ESCOLA DE CIÊNCIAS DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM PSICOLOGIA
DOUTORADO EM PSICOLOGIA

BRENO SANVICENTE VIEIRA

A COMPREHENSIVE CLINICAL AND NEUROIMAGING APPROACH OF SEX DIFFERENCES IN CRACK COCAINE USE DISORDER

Porto Alegre
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PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
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Tese apresentada ao Programa de Pós-Graduação em Psicologia da Pontifícia Universidade Católica do Rio Grande do Sul como requisito parcial para a obtenção do título de Doutor em Psicologia.

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DEDICATION

I dedicate this thesis to my beloved father and grandfather, Catarino Bagic Vieira and Breno Sanvicente. They were two of my first and best teachers, but could not be here to see me accomplishing this achievement.

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My thesis is about men and women; it is about the differences among them and the way that they build their lives, particularly their relations. To accomplish my work, I needed help from a group of males and females in addition to assistance from organizations. For this reason, I must acknowledge all support, guidance and especially the good times I experienced. I am sorry about the list's length, but I would like to make the effort to mention everyone who contributed, since this is the least that I could give them.

Undoubtedly, I need to first thank my mentors: Rodrigo Grassi-Oliveira and Alexandre Rosa Franco. They showed me in everyday practice what inter- and multidisciplinary mean and always helped and supported me in such a way that I believe I could not have had better advisors. More than that, they inspired me all the way along in my Ph.D.; it was an honor to learn with them—thank you, bosses!

Rodrigo has been my advisor since I was a research assistant. I have no words to thank him for all he taught, showed, and gave me (from statistical and methodological discussions, neuropsychology classes, clinical advices, and fancy lunches). The real interest I always saw him have for his students, their learning, and science are what I most hope to give to a student someday.

Furthermore, I need to make a second round of thanks to him. I must say that Rodrigo always said that "thesis' acknowledgements should be restricted to those who gave academic contributions." Students are students because they are still learning and are always stubborn. I will not hear that. In fact, I could argue against it and state that I lived my work, and thus my everyday life also was part of the academic construction. However, I do not really care if it is not the most correct thing to do. I stated in the beginning that this work is about how people build relations, so I must acknowledge Rodrigo for more than being an excellent advisor but also for having been a true friend. For the last nine years, he was there to celebrate good

moments and to cry with me in sad ones. That was not an academic activity but a friendship. In the time of my dissertation, I wrote, “I am a better researcher because of you.” That is still true, but now I say it differently—I am a better person because of you!

Until the end of my master’s degree, I worked mainly with behaviors. A turning point was when I started to work with neuroimaging. To be more specific, Alexandre was a turning point. My co-advisor introduced me to a field far away from my comfort zone. I thank him for the smooth way that he taught me and for his patience, sympathy, and encouragement. He was comprehensive as many psychologists could not had been. I wish that I had met him before. Alexandre is an inspiration. I wish that I could teach difficult subjects in the same light way that he does, keeping everything simple; regardless, he is doing awesome things.

In addition to mentors, a big team was crucial to make this thesis possible. I want to thank everyone at the Developmental Cognitive Neuroscience Lab (DCNL). Special thanks for some hard-working research assistants who were dedicated, trustworthy, and ethical all of the time. Big thanks to Leonardo Rothmann and his obstinacy, availability, and real right-arm work! Thanks also to Sândhya Marques for all of her correction, caution, and readiness and to João Niederauer for his creativity, management, and endurance. Besides them, some other students worked with me, and I ought to recognize them as well. Thanks to Gabriela Jacobsen and Raffaelly Pazzin, who helped in the first steps of the project, and to Leonardo Wainer, Luiz Fernando Dresch, and Renata Rodrigues, who also contributed along my way to my PhD.

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I also participated in Laboratório de Imagens (LABIMA). I would like to thank everyone in LABIMA. Their expertise was crucial for my work, together with their patience and readiness to help me. I already mentioned some LABIMA's research assistants, but I need to mention some post-graduation students as well: José Osmar and Nathalia Esper Bianchini.

Among my collaborators, a special person to whom I am grateful for having met and worked with is Diego Rovaris. He taught me things of which I was unaware, discussed ideas, and shared frustrations and celebrations. Thus, I thank him for his contributions and time. There were also collaborators that at the same time were teachers and gave me important contributions and inspiration. Augusto Buchweitz, for whom I have great admiration, helped me to discover neuroimaging together with Alexandre. Pedro Eugênio Ferreira is a professor who never gave me a class but opened doors for me to get his project and to start what became my PhD; I thank him especially for the partial financial support he gave for our work and all his effort in data collection. People like him do not get enough credit. He works hard for his own, although he could have someone doing that for him; it is dedication, which is inspirational for me. I am thankful to Pedro and to all of his team.

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Although people can make remarkable achievements, I required institutions for me to accomplish my objectives. Thanks to the Sistema de Saúde Mãe de Deus from Porto Alegre (SSMD), whose patients took part in our studies for all these years. I have special thanks for everyone at São Rafael Unity at SSMD, particularly Júlio Carlos Pezzi and Alessandra Martins, who encouraged the research and truly participated in the study. Thank also to the staff of the unity, including nurses, nursing assistants, and others, from whom I namely remember Gladis Luz, who always gave us information that we could have missed. Moreover, thanks to Janaína Silvestre, who helped by accompanying patients to neuroimaging exams with me.

