mm^3, which facilitated the localization and corregistration of functional data.

fMRI preprocessing and analysis

Analyses focused on changes in the blood oxygen-level-dependent (BOLD) contrast which took place during anticipatory delay periods and outcomes. The data were preprocessed and analyzed using the SPM8 software package (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first two scans in each run were excluded from the analyses to discount artifacts relating to the transient phase of magnetization. For pre-processing purposes, we applied a slice-timing correction, realignment, corregistration, segmentation and spatial normalization of the functional scans. This normalization was done according to the Montreal Neurological Institute´s (MNI) template by applying an affine transformation, followed by the non linear deformation using basis functions defined in the SPM program. The computed transformation parameters were applied to all the functional images, interpolating to a final voxel size of 3 × 3 × 3 mm^3. Subsequently, images were spatially smoothed with an 8-mm isotropic Gaussian kernel.

A general linear model was used to calculate any significant hemodynamic changes between conditions. At the first level analysis (fixed effects), the preprocessed time series of each participant was modeled for each condition of interest using the hemodynamic response function and its temporal derivate. In addition, a high-pass filter (128 s) was applied to eliminate low frequency components. The parameters from each subject's motion correction were included in the model as "nuisance" variables. Then, statistical contrasts were generated to obtain the brain activation for anticipatory delay and outcome periods. To obtain the brain activation for incentive anticipation and reactivity in the task, we separately extracted eight contrast weights (high reward cue vs. non incentive cue, low reward cue vs. non incentive cue, high punishment cue vs. non incentive cue, low punishment cue vs. non incentive cue, high reward outcome vs. baseline, low reward outcome vs. baseline, avoidance of high punishment outcome vs. baseline and avoidance of low punishment outcome vs. baseline) for each subject. Then, the contrasts images obtained from the first-level analysis were used in a second-level

random effect model. By considering the objective of the study, we centered our analyses on the contrasts over the extreme higher monetary reward conditions (for anticipation condition, high reward cue vs. non incentive cue; and for the reactivity condition, high reward outcome vs. baseline). The predicted activation differences and correlations in the striatum were tested using small volume correction in anatomically defined regions of interest (ROIs).

The ROI mask analysis was performed based on a previous study (26). We applied an anatomically defined ROIs analysis based on two different masks of the striatum comprising the caudate, putamen and nucleus accumbens (Nacc). The two striatal ROIs were derived from automatic anatomical labeling WFU Pickatlas (29). The VS ROIs (including Nacc bilaterally) were defined as a 10-mm radius sphere at 10, 8, 0/-10, 10, –2 (x, y, z, MNI coordinates; based on 30). DS ROIs, including caudate bilaterally and putamen bilaterally, were defined as discrete ROIs and were selected from pre-established regions of the Pickatlas toolbox. The ROI masks were applied to the analyses of both the contrast between and within groups and of the correlation between brain activation during reward anticipation and reactivity, and clinical variables Time on Treatment and Time of Abstinence. Small volume correction was applied at a voxel-wise and cluster-corrected threshold (FWE at $p<0.05$).

Results

Behavioral data

Behavioral performance was analyzed in terms of reaction time (RT) and response accuracy (hits). We performed repeated measure 2 Condition (High reward, Low reward) × 2 Groups (controls, patients) ANOVA analysis for each variable, which showed neither a significant main effect nor interaction in terms of accuracy or RT ($p>0.1$). Thus, both groups of participants maintained a consistent and similar rate of effort across trials, regardless of incentive conditions. Table 1 shows the behavioral results obtained for both groups during the reward conditions only, by taking into account their relevance for the rationale of the manuscript.

ROI analyses

One-sample t-tests

For the one-sample t-tests, both the control and patient groups (see Table 2) showed significant activations during the anticipation condition (high reward cue vs. non incentive cue contrast) in the DS ROIs including the caudate and putamen bilaterally, and in the VS ROIs including Nacc bilaterally. During the outcome reactivity condition (high reward outcome vs. baseline contrast), the patients group showed activation in the left putamen.

Two-sample t-tests

The two-sample t-tests showed that the patient group displayed less activation in the right caudate in comparison with the control group during the anticipation condition (see Table 2 and Figure 1). There were no significant between-groups differences in the VS during reward anticipation. There were no between-group differences during reactivity in any of the ROI masks.

Regression analyses

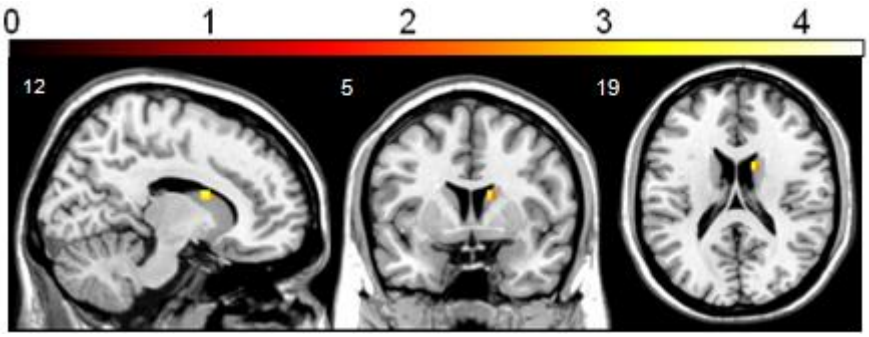
For the correlation analyses, we obtained a positive correlation during anticipation between activity in the left caudate and Time on Treatment (see Table 2 and Figure 2). Moreover, the activations during reactivity in the left and right Nacc negatively correlated with Time of Abstinence.

Table 2. Functional effects for ROI analyses in one-sample t-tests, two-sample t-tests and regression analyses.

ROI analyses	***Reward condition***	***Brain region***	***MNI Coordinates***	***Cluster size****	***z score***
Comparison group	Anticipation	Right caudate	9, 8, 1	168	5.00
		Left caudate	-12, 8, 7	170	4.67
		Right putamen	21, 8, -5	186	4.69
		Left putamen	-21, 5, 1	289	5.72
		Right Nacc	15, 2, 4	137	5.56
		Left Nacc	-15, 5, 4	123	5.36
Abstinent cocaine patients	Anticipation	Right caudate	9, 8, 4	140	5.08
		Left caudate	-9, -1, 16	157	5.01
		Right putamen	18, 11, -2	178	4.63
		Left putamen	-18, 5, 7	240	4.80
		Right Nacc	9, 8, 4	140	5.08
		Left Nacc	-9, 8, 4	125	4.95
	Outcome	Right putamen	24, 11, -2	31	3.50
Controls > Patients	Anticipation	Right caudate	12, 5, 19	10	3.80
Regression analyses					r
Time on treatment	Anticipation	Left caudate	-15, 23, -2	11	4.39	0.805
Time of abstinence	Outcome	Right Nacc	9, 8, -5	18	2.96	-0.704
		Left Nacc	-3, 17, -2	19	3.79	-0.743

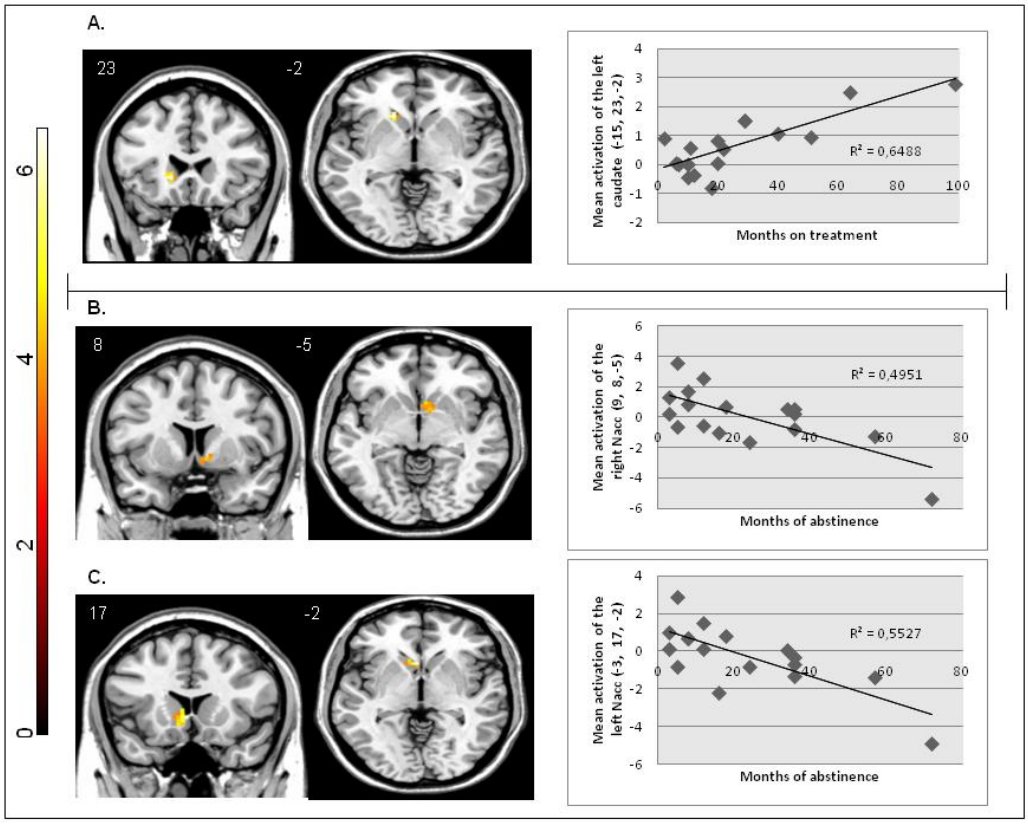
* number of contiguous voxels activated.
z score, standardized score.
r, Pearson's correlation value.

Figure 1. Functional effects for ROI analyses in two-sample t-tests (comparison group> patients group: right caudate; FWE at p<0.05).



Right is right.
Bar plot represents z-values.
White labels indicate the coordinate of each slice in the MNI frame of reference (x,y,z).

Figure 2. Functional effects for ROI analyses in regression analyses (FWE at p<0.05).



A. Positive correlation between activation in the left caudate during the anticipation condition and months on treatment. B. Negative correlations between activation in the right Nacc and left Nacc during reactivity condition and months of abstinence.
Right is right.
Bar plot represents z-values.
White labels indicate the coordinate of each slice in the MNI frame of reference (x,y,z).

Discussion

Our study shows that both cocaine addicts and healthy controls activated striatal regions (DS and VS) during reward cues processing. Cocaine addicts displayed lower activation in the right caudate during reward-response anticipation when compared with the comparison group. The crucial results of this study were that the clinical variables, such as Time on Treatment and Time of Abstinence have been positively and negatively associated with DS (caudate) and VS (Nacc) activity during reward anticipation and reactivity, respectively. Therefore, our results suggest that striatum reactivity to reward anticipation and outcome dynamically change depending on Time on Treatment and abstinence progress.

Cocaine-dependent patients showed lower activation in the caudate during the presentation of the high reward-response anticipation cue. This result may be related with the codification of a lower motivational value for the monetary incentive in cocaine addiction (3,16). The DS is involved in the anticipation and emission of motivated or approach responses when faced with reward cues (31,32). The present data are consistent with data demonstrating that addicted patients show a diminished emotional response to natural reinforcers in general, except for drugs (33,34,35). Some neuroimaging studies have also shown blunted responses to natural reinforcers in brain reward areas (19,20). Previous results have revealed abnormal activity in the DS in cocaine-dependent subjects (7). The role of the DS in addiction is related with cue-induced drug seeking rather than with drug taking (36,37,38). Exposure to drug cues in cocaine addicts increases dopamine activity in the DS, and this increase in dopamine activity correlates with the intensity of cue-induced craving (8,9). Hence, our data are consistent with the existence of an opposite pattern in DS functionality while processing drug or natural reinforcing cues.

Our analysis reveals that longer Time on Treatment relates to increased DS function during reward-response anticipation, suggesting a functional recovery of the caudate. Thus, treatment retention was associated with a recovered functional response, which may be related with the adjudication of a higher motivational-incentive value to monetary-related cues (39). Therefore, DS activity during processing of cues of reward may serve as a clinical index of recovery from addiction.

The results of the present study did not find between-groups differences in VS responses to cues of reward and outcomes. These results differ from those reported by Jia et al. (11) using a similar version of the MID task. However, there are some important differences between both studies that may serve to explain these discordant results. First, we modified the task in order to enhance DS activity which, in turn, may affect VS activity (26). Second, and maybe more importantly, we selected cocaine-abstinent patients instead of treatment-seeking patients with shorter periods of abstinence. In this sense, we did not obtain between-group differences effects in the VS, but we obtained a negative correlation between months of abstinence and VS activity during outcome processing, as also reported by Jia et al. (11). Our results show that those patients with less Time of Abstinence are those who exhibit stronger VS responses during monetary outcome. By considering all the results together, we may tentatively conclude that there is increased VS activity to outcomes, which is enhanced when abstinence begins (11), but it becomes normal or decreases as Time of Abstinence prolongs. One possible explanation is that money could act as a secondary reinforcer toward substance use by increasing monetary outcome responses, which may represent a more resistant neural mechanism to intervention (11).

Study limitations include a relatively small sample size. Nevertheless, several studies in cocaine dependence have used similar sample sizes given the difficulty of recruiting homogeneous groups. Moreover, the sample is restricted to male participants. Nonetheless, restricting the present study to males offers the advantage of maximizing the patient group's homogeneity. Finally, the present study does not include other psychometric psychological assessments, such as impulsivity or compulsivity, or severity of consumption indexes. In addition, a limited assessment ignores the effect of variables whose association with brain activation in substance dependence such as craving has already been shown (40). Future research will overcome the limitations of the present study.

To summarize, we suggest that the DS and VS seem to have different brain patterns of activation in response to monetary rewards, which could be modulated by abstinence and Time on Treatment. During addiction and when abstinence begins, the VS responds strongly to reward outcomes. This response may disappear when Time of Abstinence is

longer. The DS's response to reward anticipation may decrease during abstinence, thus increasing the vulnerability to relapse if there is not treatment present. However, the recovery of the DS's response to normal levels may occur as long as patients are free of cocaine consumption and, after learning new habit responses, it may be a good indicator of success in treatment. Striatal activations during monetary reward processing and their association with variables involving effectiveness of treatment may have motivational implications that elucidate the comprehension of the maintenance of the compulsive/impulsive behavioral pattern in cocaine addiction. Further studies are needed to test the clinical utility of this differential response in the VS and DS.

Disclosures and Acknowledgements:

The authors report no financial relationship with commercial interests. Also, authors report no competing interests.

We thank the professional group at the Addictive Behaviors Unit San Agustín of Castellón (UCA; Unidad de Conductas Adictivas de Castellón) for their collaboration. This research was supported by the Brainglot project of the CONSOLIDER-INGENIO 2010 Programme (CSD2007-00012). Also, the project was supported by grants PSI2010-20168 from MINECO, P1-1B2011-09 from Universitat Jaume I and FEPAD to CA, GV/2012/042 from the Generalitat Valenciana, P1-1A2010-01 from Universitat Jaume I to ABL, and grants 4623/2011 and from Spanish National Drug Strategy Ministerio de Sanidad y Consumo.

References

1. Volkow ND, Wang GJ, Fowler JS, Tomasi D: Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol 2011; 52: 321-326.
2. Goldstein RZ, Volkow ND: Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 2002; 159: 1642-1652.
3. Robinson TE, Berridge KC: Addiction. Annu Rev Psychol 2003; 54: 25-53.
4. Fowler JS, Volkow ND, Kassed CA, Chang L: Imaging the addicted human brain. Sci Pract Perspect 2007; 3: 4-16.
5. Malison RT, Best SE, Van Dyck CH, McCance EF, Wallace EA, Laruelle M, Baldwin RM, Seibyl JP, Price LH, Kosten TR, Innis RB: Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT. Am J Psychiatry 1998; 155: 832-834.
6. White FJ, Kalivas PW: Neuroadaptations involved in amphetamine and cocaine dependence. Drug Alcohol Depen 1998; 51: 141–153.
7. Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE: Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 1997; 386: 827-830.
8. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C: Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci 2006; 26: 6583-6588.
9. Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A, Brasić JR, Kimes AS, Maris MA, Kumar A, Contoreggi C, Links J, Ernst M, Rousset O, Zukin S, Grace AA, Lee JS, Rohde C, Jasinski DR, Gjedde A, London ED: Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. Neuropsychopharmacology 2006; 31: 2716-2727.
10. Hanlon CA, Wesley MJ, Porrino LJ: Loss of functional specificity in the dorsal striatum of chronic cocaine users. Drug Alcohol Depen 2009; 102: 88-94.
11. Jia Z, Worhunsky PD, Carroll KM, Rounsaville BJ, Stevens MC, Pearlson GD, Potenza MN: An Initial Study of Neural Responses to Monetary Incentives as

Related to Treatment Outcome in Cocaine Dependence. Biol Psychiatry 2011; 70: 553-560.

12. Wise RA: Dopamine, learning and motivation. Nat Rev Neurosci 2004; 5: 483–94.
13. Pierce RC, Kumaresan V: The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neurosci Biobehav Rev 2006; 30: 215-38.
14. Packard MG, Knowlton BJ: Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 2002; 25: 563-93.
15. Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW: Neural mechanism underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philos Trans R Soc Lond B Biol Sci 2008; 363: 3125-3135.
16. Goldstein RZ, Tomasi D, Alia-Klein N, Zhang L, Telang F, Volkow ND: Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am J Psychiatry 2007; 164: 43-51.
17. Knutson B, Adams CM, Fong GW, Hommer D: Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 2001; 21: 1-5.
18. Delgado MR, Locke HM, Stenger VA, Fiez JA: Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. Cogn Affect Behav Neurosci 2003; 3: 27-38.
19. Asensio S, Romero MJ, Palau C, Sanchez A, Senabre I, Morales JL, Carcelen R, Romero FJ: Altered neural response of the appetitive emotional system in cocaine. Addict Biol 2010; 15: 504-516.
20. Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ: Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimulus. Am J Psychiatry 2000; 157: 1789-1798.
21. Beveridge T, Smith HR, Nader MA, Porrino LJ: Abstinence from chronic cocaine self-administration alters striatal dopamine systems in rhesus monkeys. Neuropsychopharmacology 2009; 34: 1162-1171.
22. Volkow ND, Chang L, Wang G-J, Fowler JS, Franceschi D, Sedler MJ, Gatley SJ, Miller E, Hitzemann R, Ding Y-S, Logan J: Loss of dopamine transporters in

methamphetamine abusers recovers with protracted abstinence. J Neurosci 2001; 21: 9414–9418.

23. Bell RP, Foxe JJ, Nierenberg J, Hoptman MJ, Garavan H: Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. Drug Alcohol Depen 2011; 114: 159-168.
24. Connolly CG, Foxe JJ, Nierenberg J, Shpaner M, Garavan H: The neurobiology of cognitive control in successful cocaine abstinence. Drug Alcohol Depen 2012; 121: 45-53.
25. Moeller SJ, Tomasi D, Woicik PA, Maloney T, Alia-Klein N, Honorio J, Telang F, Wang GJ, Wang R, Sinha R, Carise D, Astone-Twerell J, Bolger J, Volkow ND, Goldstein RZ: Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. Addict Biol 2012; in press.
26. Guitart-Massip M, Fuentemilla Ll, Bach DR, Huys QJM, Dayan P, Dolan RJ, Duzel E: Action dominates valence in anticipatory representations in the human striatum and dopaminergic midbrain. J Neurosci 2011; 31: 7867-7875.
27. Oldfield, RC: The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.
28. Wechsler, D., 2001. Escala de inteligencia de Wechsler para adultos-III (Intelligence Scale Weschler, WAIS-III). TEA Ediciones, Madrid.
29. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH: An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of Fmri data sets. Neuroimage 2003; 19: 1233-1239.
30. Knutson B, Greer SM: Anticipatory affect: neural correlates and consequences for choice. Philos Trans R Soc Lond B Biol Sci 2008; 363: 3771-3786.
31. Delgado MR, Stenger VA, Fiez JA: Motivation-dependent responses in the human caudate nucleus. Cereb Cortex 2004; 14: 1022–1030.
32. Hikosaka O: Basal ganglia mechanisms of reward-oriented eye movements. Ann N Y Acad Sci 2007; 1104: 229–249.
33. George MS, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, Nahas Z, Vincent DJ: Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Arch Gen Psychiatry 2001; 58: 345-52.

34. Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KP: Neural activity related to drug craving in cocaine addiction. Arch Gen Psychiatry 2001; 58: 334-41.
35. Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC: Functional magnetic resonance imaging of cocaine craving. Am J Psychiatry 2001; 158:86–95.
36. Vanderschuren L, Di Ciano P, Everitt B J: Involvement of the dorsal striatum in cue-controlled cocaine seeking. J. Neurosci 2005; 25: 8665–8670.
37. Fuchs RA, Branham RK, See RE: Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. J. Neurosci 2006; 26: 3584–3588.
38. Belin D, Everitt BJ: Cocaine seeking habits depend upon doparnine-dependent serial connectivity linking the ventral with the dorsal striatum. Neuron 2008; 57: 432–441.
39. Robinson TE, Berridge KC: Review. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc Lond B Biol Sci 2008; 363, 3137-3146.
40. Wrase J, Schlagenhauf F, Kienast T, Wüstenberg T, Bermpohl F, Kahnt T, Beck A, Ströhle A, Juckel G, Knutson B, Heinz A: Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 2007; 35: 787-94.

Chapter 3.General Discussion

The aim of this doctoral thesis was to present more evidence for the possible alterations that could produce chronic cocaine use from a neurobiological perspective by taking into account the results related with structural and functional alterations in the dopaminergic mesocorticolimbic circuit, which is clearly implicated in cocaine addiction (Goldstein and Volkow, 2002). This thesis presents one study related with morphometric results and three studies related with functional results. Specifically, the VBM study shows that cocaine-addicted individuals present reduced GM volume in the DS. Moreover, this study reveals that the regional GM volume of the amygdala correlates inversely with years of cocaine use. These results support the neuroadaptations presented in cocaine addiction (Koob and Le Moal, 2008) and may be related with the cognitive and motivational components of cocaine dependence that implicate disinhibitory drug stimuli-driven behaviours and compulsion. Regarding fMRI studies, the results relate with the two main components of the vicious circle that represent current theoretical cocaine addiction models: cognitive control and salience attribution (Koob et al., 1993; Koob and Lemoal, 1997; Blum et al., 2000; Goldstein and Volkow, 2002; Robinson and Berridge, 2003, 2008; Leyton, 2007; Volkow et al., 2011b). Two studies show functional frontoparietal implications in attentional-control alterations that are present in cocaine addiction. One functional study reports that cocaine-dependent patients may present hypoactivation in the inferior parietal gyrus (IPG) during a working memory n-back task. The second functional study reveals that cocaine-dependent patients can also present hypoactivation in the IFC, the inferior parietal cortex (IPC) and the superior temporal cortex (STC) during an interference-control Counting Stroop task in comparison to a control group.

The last fMRI study presents a new perspective related with the alterations presented in cocaine patients in monetary reward processing. Cocaine-dependent patients exhibit hypoactivation in the caudate during the presentation of incentive

anticipation cues that might be related with the codification of a lower motivational value for the monetary incentive. Some studies have shown that presentation of drug cues induces drug craving, which is related with the activation of the amygdala and the limbic prefrontal cortical areas (Grant et al. 1996; Childress et al. 1999; Garavan et al. 2000), and also marks the activation of the DS (Garavan et al. 2000; Volkow et al. 2006a). Thus, in this third study, the results support the increasing importance of the DS in well-established or habitual drug seeking by placing importance on the shift from the VS to the DS (Everitt et al., 2008). In addition, this study indicates that abstinence and time on treatment are related with striatal functional regulation during anticipation and reactivity to non-drug related stimuli. Treatment retention is associated with recovery of caudate functionality during anticipation, which may be related with adjudication of a higher motivational-incentive value to monetary-related cues. The DS mediates the stimulus-response instrumental learning process; instrumental responding for reward is induced by reward-associated stimuli (Everitt et al., 2008). This mediation, based on DS functioning, is conditioned by the motivational non-drug reward value. Another interesting result is related with the fact that Nacc reactivity is enhanced during monetary outcome with a short abstinence time, as occurs in a previous study (Jia et al., 2011), and as we show it becomes normal or lowers when patients have achieved protracted abstinence. Hypersensitivity of ventral striatal regions during monetary outcome may represent a neural mechanism that is more resistant to intervention. Money may act as secondary reinforcer towards substance use (Jia et al., 2011). Drug-seeking behaviour is a response habit triggered and maintained by drug-associated stimuli (Everitt et al., 2001), and these habits initially depend on the ventral striatal mechanism (Everitt et al., 2008). Drug-free states can be related with functional effects, which might represent the recovery or regulation of the motivational value for non-drug related stimuli, thus promoting a healthy approach-behavioural pattern to non-drug-related rewards.

Addiction involves complex interactions between biological (genome, protein expression, neurotransmission circuits, neurostructural and neurofunctional implications), behavioural and environmental variables (Volkow et al., 2003). This work presents neurobiological findings related with previous studies that establish structural and functional alterations in cocaine dependence in frontal, parietal and

striatal structures (Jacobsen et al., 2001; Fein et al., 2002; Franklin et al., 2002; Matochik et al., 2003; Kubler et al., 2005; Sim et al., 2007; Tomasi et al., 2007; Goldstein et al., 2007; Goldstein et al., 2009; Asensio et al., 2010, Bjork et al., 2010; Jia et al., 2011; Ersche et al., 2011; Moreno-López et al., 2012). As we show in our neuroimaging studies, cocaine-addicted subjects display marked alterations in brain dopaminergic regions which lead to structural and functional alterations of the circuits involved in cognitive processing (cognitive control dysregulation) and reward processing (motivational dysregulation), giving rise to a compulsive drug intake pattern in cocaine addiction. This work confirms the significant attentional problems that have been previously reported in cocaine users (Horner, 1999; Aharonovich et al., 2003, 2006; Jovanovski et al., 2005; Goldstein et al., 2007; Tomasi et al., 2007; Gooding et al., 2008). Moreover, our results are related with other studies that have demonstrated altered working-memory and related executive components in substance abusers which, at the same time, might implicate alterations in inhibitory control and decision-making processes (Bechara and Martin, 2004). Other studies have reported cocaine users having difficulties in executing interference-control tasks (Simon et al., 2000; Fillmore and Rush, 2002; Salo et al., 2002; Monterosso et al., 2005; Verdejo-García et al., 2005, 2007).

We have also rendered support to the existence of alterations in non-drug-related motivational drives in cocaine patients (Goldstein et al., 2007), which can trigger compulsive drug use (Volkow et al., 2008). In this sense, the majority of the previous literature is related with the fact that stimulant drug-paired stimuli can elicit many of the subjective and reinforcing effects of the drug itself (Leyton, 2007). Lowered mood state associated with a diminished ability of natural rewards to sustain interest can persist for months in addicted people (Cottler et al., 1993). Drug cues may be among the few events that can elicit interest and goal-directed behaviour; once the drug has been ingested, the discovery that it can alleviate low mood states may give the drug additional reward value (Leyton, 2007). Behavioural effects due to addiction include enhanced approach behaviour, increased salience of emotionally relevant cues, and greater motivation to seek rewards (Wise, 2004; Stewart, 1992; Koob and Nestler, 1997; Berridge and Robinson, 1998; Phillips et al., 2003; Berridge, 2007). Long-term cocaine use may lead to sensitisation and increased DA transmission in the presence of

drug-related cues (for a review, see Two Factor Dopamine Model in Leyton, 2007). This fact might produce an over-ride of mechanisms of behavioural inhibition by producing intense craving, and may focus the drive to obtain the drug. Chronic cocaine use can also lead to diminish DA transmission in the absence of drug-related cues, thus reducing and making the ability to sustain goal-directed behaviour and decision-making processes difficult (Leyton, 2007). Impairment of executive control plays an important role in making bad choices about drugs, especially when combined with the pathological incentive motivation for drugs induced by incentive sensitisation (Robinson and Berridge, 2008). Cognitive deficits in the ability to inhibit or properly assess the future consequences of one's actions owing to dopaminergic system dysfunction, combined with excessive incentive salience due to sensitisation of mesocorticolimbic reward circuitry, lead to a disproportionate compulsive/impulsive pursuit of drugs in the face of negative consequences (Robinson and Berridge, 2003). Impulsive individuals seem to be at greater risk of making the transition from recreational to compulsive cocaine use (Verdejo-García et al., 2008; Potenza and Taylor, 2009). Previous literature has shown that cocaine addicts perceive themselves as highly impulsive (Ersche et al., 2011). Impulsivity is enhanced with chronic cocaine exposure (Ersche et al., 2010) and increases the risk of adverse life events (Hayaki et al., 2005) and treatment drop-out (Moeller et al., 2001) in substance-dependent patients.