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Finally, and again, although not directly involved in the academic work, I thank all my friends and particularly my family in supporting me through my journey. The comprehension and encouragement I received from my mother and brother was fundamental and remains strong.

From my family, I mention my wife in particular. However, it is not a personal acknowledgement; Aline Romani-Sponchiado contributed directly to the study. She worked in data extraction, taking interpretations, managing participants, and training the team. I am indeed in love with her and am thankful for all of her personal support and partnership, obviously. Furthermore, I am thankful for her dedication, competence, abnegation, and effort for the team, making this work in the field possible.

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Resumo expandido

No Brasil, cerca de 1.4% da população refere já ter feito uso de cocaína através de sua forma fumada (crack). O uso da droga gera repercussões sociais e econômicas para a sociedade, além de ser um grave problema de saúde relacionado, inclusive, com a morte precoce. Considerando o Transtorno por Uso de Cocaína (TUC) a manifestação patológica relacionada ao uso da droga, alguns dos desfechos desfavoráveis incluem: maiores taxas de infecção por HIV e HCV; problemas judiciais e familiares, além maior prevalência de transtornos mentais em comorbidade. Iniciativas científicas estimulam que propostas baseadas em evidências sejam realizadas na tentativa de melhores resultados para o tratamento e prevenção do TUC. Neste sentido, maiores aprofundamentos em lacunas do conhecimento na área são importantes. Assim, homens e mulheres possuem fatores de vulnerabilidade ao uso da droga distintos: Mais homens usam cocaína (proporção de 3:1), mas mulheres apresentam uma evolução mais rápida ao TUC após o início do uso. O curso da doença também é diferente, mulheres sentem mais fissura pela droga, enquanto homens tem mais consequências relacionadas a crimes violentos. Assim sendo, iniciativas científicas destacam a necessidade de integração de modelos biopsicossociais, que levem em conta as características individuais, mas que também considerem transtornos aditivos "doenças do cérebro", favorecendo a interdisciplinaridade entre antigas e robustas bases teóricas e avanços tecnológicos. Neste sentido, o objetivo desta tese foi investigar diferenças entre homens e mulheres usuários de crack. Para tanto, dois estudos foram realizados com grupos de portadores de TUC internados para desintoxicação do uso de crack, tendo sempre um grupo de homens (TUC-H) e outro de mulheres (TUC-M). No Estudo 1, o objetivo foi traçar um claro perfil de diferenças psicossociais e de gravidade do uso de drogas, enquanto no Estudo 2 o objetivo foi identificar a existência de diferenças em um nível de funcionamento cerebral. O Estudo 1 teve 798 TUC-H e 546 TUC-M. Resultados identificaram robustas diferenças, com TUC-H possuindo uma história mais grave de uso de álcool, bem como uma maior prevalência para o transtorno por uso de álcool. Em contrapartida, TUC-M apresentam uma idade mais precoce do início do uso de crack, maior severidade do uso de drogas em geral, prejuízos mais significativos nas esferas de trabalho e família, além taxas mais altas de prevalência de transtornos mentais (em especial transtornos relacionados a trauma e estresse). No Estudo 2, com 80 participantes além dos grupos TUC-H (n = 20) e TUC-M (n=20), participaram 20 homens saudáveis e 20 mulheres saudáveis. O método utilizado foi um exame de Ressonância Magnética funcional (fMRI) em estado de repouso (rs-fMRI). Rs-fMRI permite avaliar associações na flutuação do sinal BOLD (blood oxygen-level dependente, do inglês nível dependente de oxigênio no sangue), que é uma medida indireta de consumo energético, entre áreas cerebrais anatomicamente distintas, o que é aceito como um dado de conectividade funcional (CF). Os resultados indicaram que de maneira geral, TUC-H apresentam um aumento na CF entre diferentes redes cerebrais, enquanto TUC-F apresentam redução na CF. Com base nos resultados, a tese conclui que homens e mulheres usuários de crack apresentam diferenças em características que permeiam todos os domínios biopsicossociais, o que deve ser considerado ao levar em conta interpretações de estudos na área e, principalmente, ao planejarem-se possíveis intervenções no futuro. Portanto, espera-se que modelos sexo-específicos para o uso de cocaína e do TUC sejam formulados, bem como que intervenções, pesquisas e inclusive políticas de saúde pública considerem possíveis diferenças em suas fundamentações.

Palavras-chave: Cocaína, crack, sexo, conectividade funcional, psicopatologia.

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Expanded abstract

In Brazil, 1.4% of the population reports lifetime use of smoked cocaine (crack). The use of the drug relates to social and economic issues for society and poses serious health problems, including early death. Crack cocaine use disorder (CUD) is the medical condition which refers the pathological use of the drug. CUD relates to several negative outcomes such as higher rates of HIV and HCV infections, familiar problems and crime involvement, in addition to a higher prevalence of concurrent mental disorders. Scientific agendas promote evidence-based studies as a need for better therapeutics. In this regard, some gaps in the field require attention. In this line, distinct factors confer vulnerability for crack cocaine use in males and females: more males use the drug (a 3:1 proportion), but females show a faster transition from initial drug use to CUD. The course of the disease also show differences; females report a higher craving for the drug, while males have more frequent involvement with violent crimes. Thus, scientific commitments highlight a calling for the integration of those biopsychosocial models that consider individual characteristics in addition to those who consider addictive disorders as "brain diseases." A more consistent interdisciplinary integration of knowledge from classical theories in combination with advances provided for technologic methods is a promising route. Hence, the aim of this doctoral thesis was to investigate sex differences in crack cocaine users. To address the main objective, the thesis has two studies with groups of participants diagnosed with CUD and hospitalized for drug detoxification. These two groups were one of males (CK-M) and a second of females (CK-F). Study 1 had as its objective to get a picture of sex differences in the psychosocial profile. Study 2 had as its objective the identification of sex differences in brain functioning level. Study 1 had 798 CK-M and 546 CK-F. Results consistently revealed CK-M as having a more severe alcohol use history and higher rates of concurrent alcohol use disorder than CK-F. On the other hand, CK-F showed an earlier crack cocaine use onset, higher drug use severity, and more familiar and work problems along with a higher prevalence for lifetime mental disorders. Particularly, CK-F showed higher rates for trauma and stress. Study 2 had a sample of 80 participants: CK-M (n = 20), CK-F (n = 20), a group of males (HC-M, n = 20), and another of healthy female controls (HC-F, n = 20). Participants did a resting-state functional magnetic resonance imaging (rs-fMRI) scan. The method makes it possible to investigate temporal associations between nonspatially related brain areas by using as a measure fluctuations in the blood oxygen-level dependent (BOLD) level. It is an indirect measure of energy consumption, and by testing those correlations, functional connectivity (FC) can be investigated. Results supported CK-M as having an overall higher intra- and internetwork FC, while CK-F showed an overall lower FC in this regard. Taking both studies, the conclusions of this thesis point toward the existence of sex differences in all biopsychosocial domains. Thus, the interpretation of studies in crack cocaine use, particularly those testing interventions, need to resemble the possible existence of sex differences. Therefore, a hope from studies like this is that sex-specific models for crack cocaine use and CUD emerge and become tested. Similarly, possible interventions, also need to be aware of such backgrounds and consider possible sex differences when developing interventions, researches and public health policies as well.

Keywords: cocaine, crack, sex, functional connectivity, psychopathology.

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LIST OF ABBREVIATIONS

ACC – Anterior cingulate cortex

Ach – Acetylcholine

ACTH – adrenocorticotropic hormone

ANPP – Agenda Nacional de Prioridades de Pesquisa em Saúde

ASI-6 – Addiction Severity Index 6

ATP – Adenosine Triphosphate

BA – Broadmann Areas

BDI – Beck Depression Inventory

BDNF – Brain Derived Neurotrophic Factor

BOLD - Blood oxygenation-level dependent

CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CI – Confidence Interval

CF – Conectividade Funcioncal

CK – Crack-cocaine user participants

CK-F – Female crack cocaine users with CUD participants.

CK-M – Male crack cocaine users with CUD participants.

CNPq – Conselho Nacional de Desenvolvimento Científico

CNS – Central Nervous System

CPP – Conditioning place preference

CRF – Corticotropin-releasing fator

CRH – Corticotrophin-releasing hormone

CRK – crack-cocaine dependent users (in Complementary Section 1)

CS – Cluster size

CSSA – Cocaine Selective Scale Assessment

CTQ – Childhood Trauma Questionnaire

CUD – Crack cocaine use disorder

DA – Dopamine

DACC – Dorsal anterior cingulate cortex

DALY – Disability-adjusted life years

DAN – Dorsal attention network

DAT – Dopamine transporter

DCNL – Developmental Cognitive Neuroscience Lab

DECIT – Departamento de Ciências e Tecnologia

DHb – Deoxygenated hemoglobin

DLPFC – Dorsolateral prefrontal cortex

DMN – Default mode network

DSM – Diagnostic and Statistical Manual for Mental Disorders

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders-IV

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders-5

ECN – Executive control network

EP – Endogenous opioids

FC – Functional connectivity

FDR – False discovery rate

FOV – Field of view

FPN – Frontoparietal network

FMRI – Functional Magnetic Resonance Imaging

GDS – Global Drug Survey

Hb – Oxygenated hemoglobin

HC – Healthy control participants.