Proneness to relapse, even after months on treatment and long periods of abstinence, is based on changes in brain structure and brain function, which continue for months or years after the last use of the drug (O'Brien, 2008). In line with this, it is interesting to establish how the degree of severity or free state from the drug can determine brain structure and functioning. Thus, adaptation of treatment approaches can be more accurate because it is possible that the clinician develops methods that target the biological substrate sustaining reward processing and cognitive control difficulties in patients during treatment periods, as well as those who may partially recover from successful treatment. Our results and the previous literature allow us to suggest that treatment processes have to target the interplay between impaired salience attribution and cognitive control functions. Therapeutic approaches have to include the development of cognitive strategies that aim to strengthen the frontoparietal network control of behaviour, especially in salient emotional/motivational situations (Goldstein

et al., 2007a). Moreover, treatment approaches have attempted to not only weaken the strength of these conditioned associations between drug and environmental stimuli, which lead to relapse by craving processes, but to facilitate the development of new memories producing the natural rewards targeting the striatal reward mechanism that we have shown, which could implicate resistance to intervention or recovery/regulation in brain functioning (O'brien, 2008). Additionally, understanding the roles of the neurobiological substrates of executive processes in relation to substance abuse can facilitate the development of more appropriately targeted prevention and treatment programmes for those suffering from addiction (Bolla et al., 2003). If tolerance and withdrawal symptoms are unique elements of addiction, then the objective of the treatment is detoxification; however, detoxification allows a drug-free state only and is the first step in treatment (O'Brien, 2008; 2006). Eliminating affective withdrawal and also the reward-need state are both critical in the treatment (Koob and Lemoal, 1997). Thus, the interventions that help drug abusers to recognise the external situations that produce stress, craving, or risk of relapse, and teaching them cognitive behaviour skills to manage these situations, would be beneficial. Therapeutic approaches would have to lower the reinforcing effects of drugs, enhance the rewarding effects of natural reinforcers, inhibit conditioned learned associations, enhance motivation for non-drug-related stimuli and other personal targets, and strengthen executive cognitive control functions (Volkow et al., 2011b).

To summarise, studying the implication of the neural substrates of processes, such as cognitive control and incentive salience processing in cocaine addiction, could allow a better comprehension of the neurobehavioural pattern inherent to chronic substance abuse. Moreover, these experimental approaches could add help concerns to the development of improved behavioural and pharmacological treatments for addiction (Jia et al., 2011; Kampman, 2010).

3.1.*General conclusions*

After presenting the studies, we can conclude that:

1) Cocaine-dependent patients show reduced GM volume in subcortical and cortical brain regions associated with cognitive, motivational and emotional deficits.

2) Years of cocaine use in cocaine-dependent patients determines structural alterations in limbic, frontal and parietal areas related with executive-control and motivational functions.

3) Chronic cocaine use is related with the alteration of the attentional executive system, which implicates not only frontal areas, but also parietal regions, and is associated with attentional and cognitive control deficits.

4) The morphometric intersubject variability in the samples used is an important variable which functional studies need to take into account as a nuisance variable given its possible implications in functional effects.

5) Matching performance between groups in the fMRI clinical studies is a good methodological approach to interpret the functional effects. It confers validity to the functional effects obtained, but also validity and reliability to those studies based on unmatched task performance.

6) Cocaine-dependent patients display alterations in motivational-reward mechanisms which implicate an altered striatal pattern activation during non-drug-related reward processing.

7) The duration of successful treatments and the time that patients are free of cocaine could differently determine the regulation of the altered VS and DS pattern activation during monetary reward processing by taking into account the dichotomy in the role of both regions in addiction, and by implicating a change in the motivational value of non-drug and drug-related cues for patients.

Chapter 4.Future research lines

Drug addiction is a disorder resulting from the complex interplay of genetic, biological and environmental variables (Volkow et al., 2002), and also cognitive and motivational variables. Moreover, other neurotransmitters, different to DA, are known to be involved (Volkow et al., 2011b). By considering the complex nature of cocaine addiction and all the possibilities that neuroimaging techniques such as magnetic resonance imaging could offer the scientific community to study this phenomenon, it is feasible to propose other experimental approaches for future endeavors in our lab to lead to new projects:

1) The analyses of the brain effects of anticipation and reactivity of cocaine-conditioned cues during cognitive control tasks could explain the cognitive/motivational alterations present in cocaine addiction, thus providing more evidence for the neural bases of the interaction between cognitive and motivational processes in this disinhibitory and motivated drug-cues bias behavioural pattern. As seen from the previous literature and the studies presented in this work, the interaction between cognitive and motivational processes could be considered to be clear elements to account for the addiction and relapse phenomenon. The motivational responses for the drug seem to control the cognitive processes to obtain the substance, irrespectively of the negative consequences of consumption and of making the effectiveness of treatment processes difficult. However, it remains unclear why drugs have a greater effect on motivated behaviour. It could be possible to analyse these effects by making contingent to the behaviour drug or natural reinforcer obtaining. In this sense, the receiver of drugs or signals that anticipate their arrival seems to determine the cognitive processes related with motivated behaviour.

2) The study of brain connectivity in cocaine-dependent patients could allow us to understand the brain functioning between the cortical and subcortical areas that work

in tandem and are implicated in motivational and cognitive processes which subserve the vicious circle of cocaine addiction. The functional connectivity pattern between a group of regions has been related with the functional integrity of those regions during a specific task. Thus, a reduced pattern of connectivity in addiction is related with variables like execution of cognitive task or number of years of consumption (Gu et al., 2010). Addicted cocaine patients have exhibited reduced connectivity brain patterns between regions like the OFC, the amygdala, the hippocampus, and PFC regions (Gu et al., 2010). Moreover, Kelly et al. (2011) found reduced interhemispheric connectivity patterns in frontal regions in addicted patients. On the other hand, some studies (Gu et al., 2010; N. Ma et al., 2011; 2010) have reported an increment in functional connectivity between the Nacc and brain regions like the amygdala, the ACC and the OFC in cocaine and heroin addicts.

3) The study of possible neurofunctional implications which may produce alterations in other neurotransmission systems, and which differ from the DA system, in the different cocaine addiction process phases, could allow us to consider the addicted brain in holistically by analysing all the neurobiological components implicated in the addictive process. Cocaine has potent pharmacological actions on a number of neurotransmission systems in the brain, including those that use dopamine, serotonin, glutamate and GABA. Cocaine enhances monoamine system activity through the blockade of not only dopamine, but also serotonin reuptake, which contributes to the development of cocaine sensitisation (Lason, 2001; Cunningham et al., 1992). Serotonin receptors, which play a role in the reinforcing effects of cocaine by modulating the release of GABA in the ventral tegmental area (VTA), show a down-regulation during long-term cocaine self-administration and a compensatory up-regulation during protracted withdrawal (Parsons et al., 1998). Low serotonin transmission can increase dopaminergic and appetitive responses to cocaine, which could be related with craving (Cox et al., 2011). Functional changes within the brain reward circuitry are related with abnormalities in serotonergic transmission in the Nacc (Weiss et al., 2001). Moreover, repeated cocaine self-administration and subsequent withdrawal decrease basal levels of Nacc glutamate (McFarland et al., 2003). Cocaine reinstatement is related to the activation of the dorsal PFC-Nacc core glutamate pathway, and to the subsequent activation of the Nacc core GABAergic pathway (Kalivas and McFarland, 2003).

In short, alterations in motivational and cognitive processing are related with long-term cocaine consumption and the compulsive addiction pattern. The analysis of the neural bases of the interaction between cognitive and motivational processes could help us gain a better understanding of brain drug effects. Moreover, changes in brain structure and functioning in specific regions and the association and connectivity between them could explain the addictive behavioural pattern with more evidence. Additionally, the clarification of the implication of other neurotransmission systems, other than DA, in the neurofunctional and structural bases of cocaine addiction could provide more data to the cerebral reality in the recreational consumption process of the drug towards chronic drug use. Finally, all these approaches could lead to new treatment strategies at the pharmacological and psychological levels.

References of general introduction and general discussion

A

- Adinoff B., Devous M., Best S., George M., Alexander D., Payne K., (2001). Limbic responsiveness to procaine in cocaine-addicted subjects. *The American journal of Psychiatry, 158*, 390–398.
- Adinoff B., Devous M.D., Cooper D.B., Best S.E., Chandler P., Harris T., Cervin C.A., Cullum C.M. (2003). Resting regional cerebral blood flow and gambling task performance in cocaine-dependent subjects and healthy comparison subjects. *The American Journal of Psychiatry*, 160, 1892-1894.
- Aharonovich E., Nunes E., Hasin D. (2003). Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug and Alcohol dependence*, 71, 207-211.
- Aharonovich E., Hasin D.S., Brooks A.C., Liu X., Bisaga A., Nunes E.V. (2006). Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug and Alcohol dependence*, 81, 313-322.
- Ahmadi J., Kampman K., Dackis C. (2006). Outcome predictors in cocaine dependence treatment trials. *The American journal on addictions*, 15, 434-439.
- Ardila A., Rosselli M., Strumwasser S. (1991). Neuropsychological deficits in chronic cocaine abusers. *The International Journal of Neuroscience*, 57, 73-79.
- Aron J.L., Paulus M.P. (2007). Location, location: using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. *Addiction, 102* (Suppl.1), 33-43.
- Asensio S., Romero M.J., Palau C., Sanchez A., Senabre I., Morales J.L., Carcelen R., Romero F.J. (2010). Altered neural response of the appetitive emotional system in cocaine. *Addiction Biology*, 15, 504-516.
- Ashburner, J., Friston, K.J. (2000). Voxel-Based Morphometry- The methods. *Neuroimage, 11*, 805-821.

B

- Baler R.D., Volkow N.D. (2006). Drug addiction: the neurobiology of disrupted self-control. *Trends in Molecular Medicine*, 12, 559-566.
- Barrós-Loscertales A, Belloch-Ugarte V, Mallol R, Martínez-Lozano MD, Forn C, Parcet MA, Campos S., Ávila C. (2008). Volumetric differences in hippocampal volume affect fMRI differences in the brain functional activation for Alzheimer's disease during memory encoding. In: Chan AP, editor. *Current Research on Alzheimer's disease*: Nova Editions, pp. 147-173.
- Bartzokis G., Beckson M., Lu P.H., Edwards N., Rapoport R., Wiseman E., BridgeP.(2000a).Agerelated brain volume reductions in amphetamine and co caine addicts and normalcontrols: implications for addiction research. *Psychiatry Research*, 98, 93-102.
- Bartzokis G., Lu P.H., Beckson M., Rapoport R., Grant S., Wiseman E.J., London E.D. (2000b). Abstinence from cocaine reduces high-risk responses on a Gambling task. *Neuropsychopharmacology*, 22, 102-103.
- Bauer L.O. (2001). Antisocial personality disorder and cocaine dependence: their effects on behavioral and electroencephalographic measures of time estimation. *Drug and Alcohol Dependence*, 63, 87 –95.
- Beatty W.W., Katzung V.M., Moreland V.J., Nixon S.J. (1995). Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug and Alcohol dependence, 37*, 247–253.
- Bechara A., Damasio A.R., Damasio H., Anderson S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50, 7–15.
- Bechara A., Damasio H., Tranel D., Anderson S.W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience*, 18, 428- 437.
- Bechara A., Dolan S., Hindes A. (2002). Decision-making and addiction (part II): Myopia for the future or hypersensitivity to reward? *Neuropsychologia,* 40, 1690 –1705.

- Bechara A., Martin E.M. (2004). Impaired decision making related to working memory deficits in individuals with substance addictions. *Neuropsychology, 18*, 152-162.
- Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience*, 8, 1458–1463.
- Becker J.B., Hu M. (2008). Sex differences in drug abuse. *Frontiers in Neuroendocrinology*, 29, 36-47.
- Benjamini, Y., Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc., 57*, 289–300.
- Berger S.P., Hall S., Mickalian J.D., Reid M.S., Crawford C.A., Delucchi K., Carr Kirkland, Hall S. (1996). Haloperidol antagonism of cue-elicited cocaine craving. *Lancet*, 347, 504-508.
- Berridge K.C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology*, 191, 391–431.
- Berridge K.C., Robinson T.C. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, 28, 309-369.
- Berry J., Van Gorp W., Herzberg D., Hinkin C., Boone K., Steinman L., Wilkins J.N. (1993). Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence. *Drug and Alcohol dependence, 32,* 231-237.
- Bickel W.K., Miller M.L., Yi R., Kowal B.P., Lindquist D.M., Pitcock J.A. (2007). Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. *Drug and Alcohol Dependence*, 90 (Suppl 1), S85–S91.
- Biggins C.A., MacKay S., Clark W., Fein G. (1997). Event-related potential evidence for frontal cortex effects of chronic cocaine dependence. *Biological Psychiatry*, 42, 472 –485.
- Bjork J.M., Smith A.R., Hommer D.W. (2008). Striatal sensitivity to reward deliveries and omissions in substance dependence patients. *Neuroimage*, 42, 1609-1621.

- Blum K., Braverman E.R., Holder J.M., Lubar J.F., Monastra V.J., Miller D., Lubar J.O., Chen T.J., Comings D.E. (2000). Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *Journal of Psychoactive Drugs*, 32, 1–112.
- Bolla, K.I., Cadet, J.L., London, E.D. (1998). The Neuropsychiatry of Chronic Cocaine Abuse. *Journal of Neuropsychiatry, 10,* 280-289.
- Bolla K.I., Funderburk F.R., Cadet J.L. (2000). Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology, 54*, 2285–2292.
- Bolla K.I., Eldreth D.A., London E.D., Kiehl K.A., Mouratidis M., Contoreggi C., Matochik J.A., Kurian V., Cadet J.L., Kimes A.S., Funderburk F.R., Ernst M. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage*, 19, 1085-1094.
- Bolla K., Ernst M., Kiehl K., Mouratidis M., Eldreth D., Contoreggi C., Matochik J., Kurian V., Cadet J., Kimes A., Funderburk F., London E. (2004). Prefrontal cortical dysfunction in abstinent cocaine abusers. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 16, 456–464.
- Bonson K.R., Grant S.J., Contoreggi C.S., Links J.M., Metcalfe J., Weyl H.L., Kurian V., Ernst M., London E.D. (2002). Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology*, 26, 376-386.
- Bottlender M., Soyka M. (2005). Impact of different personality dimensions (NEO Five-Factor Inventory) on the outcome of alcohol dependent patients 6 and 12 months after treatment. *Psychiatry Research*, 136, 61–67.
- Brewer J.A., Potenza M.N. (2008). The neurobiology and genetics of impulse control disorders: relationships to drug addictions. *Biochemical pharmacology*, 75, 63-75.
- Bustamante J.C., Barrós-Loscertales A., Ventura-Campos N., Llopis J.J., Ávila C. (2008). Inferior frontal cortex activation in an inhibitory control task with reinforcement contingencies in cocaine dependent-patients (Activación del córtex frontal inferior en una tarea de control inhibitorio con contingencias de reforzamiento en pacientes con dependencia a la cocaína). *Forum de Recerca, 13*, 1-18 (ISSN: 1139-5486). http://www.uji.es/bin/publ/edicions/jfi13/10.pdf.