HCPA – Hospital de Clínicas de Porto Alegre

HIV – human immunodeficiency virus

HO – Female healthy older adults

HO – healthy older participants

HPA – Hypothalamus-pituitary-adrenal

ICA – Independent component analysis

InsCer – Instituto do Cérebro

IQ – Intelligence quotient

KCC – Kendal's coefficient concordance

LABIMA – Laboratório de Imagens

LENAD – Levantamento Nacional de Álcool e Drogas

LIPL - Left inferior parietal lobule

LITG – Left inferior temporal gyrus

LMFG – Left middle frontal gyrus

LMTG – Left middle temporal gyrus

LSFG – Left superior frontal gyrus

LSTG – Left superior temporal gyrus

M – Mean

MCL – Mesocorticolimbic

MNI – Montreal Neurological Institute

MMSE – Mini-Mental State Examination

MPFC – Medial Prefrontal Cortex

MRI – Magnetic Resonance Imaging

MTG – Medial temporal gyrus

NAcc – Nucleus accumbens

NE – Norepinephrine

NIDA – National Institute on Drug Abuse

NIH – National Institute of Health

NSDUH - National Survey onDrug Use and Health

OFC – Orbitofrontal Prefrontal Cortex

OR – Odds ratio

PCC – Posterior cingulate cortex

PET – Positron emission tomography

PFC – Prefrontal Cortex

PHG – Parahippocampal gyrus

PSC – Percent signal change

PTSD – Posttraumatic stress disorder

PUCRS – Pontifícia Universidade Católica do Rio Grande do Sul

ReHo – Regional homogeneity

RIFG – Right inferior frontal gyrus

RIPL – Right inferior parietal lobule

RMFG – Right middle frontal gyrus

ROI – Region of interest

RPHG – Right parahippocampal gyrus

RSFG – Right superior frontal gyrus

Rs-fMRI – resting-state functional magnetic resonance imaging

RSTG – Right superior temporal gyrus

SAMHSA – Substance Abuse and Mental Health Services Administration

SCID-I – Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV

SCTIE – Secretaria de Ciência, Tecnologia e Insumos Estratégicos

SD – Standard Deviation

SENAD – Secretária Nacional de Álcool e Drogas

SFG – Superior frontal gyrus

SMN – Sensory-motor network

SN – Salience Network

SSMD – Sistema de Saúde Mãe de Deus

SUD – Substance use disorder

ToM – Theory of mind

TUC – Transtorno por Uso de Cocaína

TUC-H – Grupo de homens portadores de TUC

TUC-M – Grupo de mulheres portadoras de TUC

UNODOC – United Nations Office on Drugs and Crime

VmPFC – ventromedial PFC

VTA – ventral tegmental area

WASI – Wechsler Abbreviated Scale of Intelligence

WHO – World Health Organization

WM – Working memory

CONTENTS

PRESENTATION – ABOUT THIS THESIS

The aim of this doctoral thesis was to investigate sex differences in crack cocaine users. Its results and conclusions highlight the need for taking differences between males and females on crack cocaine use into consideration when interpreting data, suggesting models, and treating and developing therapeutic and preventive strategies.

The selection of such a theme had a background in data but also in some personal strands acquired through my academic trajectory. My research advisor and I always have the same view: Projects need to have some general objectives in addition to obvious ethical and methodological rigors. Research need to: (a) add something to society; (b) likewise to academic field, particularly with (c) innovation and relevance for future scientific applied steps. Moreover, it must be: (d) accessible not only for post-graduates but for graduation students as well. At least, every single project requires that (e) the researcher produce personal motivation, to give him/her the strength for further discoveries.

Therefore, there is a scenario in which crack cocaine use is a well-recognized health problem, particularly in countries such as Brazil. Research on the topic has had few promising interventions and requires more evidence-based strategies. In this regard, it is well established there is a lack in studies on some interactional variables, such as sex, that could bias the effects of interventions. Because of this, there are scientific agencies promoting research agendas on sex differences in addictive disorders. Particularly, psychobiological mechanisms are of interest to help in building up new interventions. New neuroscientific techniques are remarkable tools in such regard.

Given the background and the need for research on the topic, it was planned to build up a strong strand for sex differences, using classical and novel strategies to research them. As always, we committed to conduct the study using graduate students and to produce basic informative material in addition to high-quality research.

Finally, I need to recount a little of my academic career to explain about my personal motivation. In my master's course, I investigated the theory of mind (ToM), which is the ability to interpret the thoughts of other people, in female inpatients with crack cocaine use disorder (CUD). At that time, I adapted ToM instruments (Sanvicente-Vieira, Brietzke, & Grassi-Oliveira, 2012; Sanvicente-Vieira et al., 2014), made a systematic review on ToM in substance use disorders (SUD; Sanvicente-Vieira, Romani-Sponchiado, et al., 2017), and tested the ToM of female inpatients with CUD (Sanvicente-Vieira, Kluwe-Schiavon, Corcoran, & Grassi-Oliveira, 2017). At the end of my dissertation, I concluded that social cognitive impairments could support the development and progression of CUD.

However, at that time, my colleagues and I flagged as a limitation of my study that one could not take generalizations to CUD because we had a female-only sample. In fact, it was true that results with females could not be used as background for conclusions on males (after my thesis, I hope you were pretty convinced of that). Taking my findings and previous work in my research group (i.e., DCNL; Francke, Viola, Tractenberg, & Grassi-Oliveira, 2013; Grassi-Oliveira et al., 2012; Grassi-Oliveira et al., 2013; Kluwe-Schiavon, Viola, Sanvicente-Vieira, Pezzi, & Grassi-Oliveira, 2016; Levandowski et al., 2013; Levandowski et al., 2016; Pazzin, Niederauer, Sanvicente-Vieira, & Grassi-Oliveira, 2017; Saulo Gantes Tractenberg et al., 2012; Tractenberg et al., 2014; Viola et al., 2012; Viola, Tractenberg, Pezzi, Kristensen, & Grassi-Oliveira, 2013; Viola et al., 2014 ; Viola, Tractenberg, Pezzi, Kristensen, & Grassi-Oliveira, in press), it becomes clear that this limitation is commonly noted. We indeed have a focus on female crack cocaine users, and because of that, conclusions hardly can be generalized for male crack cocaine users. We investigate predominantly female crack cocaine users through convenience, which is readiness and easier access because of professional, academic, and social networks.

If in scientific terms, I agree to point out such an issue, I could not say that personally I truly accepted that. I never felt comfortable noticing that the opposite is not always true—research with male-only samples is not so much concerned about problems in taking generalized conclusions for one pathological group. Thus, I started to study and realized that in fact it seems that male and female crack cocaine users have several differences (Becker, 2016; Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005), meaning that to do generalizations would be a limitation in the first place. Then, I became hungry for make that clear!

Nevertheless, the study on such differences is initial and was mostly conducted for few researchers, and it seems that the evidence has not convinced everyone, including editors and reviewers, to pay attention to that need. For this reason, there are some strands that support the need of my thesis: a health care need on basic research on crack cocaine, scientific concern on the topic, and existence of a political and scientific agenda requiring novel studies in the field of sex differences of addictive disorders. Thus, with the aim to produce work that has an impact and with the commitment to provide a strong background, we could accomplish those generic needs.

Therefore, the general objective of my thesis was to investigate biopsychosocial sex differences in crack cocaine users. As secondary and more specific objectives, we aimed to: Investigate whether or not there was drug use, social, psychiatric, and general medical sex differences in crack cocaine users. In addition, to: Test if there is brain functional evidence that could support sex differences in crack cocaine users and if it is a sex-dependent or interactional effect of a sex–crack combination. Hypotheses were exploratory, but for all those objectives, it was expected that there were sex differences in crack cocaine users.

To accomplish such objectives, my thesis was built with a central line that keeps the main objective of the thesis. This central line encompasses five chapters that give an

extensive theoretical background (the first three chapters accomplish the justification of the study and explain the general aim) and two empirical works, which are independent chapters. One chapter investigates general psychosocial sex differences in a large sample of CUD participants (to accomplish the first objective), and the second paper investigates intrinsic brain functional sex differences in CUD participants (to accomplish the second objective).

However, reaffirming my commitment, my thesis has a complementary part, which has two productions that contribute to the thesis. One of the complementary sections details an empirical testing of a theory that the detrimental progressive effects of crack cocaine use leads to early aging. The motivation came from the context in which there are several theories about addiction, but few that were truly tested. The second complementary paper is a narrative review about resting-state functional magnetic resonance imaging (rs-fMRI) use in psychological studies. It accomplishes that commitment by providing information for those who are not entirely aware about such a novel neuroscience method. Therefore, I hope that this complementary section can inform researchers and reduce resistance that psychologists or students can have when entering the neuroscience field.

When reading this thesis, take in mind that it has the following structure:

- theoretical section—background
- empirical section
- conclusion
- complementary sections

In addition to appendices, my post-graduation program normatively incentivizes the inclusion, as appendices, of publications in which students worked and which are related to the theme of the thesis but are not part of it. The objective is to show the involvement of the student in the field as not only restricted to his own work.

The theoretical section has three chapters. Chapter 1 examines crack cocaine use in general terms. This chapter reviews estimates, general impacts, and theories. Among the theories is one that assumes that CUD causes early aging. If you are unaware or doubtful about this theory, take a look in Complementary Section 1—the paper "Crack-Cocaine Dependence and Aging Effect on Working Memory" tests such a theory in female participants. In that paper, I did so by comparing the working memory (WM) performance of groups of female elders, healthy controls, and CK-F.

The theoretical section has also Chapter 2, which addresses the need for sex differences studies. This chapter reviews some historical research on the field and briefly reviews some concepts to avoid common misinterpretations. Chapter 3 reviews some literature on sex differences in crack cocaine, including theoretical proposals on the topic as the telescoping effect.

The empirical section starts with Chapter 4, which is the first empirical work and is a comparative study with a large sample of participants with CUD whose preferred drug was crack cocaine and who were inpatients in detoxification treatments. This study, named "Sex Differences in Multidimensional Clinical Assessment of Crack Cocaine Users", compared the prevalence of mental disorders, differences in sociodemographic issues, and the severity of drug use outcomes between CK-M and CK-F. Results support that differences in the prevalence of concurrent mental disorders and the impact of negative issues show sex differences between participants. Overall, CK-F showed a more negative general outcome, supporting that CUD is more severe in females.

Chapter 5 is another comparative study between CK-M and CK-F, but this study also includes groups of healthy controls (HC). It compares intrinsic brain functioning with rs-fMRI. This study, named "Sex Differences In Intrinsic Brain Connectivity In Crack Cocaine Users", shows that the way that the brains of CK-M and CK-F intrinsically connect have

differences, which also associates with psychosocial outcomes in different patterns. If rs-fMRI is not familiar, Complementary Section 2 gives some basic support for those readers less familiarized with the technique, what it measures, and how it can be applied for psychological studies.