C

- Carpenter K.M., Schreiber E., Church S., McDowell D. (2006). Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addictive Behaviors, 31,* 174-181.
- Carroll K.M. (1997). Integrating psychotherapy and pharmacotherapy to improve drug abuse outcomes. *Addictive behaviors*, 22, 233-245.
- Carter B.L., Tiffany S.T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction*, 94, 327–340.
- Casanova, R., Srikanth, R., Baer, A., Laurienti, P.J., Burdette, J.H., Hayasaka, S., Flowers, L., Wood, F., Maldjian, J.A. (2007). Biological Parametric Mapping: A statistical toolbox for multimodality brain image analysis. *Neuroimage, 34*, 137-143.
- Casey B.J., Trainor R., Orendi J., Schubert A. (1996). A functional Magnetic resonance imaging (fMRI) study of ventral prefrontal cortex mediation of response inhibition. *Society of Neuroscience Abstract*, 22, 1107.
- Chamberlain S.R., Fineberg N.A., Blackwell A.D., Robbins T.W., Sahakian B.J. (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *American Journal of Psychiatry*, 163, 1282–1284.
- Chamberlain S.R., Sahakian B.J. (2007). The neuropsychiatry of impulsivity. *Current Opinion in Psychiatry*, 20, 255–261.
- Chen X., Sachdev P.S., Wen W., Anstey K.J. (2007). Sex differences in regional gray matter in healthy individuals aged 44–48 years: a voxel-based morphometric study. *NeuroImage*, 36, 691–699.
- Childress A.R., Mozely P.D., McElgin W., Fitzgerald J., Reivich M., O'Brien C.P. (1999). Limbic activation during cue-induced cocaine craving. *American Journal of Psychiatry*, 156, 11-18.
- Childress A.R., Ehrman R.N., Wang Z., Li Y., Sciortino N., Hakun J., Jens W., Suh J., Listerud J., Marquez K., Franklin T., Langleben D.,Detre J., O'Brien C.P. (2008). Prelude to passion: limbic activation by "unseen" drug and sexual cues. *Plos One*, 3, e1506.
- Colzato L.S., Van Den Wildenberg W., Hommel B. (2007). Impaired inhibitory control in recreational cocaine users. *Plos One*, e1143.

- Connolly C.G., Bell R., Jones J., Nierenberg J., Hoptman M., Butler P., et al. (2009). Changes in grey matter volumes related to cocaine abstinence. *Neuroimage,* 47, S39–S41 (Abstracts: Organization for Human Brain Mapping 2009 Annual Meeting).
- Copersino M.L., Serper M.R., Vadhan N., Goldberg B.R., Richarme D., Chou J.C.Y., Stitzer M., Cancro R. (2004). Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Research*, 128, 209–218.
- Corbetta, M., Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews, 3*, 201-215.
- Cottler L.B., Shillington A.M., Compton 3rd W.M., Mager D., Spitznagel E.L. (1993). Subjective reports of withdrawal among cocaine users: recommendations for DSM-IV. *Drug and Alcohol Dependence*, 33, 97–104.
- Cox S.M.L., Benkelfat C., Dagher A., Delaney J.S., Durand F., Mckenzie S.A., Kolivakis T., Casey K.F., Leyton M. (2009). Striatal dopamine responses to intranasal cocaine self-administration in humans. *Biological Psychiatry*, 65, 846-850.
- Cox S.M., Benkelfat C., Dagher A., Delaney J.S., Durand F., Kolivakis T., Casey K.F., Leyton M. (2011). Effects of lowered serotonin transmission on cocaine-induced striatal dopamine response: PET [^{11}C]raclopride study in humans. *The British journal of Psychiatry*, 199, 391-397.
- Cox W.M., Yeates G.N., Regan C.M. (1999). Effects of alcohol cues on cognitive processing in heavy and light drinkers. *Drug and Alcohol Dependence*, 55, 85–89.
- Cunha P.J., Bechara A., Guerra de Andrade A., Nicastri S. (2011). Decision-Making Deficits Linked to Real-life Social Dysfunction in Crack Cocaine-Dependent Individuals. *The American Journal on Addiction*, 20, 78-86.
- Cunningham K.A., Paris J.M., Goeders N.E. (1992). Chronic cocaine enhances serotonin autoregulation and serotonin uptake binding. *Synapse*, 11, 112-123.

D

- Damasio A.R. (1985). The Frontal Lobes. In Heilman KM, Valenstein E (eds), *Clinical Neuropsychology*. New York, Oxford University Press, pp 339–375.

- Dalley J.W., Everitt B.J., Robbins T.W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron*, 69, 680-694.
- De Wit H., Stewart J. (1983). Drug reinstatement of heroin-reinforced responding in the rat. *Psychopharmacology*, 79, 29–31.
- Di Chiara G. (1999). Drug addiction as dopamine-dependent associative learning disorder. *European Journal of Pharmacology*, 375, 13-30.
- Dosenbach N.U., Fair D.A., Cohen A.L., Schlaggar B.L., Petersen S.E. (2008). A dual-networks architecture of top-down control. *Trend in cognitive science*, 12, 99-105.
- Dunning J.P., Parvaz M.A., Hajcak G., Maloney T., Alia-Klein N., Woicik P.A., Telang F., Wang G.J., Volkow N.D., Goldstein R.Z. (2011). Motivated attention to cocaine and emotional cues in abstinent and current cocaine users- an ERP study. *European Journal of Neuroscience*, 33, 1-8.
- Dutra L., Stathopoulou G., Basden S.L., Leyro T.M., Powers M.B., Otto M.V. (2008). A meta-analytic review of psychosocial interventions for substance use disorders. *American journal of psychiatry*, 165, 179-187.

E

- Elkashef A., Biswas J., Acri J.B., Vocci F. (2007). Biotechnology and the treatment of addictive disorders: new opportunities. *Biodrugs: clinical inmunotherapeutics, biopharmaceutical and gene therapy*, 21, 259-267.
- Ersche K.D., Turton A.J., Pradhan S., Bullmore E.T., Robbins T.W. (2010). Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biological Psychiatry*, 68, 770–773.
- Ersche K.D., Barnes A., Simon Jones P., Morein-Zamir S., Robbins T.W., Bullmore E.T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*, 134, 2013-2024.
- Ettenberg A. (1990). Haloperidol prevents the reinstatement of amphetamine-rewarded runway responding in rats. *Pharmacology, Biochemistry and Behavior*, 36, 635-638.

- Everitt, B.J., Dickinson, A., Robbins, T.W. (2001). The neuropsychological basis of addictive behavior. *Brain Research Review, 36,* 129-138.
- Everitt B.J., Robbins T.W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience*, 8, 1481-1489.
- Everitt B.J., Belin D., Economidou D., Pelloux Y., Dalley J.W., Robbins T.W. (2008). Neural mechanism underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical transactions of the Royal Society of London*, 363, 3125-3135.

F

- Fan L., Tang Y., Sun B., Gong G., Chen Z., Lin X., Yu T., Li Z., Evans A.C., Liu S. (2010). Sexual dimorphism and asymmetry in human cerebellum: an MRI-based morphometric study. *Brain Research*, 1353, 60–73.
- Ferris M.J., Mateo Y., Roberts D.C.S., Jones S.R. (2011). Cocaine-Insensitive Dopamine transporters with Intact Substrate Transport Produced by Self-Administration. *Biological Psychiatry*, 69, 201-207.
- Fillmore M.T., Rush C.R. (2002). Impaired inhibitory control of behavior in chromic cocaine users. *Drug and Alcohol Dependence*, 66, 265-273.
- Fineberg, N.A., Potenza, M.N., Chamberlain, S.R., Berlin, H.A., Menzies, L., Bechara A., Sahakian B.J., Robbins T.W., Bullmore, E.T., Hollander E. (2010). Probing Compulsive and Impulsive Behaviors, from Animal Models to Endophenotypes: A Narrative Review. *Neuropsychopharmacology*, 35, 591-604.
- Fontana D.J., Post R.M., Pert A. (1993). Conditioned increases in mesolimbic dopamine overflow by stimuli associated with cocaine. *Brain Research*, 629, 31-39.
- Fowler J.S.,Volkow N., Kassed C.A., Chang L. (2007). Imaging the addicted human brain. *Science and Practice perpectives*, 3, 4-16.
- Franken I.H.A., Stam C.J., Hendriks V.M., van den Brink W. (2003). Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. *Psychopharmacology*, 170, 205–212.

- Franken I.H.A., Hulstijn K.P., Stam C.J., Hendriks V.M., Van den Brink W. (2004). Two new neurophysiological indices of cocaine craving: Evoked brain potentials and cue moderated startle reflex. *Journal of Psychopharmacology*, 18,544–552.
- Franklin T.R., Acton P.D., Maldjian J.A., Gray J.D., Croft J.R., Dackis C.A., et al. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulated and temporal cortices of cocaine patients. *Biological Psychiatry*, 51, 134–142.
- Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Frith, C., Frackowiak, R.S.J. (1995). Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping, 2*, 189–202.

G

- Garavan H., Pankiewicz J., Bloom A., Cho J.K., Sperry L., Ross T.J. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimulus. *American journal of Psychiatry,* 157, 1789-1798.
- Garavan H., Ross T.J., Murphy K., Roche R.A.P., Stein E.A. (2002). Dissociable executive functions in the dynamic control of behaviour: inhibition, error detection and correction. *Neuroimage, 17,* 1820–1829.
- Garavan, H. y Hester, R. (2007). The Role of Cognitive Control in Cocaine Dependence. *Neuropsychology Review, 17,* 337-345.
- Garavan H., Kaufman J.N., Hester R. (2008). Acute effect of cocaine in the neurobiology of cognitive control. *Philosophical Transaction of the Real Society of London Serie B Biological Sciences, 362,* 3267-3276.
- Genovese, C.R., Lazar, N.A., Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using false discovery rate. *Neuroimage, 15*, 870–878.
- Goeders N.E., Smith J.E. (1986). Reinforcing properties of cocaine in the medial prefrontal cortex: primary action on presynaptic dopaminergic terminals. *Pharmacology, Biochemistry and Behavior*, 25, 191–199.

- Goldstein R.Z., Volkow N.D.,Wang G.J., Fowler J.S., Rajaram S. (2001). Addiction changes orbitofrontal gyrus function: involvement in response inhibition. *Neuroreport*, 12, 2595–2599.
- Goldstein R.Z., Volkow N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159, 1642-1652.
- Goldstein R.Z., Leskovjan A.C., Hoff A.L., Hitzemann R., Bashan F., Khalsa S.S., Wang G.J., Fowler J.S., Volkow N.D. (2004). Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia, 42*, 1447– 1458.
- Goldstein R.Z., Tomasi D., Alia-Klein N., Zhang L., Telang F., Volkow N.D. (2007a). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction?. *The American Journal of Psychiatry, 164*, 43-51.
- Goldstein R.Z., Tomasi D., Alia-Klein N., Zhang L., Telang F., Volkow N.D. (2007b). The effect of practice on a sustained attention task in cocaine abusers. *Neuroimage*, 35, 194-206.
- Goldstein R.Z., Tomasi D., Alia-Klein N., Carillo J.H., Maloney T., Woicik P.A., Wang R., Telang F., Volkow N.D. (2009). Dopaminergic response to drug words in cocaine addiction. *The Journal of Neuroscience*, 29, 6001-6006.
- Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S. (2001a). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage, 14*, 21–36.
- Good C.D., Johnsrude I., Ashburner J., Henson R.N., Friston K.J., Frackowiak R.S. (2001b).Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 456 normal adult human brain. *NeuroImage*, 14, 685–700.
- Gooding D.C., Burroughs S., Boutros N.N. (2008). Attentional deficits in cocaine-dependent patients: converging behavioral and electrophysiological evidence. *Psychiatric Research*, 160, 145-154.
- Grant S., London E.D., Newlin D.B., Villemagne V.L., Liu X., Contoreggi C., Phillips R.L., Kimes A.S., Margolin A. (1996). Activation of memory circuits during cue-induced cocaine craving. *PNAS,* 93, 12040-12045.

- Grant S.J., Contoreggi C., London E.D. (1997). Drug abusers show impaired performance on a test of orbitofrontal function. *Proceeding of the Society for Neuroscience Annual Meeting*, October 25–30, New Orleans, LA.
- Grekin E.R., Sher K.J., Wood P.K. (2006). Personality and substance dependence symptoms: modeling substance-specific traits. *Psychology of Addictive Behaviors*, 20, 415–424.
- Gu H., Salmeron B.J., Ross T.J., Geng X., Zhan W., Stein E.A., Yang Y. (2010). Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage*, 53, 593-601.

H

- Hanlon C.A., Wesley M.J., Porrino L.J. (2009). Loss of functional specificity in the dorsal striatum of chronic cocaine users. *Drug and alcohol dependence*, 102, 88-94.
- Hayaki J., Stein M.D., Lassor J.A., Herman D.S., Anderson B.J. (2005). Adversity among drug users: relationship to impulsivity. *Drug and Alcohol Dependence*, 78, 65–71.
- Heatherton T.F., Wagner D.D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences,*15, 132–139.
- Hester R., Garavan H. (2004). Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulated, and cerebellar activity. *The Journal of Neuroscience*, 24, 11017–11022.
- Hester R., Dixon V., Garavan H. (2006). A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. *Drug and Alcohol dependence*, 81, 251-257.
- Hollander E., Cohen L.J. (1996). *Impulsivity and Compulsivity*. Washington DC: American Psychiatric Press Inc.
- Horner B., Scheibe K., Stine S. (1996). Cocaine abuse and attentiondeficit hyperactivity disorder: implications of adult symptomatology. *Psychology of Addictive Behavior*, 10, 55 –60.
- Horner M.D. (1999). Attetiontional functioning in abstinent cocaine abusers. *Drug and Alcohol Dependence*, 54, 19-33.

- Huettel, S.A., Song, A.W., McCarthy, G. (2004). Functional Magnetic Resonance Imaging. Sunderland, M.A.: Sinauer Associates. Publishers.
- Hurd Y.L., Ungerstedt U. (1989). Cocaine: an in vivo microdialysis evaluation of its acute action on dopamine transmission in rat striatum. *Synapse*, 3, 48–54.
- Hurd Y.L., Pontén M. (2000). Cocaine self-administration behavior can be reduced or potentiated by the addition of specific dopamine concentrations in the nucleus accumbens and amygdale using in vivo microdialysis. *Behavioural Brain Research*, 116, 177-186.
- Hyman SE, Malenka RC. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nature Reviews. Neuroscience,* 2, 695–703.