Finally, the conclusion section revisits some theories, suggesting the need for revisions and the inclusion of sex differences in further studies. Among some crack cocaine definitions, you will read that addiction is a "brain disorder." Results support that if it is a brain disorder, caution in some interpretations are necessary, since there are brain functional characteristics differentiating male and female crack cocaine users with CUD in strong ways. In addition, more than neurobiological evidence supports that the data also hold psychosocial robust differences. Given the results and the prospect of very little success for preventive and therapeutic interventions in crack cocaine use, this thesis points to the need for consideration of sex-specific approaches for research and particularly for interventions.

THEORETICAL SECTION

CHAPTER 1: Crack Cocaine

CHAPTER 2: Research on Sex Differences and the Need for Its Inclusion in SUD Research

CHAPTER 3: Sex Differences in Crack Cocaine Users

CHAPTER 1—Crack Cocaine

Cocaine [1] use is a well-recognized social health issue. Seventeen and one hundred thousand million people used cocaine worldwide in 2016, according the World Drug Report from the United Nations Office on Drugs and Crime (UNODOC, 2017). Cocaine consumption prevalence has been stable across the last three decades, ranging around 17–18 million users worldwide. Since the 1990s, a decline in those principal cocaine markets (Europe and North America) occurred, while it increased in South America and the Caribbean. This increase in secondary markets is mostly attributed to the popularization of derived cocaine forms, particularly smoked ones, such as crack [2] (NSDUH, 2012; SAMHSA, 2007).

However, recent data on worldwide prevalence of cocaine use have shown that the picture is undergoing change. There is a return of increase in cocaine consumption in the main markets (North America and Europe). Although it is unclear if in fact the cocaine use in Brazil has decreased as much as it seems, there were changes in the trafficking market that could explain a reduction in the drug offer and distribution in South America (UNODOC, 2016).

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[1] Cocaine comes from the coca shrub (Erythoxylon coca), native to Peru and Bolivia (Gabe & Barnes, 1963). It is a tropane and has a long history: The Incas used it for religious purposes, and nowadays, it is used to cope with side-effects of high altitudes, for example (Ferreira & Martini, 2001; Goldstein, DesLauriers, & Burda, 2009; Ruetsch, Böni, & Borgeat, 2001). Abuse is not related to the plant, but to cocaine pure composite, said to have first been successfully isolated in 1859 by Albert Niemann (Ruetsch et al., 2001) and described in 1898 by Richard Willstatter (Humphrey & O'Hagan, 2001). Cocaine pure composite looks like a fine and white product. Tropane hydrochloride turns the composite into a salt, which is the most popular cocaine, powder cocaine. Nevertheless, other chemical combinations also can produce it (Goldstein et al., 2009; Humphrey & O'Hagan, 2001; Ruetsch et al., 2001)

[2] Crack is the smokable cocaine form. Its popularization in the 1980s turned cocaine into an epidemic problem due to its lower costs. Crack is the popular name for cocaine as presented in its "rock" form, which has the same main tropane composite, but it varies in presentation because it is produced by the reduction of the hydrochloride in water, which creates a tropane alkaloid. A mixture with the tropane alkaloid, ammonia, and ether can produce the "base." But most commonly, tropane alkaloid is baked with sodium bicarbonate, creating a non-water-soluble product—the crack. Because of the mixture and the processes, crack is a "less-pure" form of cocaine. Its presentation is as rocks, and by exposing these rocks to high temperatures, it "burns" a vapor, which is then inhaled by people who smoke it (Cone, 1995; Hatsukami & Fischman, 1996).

Crack Cocaine Acute Effects

Crack and cocaine (crack cocaine[3]) produce stimulant effects, which can vary in intensity, duration, and beginning latency due to the varying methods of administration and absorption (Humphrey & O'Hagan, 2001; Kiluk, Babuscio, Nich, & Carroll, 2013). Common acute effects are: Euphoria, increased energy, and alertness. It also make people talkative with increased psychomotor activity and reduces both hunger and sleepiness as part of its effects (Spronk, van Wel, Ramaekers, & Verkes, 2013). Particularly when doses are excessive, it can cause anxiety, paranoia, and angry and violent behavior (Goldstein et al., 2009).

Crack cocaine use has as a main action mechanism the blocking of the reuptake of catecholamine, which causes central nervous system (CNS) stimulation and an increase in sympathetic activity—pupil dilatation, heart rate increase, and blood vessel constriction. This means that acute use can cause strokes, for example. In fact, stimulants such as crack cocaine and amphetamines are the most common drugs related to such outcomes (Fonseca & Ferro, 2013). However, strokes are not the main health problems. The most frequent, important, high-cost impairments and related outcomes are behavioral disruptions, which many times become pathological, with the emergence of risky behaviors and social and control impairments—rising CUD (Proctor, Kopak, & Hoffmann, 2013).

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[3] In my work, you mostly will read of "crack cocaine." Because my colleagues and I planned to contribute the most to our community (which is the Brazilian one), all our participants were diagnosed with CUD and preferably had smoking as the route of administration. I did not use only "crack," because the literature has more publications on powder cocaine and because I could not deny that crack, in fact, has the same main metabolite as powder cocaine, although there is evidence of some different consequences (Martin, Macdonald, Pakula, & Roth, 2014). Thus, I always described the drug as crack cocaine to fit international literature standards. Importantly, it does not turn data useless for interpretation and for giving background and insights for future research on powder cocaine users. However, we felt it important to avoid mixing participants with predominantly powder and smoke cocaine habits in the same sample because particularly in Brazil, socioeconomic differences could be a factor in biasing interpretations, and crack cocaine has a higher burden for the country.

Crack Cocaine: Why Study It in Brazil?

Despite a possible reduction in use, Brazil is one of the main markets for crack cocaine consumption out of the two major crack cocaine centers (UNODOC, 2012). Brazilian estimates on consumption are still high and are a burden for the country, particularly because of loss in work force, increased crime, health costs, and early mortality (Abdalla et al., 2014; Bastos, 2012; Dias, Araújo, Dunn, et al., 2011; Dias, Araújo, & Laranjeira, 2011; Vernaglia, Vieira, & Cruz, 2015). According to the *Levantamento Nacional de Álcool e Drogas II* (LENAD II, 2014), which is a report of data from 2006–2012, almost 6% of the Brazilian population reported lifetime crack cocaine use. Considering last-year consumption, ~2.8 million of people reported it (around 3% of the adult population, and 2% of the adolescent population). Most participants reported previous intranasal/powder cocaine use at least once.

As already stated, the popularization of cocaine occurred due the variability in its presentation form. Thus, the observation of the specific consumption of cocaine through the smoked route is of concern. Furthermore, data indicates that those who smoke crack cocaine have more severe CUD (Martin et al., 2014), poorer treatment outcomes (Kiluk et al., 2013; Palamar, Davies, Ompad, Cleland, & Weitzman, 2015), and more severe social problems, such as number of arrests (Martin et al., 2014). By this token, 1.4% of the Brazilian population (meaning 1.8 million) reported lifetime crack use, while 1% (1.3 million people) reported last-year consumption (Abdalla et al., 2014; Laranjeira et al., 2014).

Brazil also has a not favorable role in other international estimates, as in the case of the Global Drug Survey (GDS; Winstock, Barrat, Ferris, & Maier, 2017), which is an independent initiative for reporting drug use information. GDS2017 indicated Brazil as the country in which people use crack cocaine the most days in a year (~32). In addition, it indicates that Brazil is the country in which more people seek emergency services following acute use.

Since crack cocaine represents an important and high-cost problem worldwide, it is a focus of scientific research. Moreover, crack (meaning the smokable form of cocaine) is a rising problem within crack cocaine use, since it exacerbates the issues caused by the drug. Given that Brazil has a high prevalence of crack cocaine use, studies in this area is the priority. This is clearly recognized in the policies of the *Agenda Nacional de Prioridades de Pesquisa em Saúde* (ANPP, 2015) that highlight the need to study drug use. Moreover, there are Brazilian grants that specifically indicate crack as an agenda (for example, in our research group, we had already supported two projects, including the one in which this thesis is included, because of Brazilian grants). In addition, the ANPP indicates the need to investigate drugs and its relation to HIV and violence (Brasil, 2015). By this token, the recognition that HIV infection has higher prevalence in crack cocaine users reinforces the need for studies in the field (Laranjeira et al., 2014).

Cocaine Use Disorder

Chronicity, relapse, and drug-seeking behaviors characterize CUD. Likewise, like all SUDs, CUD has diagnostic symptoms that can be grouped into: (a) risky behaviors, (b) lack of control, (c) social/personal impairments, (d) tolerance, and (e) abstinence (American Psychiatric Association, 2013). People with CUD are subject to an increased vulnerability for medical problems. They are more susceptible to, as already mentioned, strokes (Fonseca & Ferro, 2013) and HIV infection (Carvalho & Seibel, 2009; Kopetz et al., 2014; Yur'yev & Akerele, 2016) as well as cardiovascular problems (Talarico et al., 2017) and other psychiatric comorbidities (Degenhardt et al., 2014; Falck, Wang, Siegal, & Carlson, 2004; Pope, Falck, Carlson, Leukefeld, & Booth, 2011).

Those with CUD also are more likely to be homeless (Stringfellow et al., 2016), have problems in the workplace (Cross, Johnson, Davis, & Liberty, 2001), or even to be unemployed and have lower incomes (Yur'yev & Akerele, 2016). Likewise, in general, CK

have lower education levels (Abdalla et al., 2014; Yur'yev & Akerele, 2016), and those with CUD show social issues, including marital (Falck et al., 2004; Yur'yev & Akerele, 2016) and interpersonal problems (Proctor, Kopak, & Hoffmann, 2012). In psychosocial function, they are likely to have sexual involvement with unknowns or in illegal conditions (Yur'yev & Akerele, 2016), to suffer violence (Exner-Cortens, Eckenrode, & Rothman, 2013; Howard & Wang, 2003), and to have an early death (Corkery, Claridge, Goodair, & Schifano, 2017; Degenhardt et al., 2014; Dias, Ribeiro, Dunn, Sesso, & Laranjeira, 2008; Dias, Araújo, Dunn, et al., 2011; Duailibi, Ribeiro, & Laranjeira, 2008; Pavarin & Fioritti, 2017; Ribeiro, Dunn, Laranjeira, & Sesso, 2004; Ribeiro, Dunn, Sesso, Lima, & Laranjeira, 2007). The most common causes of death among CK are overdoses, other medical problems (including HIV complications), and violence victimization.