J

- Jacobsen L.K., Giedd J.N., Gottschalk C., Kosten T.R., Krystal J.H. (2001). Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *American Journal of Psychiatry*, 158, 486–489.
- Jentsch J.D., Taylor J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology*, 146, 373-390.
- Jia Z., Worhunsky P.D., Carroll K.M., Rounsaville B.J., Stevens M.C., Pearlson G.D., Potenza M.N. (2011). An Initial Study of Neural Responses to Monetary Incentives as Related to Treatment Outcome in Cocaine Dependence. *Biological Psychiatry*, 70, 553-560.
- Jovanovski, D., Erb, S., Zakzanis, K.K. (2005). Neurocognitive deficits in cocaine users: A quantitive review of the evidence. *Journal of clinical and experimental Neuropsychology, 27*, 189-204.

K

- Kalivas P.W., Pierce R.C., Cornish J., Sorg B.A. (1998). A role for sensitization in craving and relapse in cocaine addiction. *Journal of Psychopharmacology*, 12, 49-53.

- Kalivas P.W., McFarland K. (2003). Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology*, 168, 44-56.
- Kalivas P.W., O'Brien C.O. (2008). Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology*, 33, 166-180.
- Kampman K.M. (2010). What's new in the treatment of cocaine addiction? *Current Psychiatry reports*, 12, 441-447.
- Kaufman J.N., Ross T.J., Stein E.A., Garavan H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *The Journal of Neuroscience*, 23, 7839–7843.
- Kelley A.E. (1999). Neural integrative activities of nucleus accumbens subregions in relation to learning and motivation. *Psychobiology,* 27, 198–213.
- Kelley A.E., Berridge K.C. (2002). The neuroscience of natural rewards: relevance to addictive drugs. *Journal of Neuroscience,* 22, 3306–3311.
- Kelly C., Zuo X.N., Gotimer K., Cox C.L., Lynch L., Brock D., Imperati D., Garavan H., Rotrosen J., Castellanos F.X., Milham M.P. (2011). Reduced interhemispheric resting state functional connectivity in cocaine addiction. Biological Psychiatry, 69, 684-692.
- Kilts C.D., Schweitzer J.B., Quinn C.K., Gross R.E., Faber T.L., Muhammad F., Ely T.D., Hoffman J.M., Drexler K.P. (2001). Neural activity related to drug craving in cocaine addiction. *Archives of General Psychiatry*, 58, 334-341.
- King S.M., Lacono W.G., McGue M. (2004). Childhood externalizing and internalizing psychopathology in the prediction of early substance abuse. *Addiction*, 99, 1548-1559.
- Knapp W.P., Soares B.G., Farrel M., Lima M.S. (2007). Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders. Cochrane database of systematic reviews, CD003023.
- Knutson B., Westdorp A., Kaiser E., Hommer D. (2000). FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage,* 12, 20–27.
- Konishi S., Nakajima K., Uchida I., Kikyo H., Kameyama M., Miyashita Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*, 122, 981-991.

- Koob G.F., Caine B., Markou A., Pulvirenti L., Weiss F. (1994). Role for the mesocortical dopamine system in the motivating effects of cocaine. *NIDA Research Monograph*, 145, 1–18.
- Koob G.F., LeMoal M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science*, 278, 52-58.
- Koob G.F., Nestler E.J. (1997). The neurobiology of drug addiction. *The Journal of Neuropsychiatry and Clinical Neuroscience*, 9, 482-497.
- Koob G.F., Ahmed S.H., Boutrel B., Chen S.A., Kenny P.J., Markou A., O'Dell L.E., Parsons L.H., Sanna P.P. (2004). Neurobiological mechanisms in the transition from drug use to drug dependence. *Neuroscience and Biobehavioral reviews*, 27, 739–749.
- Koob G.F., Le Moal M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nature Neuroscience*, 8, 1442–1444.
- Koob G.F., LeMoal M. (2008). Neurobiological mechanism for opponent motivational processes in addiction. *Philosophical transactions of the Royal Society of London*, 363, 3113-3123.
- Koob G.F. (2009). Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*, 56, 18-31.
- Koob G.F., Volkow N.D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology*, 35, 217-238.
- Koscik T., O'Leary D., Moser D.J., Andreasen N.C., Nopoulos P. (2009). Sex differences in parietal lobe morphology: relationship to mental rotation performance. *Brain and Cognition*, 69, 451-459.
- Kosten, T., Tucker, K., Gottschalk, P., Rinder, C., Rinder, H. (2004). Platelet abnormalities associated with cerebral perfusion defects in cocaine dependence. *Biological Psychiatry, 55*, 91-97.
- Kubler, A., Murphy, K., Garavan, H. (2005). Cocaine dependence and attention switching within and between verbal and visuospatial working memory. *European Journal of Neuroscience, 21*, 1984-1992.

L

- Lane S.D., Cherek D.R., Dougherty D.M., Moeller F.G. (1998). Laboratory measurement of adaptive behavior change in humans with a history of substance dependence. *Drug and Alcohol Dependence*, 51, 239 –252.
- Lane S.D., Moeller F.G., Steinberg J.L., Buzby M., Kosten T.R. (2007). Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *The American Journal of Drug and Alcohol Abuse*, 33, 717–726.
- Lason W. (2001). Neurochemical and pharmacological aspects of cocaine-induced seizures. *Polish Journal of Pharmacology*, 53, 57-60.
- Leyton M. (2007). Conditioned and sensitized responses to stimulant drugs in humans. *Progress in neuro-psychopharmacology and biological psychiatry*, 31, 1601-1613.
- Li C.S.R., Huang C., Yan P., Baghwagar Z., Milivojevic V., Sinha R. (2008). Neural correlates of impulse control during Stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology*, 33, 1798–1806.
- Lim K.O., Choi S.J., Pomara N., Wolkin A., Rotrosen J.P. (2002). Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biological Psychiatry, 51,* 890-895.
- Lim K.O.,Wozniak J.R., Mueller B.A., Franc D.T., Specker S.M., Rodriguez C.P., Silverman A.B., Rotrosen J.P. (2008). Brain macrostructural and microstructural abnormalities in cocaine dependence. *Drug Alcohol Dependence*, 92, 164–172.
- Lubman D.I., Yucel M., Kettle J.W., Scaffidi A., Mackenzie T., Simmons J.G., Allen, N.B. (2009). Responsiveness to drug cues and natural rewards in opiate addiction: associations with later heroin use. *Archives of General Psychiatry*, 66, 205–212.
- Lyoo I.K., Streeter C.C., Ahn K.H., Lee H.K., Pollack M.H., Silveri M.M., Nassar L., Levin J.M., Sarid-Segal O., Ciraulo D.A., Renshaw P.F., Kaufman M.J. (2004). White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. *Psychiatry Research*, 131, 135-145.

M

- Ma N., Liu Y., Li N., Wang C.X., Zhang H., Jiang X.F., Xu H.S., Fu X.M., Hu X., Zhang D.R. (2010). Addiction related alteration in resting-state brain connectivity. *Neuroimage*, 49, 738-744.
- Ma N., Liu Y., Fu X.M., Li N., Wang C.X., Zhang H., Qian R.B., Xu H.S., Hu X., Zhang D.R. (2011). Abnormal brain default-mode network functional connectivity in drug addicts. *Plos One*, 6, e16560.
- Maas L.C., Lukas S.E., Kaufman M.J., Weiss R.D., Daniels S.L., Rogers V.W., Kukes T.J., Renshaw P.F. (1998). Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *American journal of Psychiatry*, 155, 124-126.
- Makris N., Gasic G.P., Seidman L.J., Goldstein J.M., Gastfriend D.R., Elman I., et al. (2004). Decreased absolute amygdale volume in cocaine addicts. *Neuron*, 44, 729–740.
- Markou, A., Koob G.F. (1992). Bromocriptine reverses the elevation in intracranial self-stimulation tresholds observed in a rat model of post-cocaine anhedonia. *Neuropsychopharmacology*, 7, 213-224.
- Martínez D., Broft A., Foltin R.W., Slifstein M., Hwang D.R., Huang Y., et al. (2004). Cocaine dependence and D2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology*, 29, 1190–1202.
- Màsse L.C., Tremblay R.E. (1997). Behavior of boys in kindergarten and the onset of substance use during adolescence. *Archives of General Psychiatry*, 54, 62-68.
- Matochik J.A., London E.D., Eldreth D.A., Cadet J.L., Bolla K.I. (2003). Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance study. *Neuroimage*, 19, 1095–1102.
- McClure S.M., Daw N.D., Montague P.R. (2003). A computational substrate for incentive salience. *Trends in Neuroscience*, 26, 423– 428.
- McFarland K., Lapish C.C., Kalivas P.W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *Journal of Neuroscience*, 23, 3531-3537.

- Moeller F.G., Dougherty D.M., Barratt E.S., Schmitz J.M., Swann A.C., Grabowski J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment*, 21, 193–198.
- Moeller F.G., Dougherty D.M., Barratt E.S., Oderinde V., Mathias C.W., Harper A., Swann A.C. (2002). Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. *Drug and Alcohol Dependence*, 68, 105–111.
- Moeller F.G., Hasan K.M., Steinberg J.L., Kramer L.A., Dougherty D.M., Santos R.M., Valdes I., Swann A.C., Barratt E.S., Narayana P.A. (2005). Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. *Neuropsychopharmacology*, 30, 610-617.
- Mogg K., Bradley B.P. (2002). Selective processing of smoking-related cues in smokers: Manipulation of deprivation level and comparison of three measures of processing bias. *Journal of Psychopharmacology*, 16, 385–392.
- Moreno-López L., Catena A., Fernández-Serrano M.J., Delgado-Rico E., Stamatakis E.A., Pérez-García M., Verdejo-García A. (2012). Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. *Drug and Alcohol dependence*, in press.
- Morgan P.T., Pace-Schott E.F., Sahul Z.H., Coric V., Stickgold R., Malison R.T. (2006). Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: Evidence for occult insomnia. *Drug and Alcohol dependence, 82*, 238-249.

N

- Namkoong K., Lee E., Lee C.H., Lee B.O., An S.K. (2004). Increased P3 amplitudes induced by alcohol-related pictures in patients with alcohol dependence. *Alcoholism, Clinical and Experimental Research*, 28, 1317–1323.
- Narayana P.A., Datta S., Tao G., Steinberg J.L., Moeller F.G. (2010). Effect of cocaine on structural changes in brain: MRI volumetry usinf tensor-based morphometry. *Drug and alcohol dependence*, 111, 191-199.

- Newman J.P., Wallace J.F. (1993). Diverse pathways to deficient self-regulation: Implications for disinhibitory psychopathology in children. Clin. Psychol. Rev. 13, 699–720.
- Nyberg, L., Dahlin, E., Neely, S., Bäckman, L. (2009). Neural correlates of variable working memory load across adult age and skill: dissociative patterns within the fronto-parietal network. *Scandinavian Journal of Psychology, 50*, 41-46.

O

- Oakes, T.R., Fox, A.S., Johnstone, T., Chung, M.K., Kalin, N., Davidson, R.J. (2007). Integrating VBM into the General Linear Model with voxelwise anatomical covariates. *Neuroimage, 34*, 500-508.
- O'Brien, C. P. (2006). Drug addiction and drug abuse. In L. Brunton, J. Lazo & K. Parker, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*, McGraw-Hill: pp. 607–627.
- O'Brien, C.P. (2008). Evidence-based treatments of addiction. *Transactions of the Royal Society of London B: Biological Sciences*, 363, 3277-3286.

P

- Parsons L.H., Weiss F., Koob G.F. (1998). Serotonin1B receptor stimulation enhances cocaine reinforcement. *Journal of Neuroscience*, 18, 10078-10089.
- Phillips P.E., Stuber G.D., Heien M.L., Wightman R.M., Carelli R.M. (2003). Subsecond dopamine release promotes cocaine seeking. *Nature*, 422, 614–618.
- Pierce R.C., Vanderschuren L.J. (2010). Kicking the habit: the neural basis of ingrained behaviors in cocaine addiction. *Neuroscience and biobehavioral reviews*, 35, 212-219.
- Ponesse J.S., Logan W.J., Schacher R.S., Tannock R., Crawley A.P., Mikulis D.J. (1998). Functional neuroimaging of the inhibition of a motor response. *NeuroImage*, 7, S972.
- Porrino L.J., Smith H.R., Nader M.A., Beveridge T.J. (2007). The effects of cocaine: a shifting target over the course of addiction. *Progress in neuropsychopharmacology and biological psychiatry*, 31, 1593-1600.

- Potenza M.N. (2007). To do or not to do? The complexities of addiction, motivation, self-control, and impulsivity. *American Journal of Psychiatry*, 164, 4–6.
- Potenza M.N., Taylor J.R. (2009). Found in translation: understanding impulsivity and related constructs through integrative preclinical and clinical research. *Biological Psychiatry*, 66, 714-716.
- Priscindaro J.J., McRae-Clark A.L., Moran-Santa María M.M., Hartwell K.J., Brady K.T. (2011). Psychoticism and neuroticism predict cocaine dependence and future cocaine use via different mechanisms. *Drug and alcohol dependence*, 116, 80-85.

R

- Reavis R., Overman W.H. (2001). Adult sex differences on a decision making task previously shown to depend on the orbital prefrontal cortex. *Behavioral neuroscience*, 115, 196–206.
- Ritz M.C., Lamb R.J., Goldberg S.R., Kuhar M.J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science*, 237, 1219–1223.
- Robbins S.J., Ehrman R.N., Childress A.R., O'Brien C.P. (1992). Using cue reactivity to screen medications for cocaine abuse: a test of amantadine hydrochloride. *Addictive behaviors*, 17, 491-499.
- Robbins T.W., Everitt B.J. (1996). Neurobehavioural mechanism of reward and motivation. *Current opinion in Neurobiology*, 6, 228-236.
- Robbins T.W. (2007). Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 362, 917-932.
- Robinson T.E., Berridge K.C. (1993). The neural basis of drug craving: an incentive sensitization theory of addiction. *Brain Research Reviews,* 18, 247–91.
- Robinson T.E., Berridge K.C. (2003). Addiction. *Annual review of Psychology*, 54, 25-53.

- Robinson T. E., Berridge K. C. (2008). Review. The incentive sensitization theory of addiction: some current issues. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 363, 3137-3146.

S

- Sáiz P.A., G-Portilla M.P., Paredes B., Delgado J., Martínez F. S., Bascarán M.T., Bobes J. (2003). Use of cocaine by secondary school students in northern Spain. *European Addiction Research*, 9, 138–143.
- Salo, R., Nordahl, T.E., Possin, K., Leamon, M., Gibson, D.R., Galloway, G.P. et al. (2002). Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Research, 111,* 65-74.
- Schultz W. (2007). Behavioral dopamine signals. *Trends in Neuroscience*, 30, 203-210.
- Schoenbaum G., Shaham Y. (2008). The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. *Biological Psychiatry*, 63, 256-262.
- Self D.W. and Nestler E.J. (1995) Molecular mechanisms of drug reinforcement and addiction. *Annual Review of Neuroscience,* 18, 463–495.
- Self D.W., Spencer J.J., Nestler E.J. (1996a). Effects of acute and chronic infusions of CREB antisense oligonucleotides in the nucleus accumbens on cocaine self-administration. Society of Neuroscience Abstract, 22, 1882.
- Self D.W., Barnhart W.J., Lehman D.A., Nestler E.J. (1996b). Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. *Science*, 271, 1586-1589.
- Self D.W., Nestler E.J. (1998). Relapse to drug-seeking: neural and molecular mechanisms. *Drug and Alcohol Dependence*, 51, 49-60.
- Shaham Y., Stewart J. (1996). Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology*, 125, 385-391.
- Shalev U., Grimm J.W., Shaham Y. (2002). Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacological reviews*, 54, 1-42.
- Shearer J. (2007). Psychosocial approaches to psychostimulant dependence: a systematic review. Journal of substance abuse treatment, 32, 41-52.

- Sher K.J., Bartholow B.D., Wood M.D. (2000). Personality and substance use disorders: a prospective study. *Journal of Consulting and Clinical Psychology*, 68, 818–829.
- Shiels K., Hawk L.W. Jr., Lysczek C.L., Tannock R., Pelham W.E. Jr., Spencer S.V., Gangloff B.P., Waschbusch D.A. (2008). The effects of incentives on visual-spatial working memory in children with Attentio-deficit/Hyperactivity Disorder. *Journal of Abnormal Child Psychology*, 36, 903-913.
- Sim M.E., Lyoo I.K., Streeter C.C., Covell J., Sarid-Segal O., Ciraulo D.A., Kim M.J., Kaufman M.J., Yurgelun-Todd D.A., Renshaw P.F. (2007). Cerebellar gray matter volume correlates with duration of cocaine use in cocainedependent subjects. *Neuropsychopharmacology*, 32, 2229–2237.
- Simon, S.L., Domier, C., Carnell, J., Brethen, P., Rawson, R., Ling, W. (2000). Cognitive impairment in individuals currently using methamphetamine. *The American Journal on Addiction,* 9, 222-231.
- Spealman R.D., BarrettLarimore R.L., Rowlett J.K., Platt D.M., Khroyan T.V. (1999). Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacology, Biochemistry and Behavior*, 64, 327–336.
- Stewart J., De Wit H., Eikelboom R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review*, 91, 251–268.
- Stewart J. (1984). Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. *Pharmacology, Biochemistry and Behavior,* 20, 917–923.
- Stewart J., Wise R.A. (1992). Reinstatement of heroin self-administration habits: morphine prompts and naltrexone discourages renewed responding after extinction. *Psychopharmacology,* 108, 79-84.
- Stewart J. (1992). Neurobiology of conditioning to drugs of abuse. In: Kalivas PW, Samson HH, editors. The neurobiology of drug and alcohol addiction. New York: NY Academic Science, pp. 335–46.
- Strickland T.L., Mena I., Villanueva-Meyer J., Miller B.L., Cummings J., Mehringer C.M., Satz P., Myers H. (1993). Cerebral perfusion and neuropsychological consequences of chronic cocaine use. *The Journal of Neuropsychiatry and Clinical Neuroscience*, 5, 419–427.

T

- Takahashi R., Ishii K., Kakigi T., Yokoyama K. (2011). Gender and age differences in normal adult human brain: voxel-based morphometric study. *Human Brain Mapping*, 32, 1050–1058.
- Tanabe J., Thompson L., Claus E., Dalwani M., Hutchison K., Banich M.T. (2007). Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. *Human Brain Mapping*, 28, 1276-1286.
- Tanabe J., Tregellas J.R., Dalwani M., Thompson L., Owens E., Crowley T., et al. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance dependent individuals. *Biological Psychiatry*, 65, 160–164.
- Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., Volkow, N.D. (2007a). Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. *Brain Research, 1171*, 83-92.
- Tomasi D., Goldstein R.Z., Telang F., Maloney T., Alia-Klein N., Caparelli E.C., Volkow N.D. (2007b). Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. *Psychiatry Research, 155*, 189-201.

V

- Vadhan N.P., Carpenter K.M., Copersino M.L., Hart C.L., Foltin R.W., Nunes E.V. (2007). Attentional bias towards cocaine-related stimuli: relationship to treatment-seeking for cocaine dependence. *The American Journal of Drug and Drug Abuse*, 33, 727-736.
- van de Laar M.C., Licht R., Franken I.H.A., Hendriks V.M. (2004). Event related potentials indicate motivational relevance of cocaine cues in abstinent cocaine addicts. *Psychopharmacology*, 177, 121–129.
- Verdejo-García A., Rivas-Pérez C., Lopez-Torrecillas F., Perez-García M. (2005). Differential impact of severity of drug use on frontal behavioral symptoms. *Addictive behaviors, 31***,** 1373-1382.
- Verdejo-García A., Bechara A., Recknor E.C., Perez-García M. (2006). Executive dysfunction in substance dependent individuals during drug use and

abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society, 12*, 405-415.

- Verdejo-García, A., Perales, J.C., Pérez-García, M. (2007). Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addictive Behaviors, 32*, 950-966.
- Verdejo-García A., Lawrence A.J., Clark L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problema gamblers and genetic association studies. *Neuroscience and biobehavioral reviews*, 32, 777-810.
- Volkow, N.D., Mullani, N., Gould, K.L., Adler, S., Krajewski, K. (1988). Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *The British journal of Psychiatry, 152*, 641–648.
- Volkow N.D., Ding Y., Fowler J.S., Wang G. (1996). Cocaine addiction: hypothesis derived from imaging studies with PET. *Journal of Addictive Diseases*, 15, 55 –71.
- Volkow N.D., Fowler J.S., Wang G.J. (1999a). Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *Journal of Psychopharmacology*, 13, 337-345.
- Volkow N.D., Wang G.J., Fowler J.S., Logan J., Gatley S.J., Gifford A., Hitzemann R., Ding Y.S., Pappas N. (1999b). Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *American Journal of Psychiatry*, 156, 1440-1443.
- Volkow N.D., Fowler J.S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral Cortex,* 10,318–325.
- Volkow N.D., Fowler J.S., Wang G.J., Goldstein R.Z. (2002). Role of Dopamine, the Frontal Cortex and Memory Circuits in Drug Addiction: Insight from Imaging Studies. *Neurobiology of Learning and Memory*, 78, 610-624.
- Volkow N.D., Fowler J.S., Wang G.J. (2003). The addicted human brain: insights from imaging studies. *The Journal of Clinical Investigation,* 111, 1444–1451.
- Volkow N.D., Wang G.J., Telang F, Fowler J.S., Logan J, Childress A.R., Jayne M., Ma Y., Wong C. (2006a). Cocaine cues and dopamine in dorsal striatum:

mechanism of craving in cocaine addiction. *Journal of Neuroscience*, 26, 6583-6588.

- Volkow N.D., Wang G.J., Begleiter H., Porjesz B., Fowler J.S, Telang F., Wong C., Ma Y., Logan J., Goldstein R., Alexoff D., Thanos P.K. (2006b). High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. *Archives of General Psychiatry,* 63, 999–1008.
- Volkow N.D., Gene-Jack W., Telang F., Fowler J.S., Logan J., Childress A.R., Jayne M., Ma Y., Wong C. (2008). Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. *Neuroimage*, 39, 1266- 1273.
- Volkow N.D.; Wang G.J., Fowler J.S., Tomasi D., Telang F., Baler R. (2010). Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays*, 32, 748-755.
- Volkow N.D., Wang G.J., Fowler J.S., Tomasi D. (2011a). Addiction circuitry in the human brain. *Annual Review of Pharmacology and Toxicology*, 52, 321-326.
- Volkow N.D., Wang G.J., Fowler J.S., Tomasi D., Telang F. (2011b). Quantification of Behavior Sackler Colloquium: Addiction: Beyond dopamine reward circuitry. *PNAS*, 108, 15037-15042.
- Volkow N.D., Tomasi D., Wang G.J., Fowler J.S., Telang F., Goldstein R.Z., Alia-Klein N., Wong C. (2011c). Reduced Metabolism in Brain ''Control Networks'' following Cocaine-Cues Exposure in Female Cocaine Abusers. *Plos One*, 6, e16573.
- Volkow N.D., Baler R.D., Goldstein R.Z. (2011d). Addiction: pulling at the neural threads of social behaviors. *Neuron*, 59, 599-602.

W

- Wanat M.J., Willuhn I., Clark J.J., Phillips P.E. (2009). Phasic dopamine release in appetitive behaviors and drug addiction. *Current Drug Abuse Reviews,* 2, 195–213.
- Wang G.J., Volkow N.D., Fowler J.S., Cervany P., Hitzemann R.J., Pappas N.R., Wong C.T., Felder C. (1999). Regional brain metabolic activation during

craving elicited by recall of previous drug experiences. *Life Science*, 64, 775-784.

- Washton A.M., Stone-Washton N. (1993). Outpatient treatment of cocaine and crack addiction: A clinical perspective. *NIDA Research Monograph*, 135, 15–30.
- Weiss F., Ciccocioppo R., Parsons L.H., Katner S., Liu X., Zorrilla E.P., Valdez G.R., Ben-Shahar O., Angeletti S., Richter R.R. (2001). Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Annals of the New York Academy of Science*, 937, 1-26.
- Weissenborn R., Deroche V., Koob G., Weiss F. (1996). Effects of dopamine agonists and antagonists on cocaine-induced operant responding for a cocaine-associated stimulus. *Psychopharmacology*, 126, 311-322.
- Weller R.E., Stoeckel L.E., Milby J.B., Bolding M., Twieg D.B., Knowlton R.C., Avison M.J., Ding Z. (2011). Smaller regional gray matter volume in homeless African American cocaine-dependent men: a preliminary report. *The open neuroimaging journal*, 5, 57-64.
- Wexler B.E., Gottschalk C.H., Fulbright R.K., Prohovnik I., Lacadie C.M., Rounsaville B.J., Gore J.C. (2001). Functional magnetic resonance imaging of cocaine craving. *American Journal of Psychiatry*, 158, 86-95.
- Whalen P.J., Bush G., McNally R.J., Wilhelm S., McInerney S.C., Jenike M.A., Rauch S.L. (1998). The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biological Psychiatry*, 44, 1219-1228.
- White F.J., Kalivas P.W. (1998). Neuroadaptations involved in amphetamine and cocaine dependence. *Drug Abuse Dependence*, 51, 141–153.
- Wise R.A. and Bozarth M.A. (1987) A psychomotor stimulant theory of addiction. *Psychological Review,* 94, 469–492.
- Wise, R.A. (1989). The brain and reward. In: Liebman, J.M. and Cooper, S.J., (Eds.). *The Neuropharmacological Basis of Reward*. Oxford University Press: Oxford, 377–424.
- Wise R.A., Murray A., Bozarth M.A. (1990). Bromocriptine self-administration and bromocriptine- reinstatement of cocaine-trained and heroin-trained lever pressing in rats. *Psychopharmacology*, 100, 355–360.

- Wise R.A. (2002). Brain reward circuitry: insights from unsensed incentives. *Neuron*, 36, 229-240.
- Wise R.A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, 5, 483–94.
- Wong D.F., Kuwabara H., Schretlen D.J., Bonson K.R., Zhou Y., Nandi A., Brasić J.R., Kimes A.S., Maris M.A., Kumar A., Contoreggi C.,Links J., Ernst M., Rousset O., Zukin S., Grace A.A., Lee J.S., Rohde C., Jasinski D.R., Gjedde A., London E.D. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology*, 31, 2716-2727.
- Worsley, K.J., Marret, S., Neelin, P., Vandal, C., Friston, K.J., Evans, A. (1996). A unified statistical approach for determining significant voxels in images of cerebral activation. *Human Brain Mapping, 2*, 58–73.

Z

- Zapata A, Chefer VI, Ator R, Shippenberg TS, Rocha BA. (2003). Behavioural sensitization and enhanced dopamine response in the nucleus accumbens after intravenous cocaine self-administration in mice. *European Journal of Neuroscience*, 17, 590-596.
- Zijlstra F., Veltman D.J., Booij J., van den Brink W., Franken, I.H.A. (2009). Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. *Drug and Alcohol Dependence*, 99, 183–192.

***The references of each paper are included in the sections of each manuscript.**

Resumen general en castellano

En la actualidad se establece que la adicción implica un uso incontrolado de la droga y no solo procesos de tolerancia y dependencia (O'Brien, 2008). Muchos estudios muestran alteraciones en funciones de control ejecutivo en dependientes a la cocaína (Garavan y Hester, 2007; Kubler et cols., 2005, Tomasi et cols., 2007a; Bolla et cols., 2003). Además, algunos estudios indican que la adicción a la cocaína altera también las funciones de procesamiento de la recompensa (Garavan et cols., 2000; Jia et cols., 2011). La interacción de los componentes neurobiológicos asociados con estos procesos cognitivos y motivacionales en la dependencia es básica para la comprensión de dicho proceso adictivo y los diferentes grados de severidad que implica.

El estudio neuroconductual de los componentes cognitivos (por ejemplo, control cognitivo) y de los componentes motivacionales (por ejemplo, procesamiento de la recompensa), y también el estudio de los cambios estructurales asociados con el consumo, pueden ofrecer una mayor evidencia empírica para el desarrollo de nuevos modelos teóricos. Estos modelos no solo deben implicar una dimensión relacionada con la "psicopatología del sujeto" sino también una dimensión más "biológica" (las bases neurales de los procesos adictivos), que a la vez puede ser modulada por variables genéticas y ambientales. La metodología aplicada en los estudios de neuroimagen puede permitir una mayor comprensión del perfil del paciente aunando aspectos como sistemas de neurotransmisión, bases estructurales y funcionales, estados cognitivos, rasgos de personalidad, situación personal y social y situación clínica. Todo este conocimiento estará relacionado, a su vez, con el establecimiento de tratamientos más completos, efectivos y eficaces (Kampman, 2010; Volkow et cols., 2011a, 2011b, 2011c).

R.1. Planteamiento y metodología utilizada

La literatura en dependencia a la cocaína muestra que la adicción implica la alteración de un circuito mesolímbico relacionado con componentes motivacionales de la misma, al igual que la alteración de un circuito mesocortical que implica funciones motivacionales y cognitivas (Goldstein y Volkow, 2002; Garavan et cols., 2002; Lim et cols., 2002, 2008; Matochik et cols., 2003; Kubler et cols., 2005; Tomasi et cols., 2007; Goldstein et cols., 2007a, 2007b; Bjork et cols., 2008; Tanabe et cols., 2009; Goldstein et cols., 2009; Asensio et cols., 2010; Jia et cols., 2011; Ersche et cols., 2011). Los pacientes dependientes a la cocaína pueden presentar un perfil neurobiológico complejo que implica áreas frontales, parietales, límbicas y estriatales. La comprensión de dicha complejidad puede ser de mucho valor para el éxito de los tratamientos (Aron y Paulus, 2007). Además, puede dar a la comunidad científica mayor evidencia empírica relacionada con el estudio de la realidad neurocognitiva de la adicción a la cocaína.

La metodología utilizada en esta tesis doctoral se basa en la aplicación de una técnica con importante relevancia científica como es la Resonancia Magnética (RM), por su alta resolución especial y buena resolución temporal (Aron y Paulus, 2007). Además, en los cuatro estudios presentados se obtienen también datos conductuales y clínicos para dar mayor validez a la interpretación de los datos funcionales. Esto implica una complejidad técnica añadida y relacionada con la preparación, programación y adaptación de los paradigmas al entorno de la resonancia.

Hombres y mujeres muestran diferencias en patrones conductuales y perfiles clínicos relacionados con el consumo, y son afectados de manera distinta por las drogas de abuso (Brady y Ryall, 1999; Sinha y Rounsaville, 2002; Becker y Hu, 2008). Además, muestran diferencias morfométricas (Chen et cols., 2007; Fan et cols., 2010; Good et cols., 2001; Takahashi et cols., 2011; Koscik et cols., 2009) y diferencias en patrones de respuesta cerebral (Wager et cols., 2003; Kim et cols., 2005; Goldstein et cols., 2005; Li et cols., 2006; Adinoff et cols., 2006). Así, en nuestros estudios solo utilizamos participantes hombres para controlar el posible efecto de dicha variable en los resultados. También utilizamos grupos equiparados en lateralidad manual, nivel educativo y nivel de inteligencia. Respecto a los patrones de consumo de los

dependientes que utilizamos en nuestros grupos de pacientes, solo utilizamos aquellos que presentan un patrón adictivo respecto al consumo de cocaína y no respecto a otras sustancias.

El uso compulsivo de la cocaína está relacionado con alteraciones a nivel de volúmenes de sustancia gris y sustancia blanca en áreas cerebrales mecocorticolímbicas (White y Kalivas, 1998; Bartzokis et cols., 2000; Franklin et cols., 2002; Matochik et cols., 2003; Lyoo et cols., 2004; Moeller et cols., 2005; Lim et cols., 2008; Tanabe et cols., 2009; Ersche et cols., 2011). Así, el primer estudio que planteamos en la tesis busca comparar las diferencias en volúmenes de sustancia gris entre un grupo de pacientes dependientes a la cocaína y un grupo control. Para ello aplicamos una herramienta de análisis morfométrico como es la morfometría basada en el vóxel (del inglés, Voxel Based Morphometry, VBM 5.1).

Hay clara evidencia empírica que apoya la existencia de una disfunción ejecutiva en dependientes a la cocaína (Bolla et cols., 1998; Cunha et cols., 2004) acompañado de mecanismos atencionales deficitarios (Jovanovski y cols., 2005; Simon y cols., 2000; Verdejo-García y cols., 2005; Morgan y cols., 2006), que pueden estar asociados a patrones de activación alterados en la red frontoparietal relacionada con funciones ejecutivas. Así, los siguientes dos estudios que se presentan en esta tesis buscan comparar a un grupo de dependientes a la cocaína y a un grupo control en dos tareas de funciones ejecutivas adaptadas al contexto de la resonancia, para así minimizar dificultades en la recogida de datos tales como movimiento durante la adquisición de los datos de RM o pérdida de datos conductuales. Un paradigma de memoria de trabajo 2-BACK auditivo cuyo uso en el contexto de la Resonancia Magnética funcional (RMf) ya ha sido validado en un estudio previo de nuestro laboratorio (Forn et cols., 2007), y una tarea "Counting" Stroop de control de interferencia (Bush et cols., 2006). Además, ambas tareas fueron adaptadas en nivel de dificultad para igualar la ejecución de la tarea en los grupos implicados en cada uno de los estudios buscando una mejor interpretación de los resultados funcionales. Esta aproximación metodológica da mayor validez a nuestros estudios cognitivos porque nos permite establecer que las alteraciones en los patrones de actividad cerebral en los pacientes están relacionadas con déficits cognitivos

asociados al consumo, pero no con el hecho de que los participantes tengan problemas con la ejecución de la tarea (Price et cols., 2006; Li et cols., 2008).

El consumo crónico de cocaína también se relaciona con el hecho de que las alteraciones anatómicas pueden afectar la respuesta cerebral dependiente del nivel de oxígeno en sangre (del inglés, Blood Oxygen Level Dependent, BOLD) (Aron y Paulus, 2007). Por ello, aplicamos en estos dos últimos estudios dos herramientas de análisis para darle a nuestros resultados mayor validez y significado experimental para así facilitar la interpretación. Por una parte, hemos aplicado la herramienta VBM para estudiar el efecto del volumen de sustancia gris en los datos funcionales utilizando, por otro lado, la herramienta BPM (del inglés, Biological Parametric Mapping) para analizar los efectos de covarianza entre los datos morfométricos y los datos funcionales (Casanova et cols., 2007).

Finalmente, las alteraciones en procesamiento de la recompensa en dependencia a la cocaína implican regiones límbicas dopaminérgicas que, junto con áreas corticales (prefrontales), representan los sustratos neurales de la atribución de saliencia de incentivo a estímulos relacionados y no relacionados con la droga (Goldstein y Volkow, 2002; Bjork et cols., 2008; Volkow et cols., 2011a). Los circuitos cerebrales de recompensa tienden a hacerse hipersensibles a los efectos de la droga y a los estímulos asociados a la misma (Robinson y Berridge, 2003). Hay diversos estudios que muestran un sistema cerebral funcional sensibilizado cuando los pacientes dependientes a la cocaína procesan estímulos relacionados con la droga (Maas et cols., 1998; Childress et cols., 1999; Garavan et cols., 2000; Kilts et cols., 2001; Wexler et cols., 2001; Bonson et cols., 2002; Grant et cols., 1996; Wang et cols., 1999). Sin embargo, son pocos los estudios que intentan elucidar la alteraciones neurofuncionales relacionadas con el procesamiento de recompensas no relacionadas con la droga (Goldstein et cols., 2007a; Asensio et cols., 2010; Jia et cols., 2011). Específicamente, nuestro cuarto estudio busca dar evidencia empírica a las posibles alteraciones en el procesamiento de recompensas monetarias en dependencia a la cocaína utilizando una adaptación de la tarea MIDT (del inglés, Monetary Incentive Delay Task) desarrollada por Knutson et cols. (2001).

En adicción a la cocaína es clara la presencia de recaídas recurrentes en los pacientes (Connolly et cols., 2012). Una importante proporción de los dependientes en tratamiento no son capaces de mantener una abstinencia prolongada (Ahmadi et cols., 2006; Carroll, 1997; Dutra et cols., 2008; Elkashef et cols., 2007; Knapp et cols., 2007; Shearer, 2007). Alteraciones neurocognitivas han sido claramente implicadas en los pocos resultados positivos obtenidos por las terapias conductuales en dependencia a la cocaína (Xu et cols., 2010). La actividad cerebral puede ser una medida más sensible, en comparación a medidas de autoinforme o de ejecución conductual, para predecir futuros resultados de tratamiento (Brewer et cols., 2008). De esta forma, es interesante estudiar las posibles relaciones existentes entre efectos funcionales y variables relacionadas con el tratamiento, para darle a la interpretación de los datos una significancia clínica basada en cambios cerebrales relacionados con el proceso terapéutico y su implicación en el mantenimiento de la abstinencia o las recaídas. En este sentido, no es mucha la evidencia respecto a la bases neurobiológicas que subyacen la posibilidad de mantener abstinencias prolongadas, y como un estudio previo refiere, el tiempo en abstinencia puede modular el funcionamiento cerebral en pacientes (Moeller et cols., 2010). Hay solo dos estudios que concluyen que las alteraciones funcionales relacionadas con demandas de control cognitivo pueden ser parcialmente recuperadas con prolongados períodos de abstinencia (Connolly et cols., 2012; Moeller et cols., 2012). Por otra parte, no hay estudios sobre el efecto de la abstinencia prolongada sobre el funcionamiento cerebral durante el procesamiento de recompensas en áreas dopaminérgicas como el estriado. En este sentido, nosotros proponemos una caracterización neurobiológica teniendo en cuenta el funcionamiento cerebral estriatal durante procesos motivacionales en aquellos pacientes que logran mantener la abstinencia durante un largo período de tiempo. Además, buscamos conocer las implicaciones neurofuncionales y neuroestructurales de variables relacionadas con la severidad del consumo (por ejemplo, edad de inicio de consumo o números de años de duración del consumo), por lo que en todos nuestros estudios realizamos análisis de correlación exploratorios entre efectos funcionales o efectos estructurales y dichas variables buscando dar a nuestros resultados una mayor relevancia clínica.

En conclusión, esta tesis doctoral estudia las bases neurobiológicas de los dos principales componentes que conceptualizan el circulo vicioso que implica el proceso

de adicción a la cocaína (Goldstein y Volkow, 2002), la alteración de la atribución de la saliencia de incentivo a los estímulos no relacionados con la droga y las alteraciones a nivel de control cognitivo. El primer estudio explora las posibles alteraciones estructurales relacionadas con la adicción. Los dos siguientes estudios se basan en la posibilidad de observar patrones de activación alterados en pacientes dependientes a la cocaína durante dos procesos cognitivos complejos como la memoria de trabajo y el control de interferencia. El último estudio busca también analizar los patrones de actividad cerebral alterados en los pacientes durante una tarea motivacional relacionada con el procesamiento de recompensas monetarias, teniendo en cuenta los posibles efectos de la abstinencia sobre los resultados.

R.2. Objetivos e hipótesis

El objetivo general de este trabajo es elucidar los sustratos neurobiológicos que implican las alteraciones en el procesamiento cognitivo y motivacional en adicción a la cocaína que puede producir el mantenimiento de las conductas compulsivas de búsqueda de la droga, y también sus posibles implicaciones relacionadas con el tratamiento. Los objetivos específicos son:

- Detectar cambios estructurales en áreas subcorticales como el estriado en un grupo de dependientes a la cocaína, en comparación con un grupo control, por medio de análisis de morfometría basada en el vóxel.
- Comparar los patrones de actividad cerebral entre un grupo control y un grupo de dependientes a la cocaína en una tarea 2-BACK de memoria de trabajo auditiva, equiparando a ambos grupos en nivel de ejecución de la tarea.
- Identificar las regiones cerebrales que están implicadas diferencialmente en un grupo de dependientes a la cocaína y un grupo control durante una tarea counting Stroop de control de interferencia, equiparando a ambos grupos en nivel de ejecución de la tarea.
- Mostrar las alteraciones funcionales a nivel estriatal en un grupo de dependientes a la cocaína durante la MIDT, y los posibles cambios neurofuncionales que la abstinencia puede producir sobre la activación del estriado ante la anticipación y reactividad a recompensas monetarias.

Teniendo en cuenta estos objetivos, las hipótesis planteadas son:

- Encontraremos cambios en el volumen de sustancia gris en las áreas cerebrales dopaminérgicas afectadas funcionalmente por la adicción a la cocaína esperando específicamente efectos a nivel del estriado.
- Los pacientes con dependencia a la cocaína mostrarán, en comparación al grupo control, un patrón de activación deficitario del sistema frontoparietal implicado en la realización de la tarea 2-BACK.

- Los pacientes con dependencia a la cocaína mostrarán una menor activación en áreas frontoparietales implicadas en la tarea de counting Stroop en comparación al grupo control.
- Encontraremos diferencias funcionales estriatales entre un grupo de pacientes dependientes a la cocaína y un grupo control y una regulación de la funcionalidad del estriado asociado a la abstinencia y al tiempo en tratamiento durante el procesamiento de recompensas monetarias.

R.3. Principales aportaciones y conclusiones

El objetivo de esta tesis doctoral ha sido presentar más evidencia empírica en relación a las posibles alteraciones que puede producir el consumo crónico de la cocaína a un nivel neurobiológico, teniendo en cuenta resultados relacionados con alteraciones a nivel estructural y funcional en el circuito dopaminérgico mesocorticolímbico que está claramente implicado en la adicción a la cocaína (Goldstein y Volkow, 2002). Así, en esta tesis se han presentado, por una parte, un estudio relacionado con resultados morfométricos y, por otra parte, tres estudios relacionados con resultados funcionales. Específicamente, el estudio de VBM mostró que los adictos a la cocaína presentan reducciones en el volumen de sustancia gris en el estriado dorsal. Además, el estudio mostró también que el volumen de sustancia gris en la amígdala correlaciona negativamente con la variable años de consumo de cocaína. Estos resultados apoyan la existencia de neuroadaptaciones estructurales presentes en la adicción a la cocaína y que pueden asociarse a componentes cognitivos y motivacionales de la dependencia que implican conductas desinhibitorias y compulsivas condicionadas por los estímulos asociados a la droga (Koob y LeMoal, 2008). Respecto a los estudios de RMf, los resultados están asociados con los dos componentes principales del círculo vicioso asociado a la adicción y que representan los elementos principales de los modelos teóricos actuales: control cognitivo y atribución de la saliencia al incentivo (Koob et cols., 1993; Koob y Lemoal, 1997; Blum et cols., 2000; Goldstein y Volkow, 2002; Robinson y Berridge, 2003, 2008; Leyton, 2007; Volkow et cols., 2011b). Dos de los estudios presentados han mostrado alteraciones funcionales frontoparietales relacionadas con problemas en control atencional presentes en la adicción a la cocaína. Uno de ellos mostró que los pacientes presentan hipoactivación en el giro parietal inferior durante una tarea de memoria de trabajo n-back. El segundo estudio mostró que los pacientes presentan también una hipoactivación en el córtex frontal inferior, en el córtex parietal inferior y en el córtex temporal superior en una tarea de control de interferencia Counting Stroop en comparación a un grupo control.

En el último estudio funcional se presentan resultados relacionados con las alteraciones en el procesamiento de recompensas monetarias. Los dependientes a la cocaína presentaban una hipoactivación en el caudado durante la presentación de

estímulos que anticipan la llegada de incentivos monetarios. Resultado que puede estar relacionado con la codificación de un bajo valor motivacional hacia las recompensas monetarias. Algunos estudios han mostrado que la presentación de estímulos relacionados con la droga induce un fuerte deseo ("craving") por la droga que se relaciona con la activación de la amígdala y áreas prefrontales límbicas (Grant et cols. 1996; Childress et cols. 1999; Garavan et cols. 2000) y también con la activación del estriado dorsal (Garavan et cols. 2000; Volkow et cols. 2006a). Así, en este tercer estudio los resultados apoyan la importancia del estriado dorsal en el establecimiento de los hábitos de búsqueda y consumo de la droga dándole importancia al proceso de cambio de estriado ventral a estriado dorsal (Everitt et cols., 2008). Además, este estudio mostró que el tiempo en abstinencia y el tiempo en tratamiento se han relacionado con procesos de regulación de la actividad en el estriado durante la anticipación y reactividad ante estímulos no relacionados con la droga. El tiempo en tratamiento se ha asociado con una recuperación de la actividad del caudado durante procesos de anticipación de recompensas, que se puede relacionar con otorgar un mayor valor de incentivo/motivacional a estímulos relacionados con recompensas monetarias. El estriado dorsal media el proceso de aprendizaje estímulo-respuesta instrumental, una respuesta con la que se busca obtener un reforzador y que es inducida por un estímulo asociado a la recompensa (Everitt et cols., 2008). Este proceso de mediación está basado en el funcionamiento del estriado dorsal y está condicionado respecto al valor motivacional de la recompensa a obtener. Otro resultado interesante está relacionado con el hecho de que la actividad en el accumbens se ve incrementada ante la aparición de recompensas monetarias cuando el tiempo en abstinencia es corto, y como mostramos en nuestro estudio se normaliza o disminuye cuando los pacientes logran mantener una abstinencia prolongada. La hipersensibilidad de regiones estriatales ante las recompensas monetarias puede representar un mecanismo neural de resistencia hacia la intervención. El dinero puede actuar como un reforzador secundario hacia el consumo (Jia et cols., 2011). Las conductas de búsqueda de la droga es un hábito inducido y mantenido por los estímulos asociados a la droga (Everitt el cols., 2001), y dichos hábitos dependen inicialmente de estriado ventral (Everitt et cols., 2008). Los estados en los que los pacientes están libres del consumo y del efecto de la droga se pueden relacionar con efectos funcionales que pueden representar una recuperación o regulación del valor motivacional de los estímulos no relacionados con la droga

promoviendo conductas de aproximación saludables hacia recompensas diferentes a la droga.

Así, del desarrollo de estos cuatro estudios podemos extraer las siguientes conclusiones:

1) Los pacientes dependientes a la cocaína muestran una reducción en el volumen de sustancia gris en regiones corticales y subcorticales asociadas con déficits a nivel cognitivo, motivacional y emocional.
2) La severidad del consumo determina las alteraciones estructurales en áreas límbicas, frontales y parietales relacionadas con funciones de control ejecutivo y motivacionales.
3) El uso crónico de cocaína está relacionado con alteraciones del sistema ejecutivo atencional, que implica áreas frontales y parietales, y está asociado con déficits atencionales y de control cognitivo presentes en la adicción.
4) La variabilidad morfométrica intersujetos es una importante variable que los estudios funcionales deben tener en cuenta por sus posibles efectos en los resultados obtenidos.
5) La equiparación de la ejecución de las tareas utilizadas entre las muestras en un estudio representa una buena aproximación metodológica para la interpretación de los efectos funcionales. Nos permite dar mayor validez a los resultados, e incluso mayor validez y fiabilidad a los estudios basados en diferencias conductuales entre muestras.
6) Los pacientes dependientes a la cocaína muestran alteraciones en mecanismos cerebrales motivacionales de recompensa que implican patrones alterados de activación estriatal durante el procesamiento de recompensas no relacionadas con la droga.
7) La duración de los tratamientos con éxito y el tiempo en abstinencia pueden determinar de forma diferenciada la regulación de los patrones alterados de activación del estriado ventral y del estriado dorsal durante el procesamiento de recompensas monetarias, teniendo en cuenta la dicotomía presente en los roles que juega cada una de estas estructuras en el proceso de adicción, e implicando un cambio en el valor motivacional de los estímulos no relacionados con la droga.

R.4. Líneas de investigación futura

La adicción es resultado de la interacción de variables genéticas, biológicas y ambientales (Volkow et cols., 2002b), y también variables cognitivas y motivacionales. Además, otros sistemas de neurotransmisión, distintos al dopaminérgico, están también implicados. Teniendo en cuenta la compleja naturaleza de la adicción a la cocaína y todas las posibilidades que ofrecen las técnicas de neuroimagen como la RM a la comunidad científica para el estudio de este fenómeno, pueden proponerse otras aproximaciones experimentales que pueden dar lugar a nuevos proyectos:

1º) El análisis de los efectos cerebrales de anticipación y reactividad a estímulos condicionados a la droga durante tareas de control cognitivo puede dar mayor explicación a las alteraciones cognitivo-motivacionales presentes en la adicción a la cocaína, dando mayor evidencia empírica a las bases neurales de la interacción entre procesos cognitivos y motivacionales en estos patrones conductuales desinhibitorios condicionados por la presencia de estímulos relacionados con la droga. Como podemos observar en la literatura previa y en los estudios presentados en esta tesis, la interacción entre procesos cognitivo y motivacionales puede ser considerado un elemento relevante para la estudio del fenómeno de la adicción y los procesos de recaída. Las respuestas motivacionales hacia la droga parecen controlar los procesos cognitivos relacionados con la obtención de la sustancia independientemente de las consecuencias asociadas al consumo, dificultando la efectividad de los procesos de tratamiento. Sin embargo, no es tan clara la evidencia que explique el efecto tan marcado de la droga sobre la conducta motivada. Podría ser posible analizar este efecto haciendo contingente a la conducta la obtención de la droga o de otro tipo de reforzador. En este sentido, la obtención de la droga o las señales que la anticipan parecen determinar los procesos cognitivos relacionados con la conducta motivada.

2º) El estudio de la conectividad cerebral en pacientes dependientes a la cocaína nos puede permitir una mayor comprensión del funcionamiento cerebral entre regiones corticales y subcorticales que trabajan en paralelo y están implicadas en procesos cognitivos y motivacionales que subyacen al círculo vicioso que explica la adicción a la cocaína. Los patrones de conectividad funcional entre un grupo de regiones se han

relacionado con la integridad funcional de dichas regiones durante una determinada tarea. Así, un patrón alterado de conectividad en la adicción está relacionado con variables como número de años de consumo o la ejecución ante una tarea cognitiva (Gu et cols., 2010). Los pacientes adictos a la cocaína han mostrado patrones de conectividad reducida entre regiones como el córtex orbitofrontal, la amígdala, el hipocampo y otras regiones prefrontales (Gu et cols., 2010). Además, Kelly et cols. (2011) han mostrado patrones de conectividad interhemisferica reducidas en regiones frontales en este tipo de pacientes. Por otra parte, otros estudios (Gu et cols., 2010; N. Ma et cols., 2011; 2010) han mostrado un incremento en la conectividad entre el accumbens y regiones cerebrales como la amígdala, el cingulado anterior y el córtex orbitofrontal en adictos a la cocaína y la heroína.

3º) El estudio de las posibles implicaciones neurofuncionales que pueden tener las alteraciones de otros sistemas de neurotransmisión, diferentes al sistema dopaminérgico, en las diferentes etapas del proceso de adicción a la cocaína puede permitirnos considerar el cerebro de un paciente adicto a la cocaína de una forma más holística analizando todos los componentes neurobiologicos implicados en el proceso de adicción. Dicha droga tiene claros efectos sobre los sistemas dopaminérgicos, serotonérgicos, glutamatérgicos y gabaérgicos. La cocaína incrementa la actividad del sistema monoaminérgico mediante el bloqueo de la recaptación no solo de la dopamina sino también de la serotonina contribuyendo al desarrollo de la sensibilización hacia la cocaína (Lason, 2001; Cunningham et cols., 1992). Receptores serotonérgicos, que juegan un importante papel en los efectos reforzadores de la droga modulando la liberación de GABA en el área tegmental ventral, muestran una regulación a la baja durante el consumo compulsivo y una regulación a la alta durante la retirada (Parsons et cols., 1998). Una disminución en la transmisión serotonérgica puede producir un aumento en las respuestas dopaminérgicas apetitivas hacia la cocaína que pueden estar relacionadas con procesos de craving (Cox et cols., 2011). Además cambios funcionales en el circuito cerebral de recompensa están relacionados con alteraciones en la transmisión serotonérgica en el accumbens (Weiss et cols., 2001). También el uso crónico de cocaína y la posterior retirada produce decrementos en los niveles basales de glutamato en el accumbens (McFarly et cols., 2003). Por otra parte, la reaparición de las conductas compulsivas de consumo de cocaína se relaciona con la activación de la vía

glutamatérgica córtex dorsolateral prefrontal-accumbens y la posterior activación de la vía gabaérgica a nivel del accumbens (Kalivas y McFarly, 2003).

En conclusión, alteraciones en procesos cognitivos y motivacionales están claramente relacionadas con el consumo prolongado de cocaína y los patrones compulsivos asociados a la adicción. El análisis de las bases neurales de la interacción entre dichos procesos puede ayudar a una mayor comprensión de los efectos de la droga a nivel cerebral. Además, los cambios en la estructura y el funcionamiento en específicas regiones cerebrales, y la asociación y conectividad entre ellas puede dar mayor evidencia al estudio de las bases biológicas de los patrones conductuales adictivos. También es importante destacar que el estudio de la implicación de otros sistemas de neurotransmisión diferentes al dopaminérgico, en las bases neurofuncionales y estructurales de la adicción, representa una interesante aproximación a los sustratos cerebrales en los que se basa el proceso de transición de un consumo recreacional de la droga hacia un abuso crónico de la misma. En suma, todas estas aproximaciones pueden dar lugar a nuevas estrategias de tratamiento tanto a nivel farmacológico como psicológico.

UNIVERSITAT JAUME·I
2012

ERRATA AT THE DOCTORAL THESIS "NEURAL BASES OF COGNITIVE AND MOTIVATIONAL PROCESSES IN COCAINE ADDICTION"

1. Inclusion of references at the section "References of general introduction and general discussion".

Adinoff B., Williams M.J., Best S.E., Harris T.S., Chandler P., Devous M.D. Sr. (2006). Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Medicine*, 3, 206-222.

Bartzokis G., Beckson M., Hance D.B., Lu P.H., Foster J.A., Mintz J., Ling W., Bridge P. (1999a). Magnetic resonance imaging evidence of "silent" cerebrovascular toxicity in cocaine dependence. *Biological Psychiatry*, 45, 1203-1211.

Bartzokis G., Goldstein I.B., Hance D.B., Beckson M., Shapiro D., Lu P.H., Edwards N., Mintz J., Bridge P. (1999b). The incidence of T2-weighted MR imaging signal abnormalities in the brain of cocaine-dependent patients is age-related and region-specific. *American journal of Neuroradiology*, 20, 1628-1635.

Bell R.P., Foxe J.J., Nierenberg J., Hoptman M.J., Garavan H. (2011). Assessing white matter integrity as a function of abstinence duration in former cocaine dependent individuals. *Drug and Alcohol dependence*, 114, 159-168.

Brady K.T., Randall C.L. (1999). Gender differences in substance use disorders, *The Psychiatrics Clinics of North America*, 22, 241–252.

Breiter H.C., Gollub R.L., Weisskoff R.M., Kennedy D.N., Makris N., Berke J.D., Goodman J.M., Kantor H.L., Gastfriend D.R., Riorden J.P., Mathew R.T., Rosen B.R., Hyman S.E. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron*, 19, 591-611.

Breiter H.C., Rosen B.R. (1999). Functional magnetic resonance imaging of brain reward circuitry in the human. *Annals of the New York Academy of Sciences*, 877, 523-547.

Bush G., Whalen P.J., Shin L.M., Rauch S.L. (2006). The counting Stroop: a cognitive interference task. *Nature Protocols*, 1, 230–233.

Connolly C.G., Foxe J.J., Nierenberg J., Shpaner M., Garavan H. (2012). The neurobiology of cognitive control in successful cocaine abstinence. *Drug and Alcohol Dependence*, 121, 45-53.

Cunha P.J., Nicastri S., Gomes L.P., Moino R.M., Peluso M.A. (2004). Neuropsychology impairments in crack cocaine-dependent inpatients: preliminary findings. *Revista Brasileira de Psiquiatría*, 26, 103-106.

Fein G., Di Sclafani V., Meyerhoff D.J. (2002). Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug and Alcohol Dependence*, 68, 87–93.

Forn C., Barrós-Loscertales A., Escudero J., Campos S., Parcet M.A., Ávila C. (2007). Compensatory activation in patients with multiple sclerosis during preserved performance on the auditory N-back task. *Human Brain Mapping*, 28, 424–430.

Goldstein J.M., Jerram M., Poldrack R., Anagnoson R., Breiter H.C., Makris N., Goodman J.M., Tsuang M.T., Seidman L.J. (2005). Sex differences in prefrontal cortical brain activity during fMRI of auditory verbal working memory. *Neuropsychology*, 19, 509-519.

Kim S.J., Lyoo I.K., Hwang J., Sung Y.H., Lee H.Y., Lee D.S., Jeong D.U., Renshaw P.F. (2005). Frontal glucose hypometabolism in abstinent methamphetamine users. *Neuropsychopharmacology*, 30, 1383-1391.

Knutson B., Adams C.M., Fong G.W., Hommer D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *The journal of Neuroscience*, 21, 1-5.

Li C.S., Huang C., Constable R.T, Sinha R. (2006). Gender differences in the neural correlates of response inhibition during a stop signal task. *Neuroimage*, 32, 1918-1929.

Moeller F.G., Steinberg J.L., Schmitz J.M., Ma L., Liu S., Kjome K.L., Rathnayaka N., Kramer L.A., Narayana P.A. (2010). Working memory fMRI activation in cocaine-dependent subjects: association with treatment response. *Psychiatry Research*, 181, 174-182.

Moeller S.J., Tomasi D., Woicik P.A., Maloney T., Alia-Klein N., Honorio J., Telang F., Wang G.J., Wang R., Sinha R., Carise D., Astone-Twerell J., Bolger J., Volkow N.D., Goldstein R.Z. (2012).Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addiction Biology*, in press.

Monterosso J.R., Aron A.R., Cordova X., Xu J., London E.D. (2005). Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug and Alcohol Dependence*, 79, 273-277.

Price C.J., Crinion J., Friston K.J. (2006). Design and analysis of fMRI studies with neurologically impaired patients. *Journal of Magnetic Resonance Imaging*, 23, 816-826.

Sinha R., Rounsaville B.J. (2002). Sex differences in depressed substance abusers. *The Journal of Clinical Psychiatry*, 63, 616-627.

Volkow N.D., Chang L., Wang G.J., Fowler J.S., Franceschi D., Sedler M., Gatley S.J., Miller E., Hitzemann R., Ding Y.S., Logan J. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *The journal of Neuroscience*, 21, 9414-9418.

Wager T.D., Phan K.L., Liberzon I., Taylor S.F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage*, 19, 513-531.

Xu J., DeVito E.E., Worhunsky P.D., Carroll K.M., Rounsaville B.J., Potenza M.N. (2010). White matter integrity is associated with treatment outcome measures in cocaine dependence. *Neuropsychopharmacology*, 35, 1541-1549.