CUD: A Brain Disorder

Some call CUD a brain disorder due to the neurobiological changes it causes (Majewska, 1996; Nestler, 2004). In fact, there are long-term neuroadaptations that can be a consequence of drug use, while other mechanisms can perpetuate the disorder. For example, a common characteristic is distinct activity within mesocorticolimbic (MCL) dopamine (DA) pathways, which is common to most SUDs (Koob & Le Moal, 1997; Koob & Le Moal, 2008; Volkow, Baler, & Goldstein, 2011a; Volkow, Tomasi, et al., 2011; Volkow, Wang, Fowler, Tomasi, & Telang, 2011; Volkow, Koob, & McLellan, 2016). Early studies found that the repetition of cocaine use leads brain areas within the MCL DA pathway—which encompass areas along the ventral tegmental area (VTA), the nucleus accumbens (NAcc), the medial prefrontal cortex (mPFC), the amygdala, and the hippocampus—to have increased DA releasing in face of rewarding cues (Koob & Bloom, 1988). The effect caused by this repetitive activity and increased DA releasing is called sensitization (i.e., cue-rewarding stimuli cause enhancement reactivity; Robinson & Berridge, 1993).

Different from rewarding-related brain areas, other areas involved with executive (orbitofrontal Prefrontal Cortex, OFC) and interoceptive functioning (cingulate gyrus) show a depletion in DA receptors. According to different theories, it causes reduced metabolism and activity, meaning that those functions would be impaired, which relates to seeking behaviors, despite all negative outcomes; likewise, the failure to stop using is caused because there is no perception of satiety (Koob & Le Moal, 2005; Volkow, Fowler, & Wang, 1999; Volkow, Wise, & Baler, 2017).

CUD—a brain disorder, but not only that: Interactional variables. Drug addictions such as CUD are indeed brain disorders, but they are even more than that—SUDs are biopsychosocial disorders. By this token, there are contextual characteristics that are important; for example, which drug is used, or the age of first drug use. Earlier use may cause higher vulnerability (Ernst, Romeo, & Andersen, 2009b; Tapert, Aarons, Sedlar, & Brown, 2001). In addition, the environmental circumstances of initial drug use also have a role—if it was used in a coercive or willing scenario, it may lead to more compulsive consumption (Yun & Kim, 2014)). Similarly, motivations and objectives are expected when predicting different patterns of use and reward—drug consumption to cope with problems brings more risks than consumption to celebrate (Martin et al., 2014; Volkow, Baler, & Goldstein, 2011b; Volkow, Wang, et al., 2011). Even past experiences have a role in this line, such as childhood maltreatment that relates to increased likelihood for developing a drug addiction (Büchel et al., 2017).

Another common characteristic that distinguishes people is sex (Barry, Bacon, & Child, 1957; Buss, 1995; Robbins, 1989), and as this could not be different among people, it also is expected to have an important influence in a different fashion in CUD for males and females (Becker, 2016; Becker, McClellan, & Reed, 2017; Bobzean, DeNobrega, & Perrotti, 2014; Fattore & Melis, 2016; Najavits & Lester, 2008). Moreover, it can also be the case that

sex differences have a role for mediation and/or modulation of some effects, as will be discussed (Becker, Perry, & Westenbroek, 2012; Bobzean et al., 2014; Li, Kosten, & Sinha, 2005).

Brain theories for CUD burden and progression. With the increasing body of neurobiological evidence on CUD, theories and assumptions began to point out possible pathways, vulnerabilities, and mechanisms that could play a role in the burden of CUD issues and disease progression (Marlatt, 1996; Robinson & Berridge, 1993, 2000; Rolls, 2000; West & Hardy, 2006). Soon, the idea that drug use is just a hedonic behavior stopped being a widely held view, since it became clear that it is a disease, not a moral failure. Some of these brain theories are important for understanding the later discussions, so some are presented here.

There are theories supporting drug use initiation and habituation as well as its progression. *Initiation* refers to experimentation, or small signs of habituation. *Habituation* regards repeated drug use and early adaptations that are not necessarily pathological (Briand & Blendy, 2010; Cheetham, Allen, Yücel, & Lubman, 2010). *Progression* means changes that confer chronicity and aggravate the course of the disease. Of course, some theories and effects about progression will include habituation aspects, since the concepts cannot be totally divided (Andersen & Teicher, 2009; Morrison, 1990; Prochaska, DiClemente, & Norcross, 1992).

Hedonic adaptation or opponent-process theory. Early theories held that as a person has a given experience much more often because of its paybacks, this person will respond to those paybacks less in the future. This is a theory that has assumptions for the initiation, habituation, and the progression of drug use. For addiction, a temporal dynamic mechanism of the CNS would reduce the pursued pleasure through the repetitive drug usage (Solomon & Corbit, 1974). This occurrence would cause two different consequences: (a) an increased

valuation of the expectation and (b) tolerance due to the need for higher doses for effects previously reached with lower doses. Because of that, recent theories state that after using drugs, the organism does not return to homeostasis but instead develops a tolerance in the reward-brain systems, which makes higher doses and shorter withdrawal times necessary (Koob, 2013). Figure 1.B illustrates this.

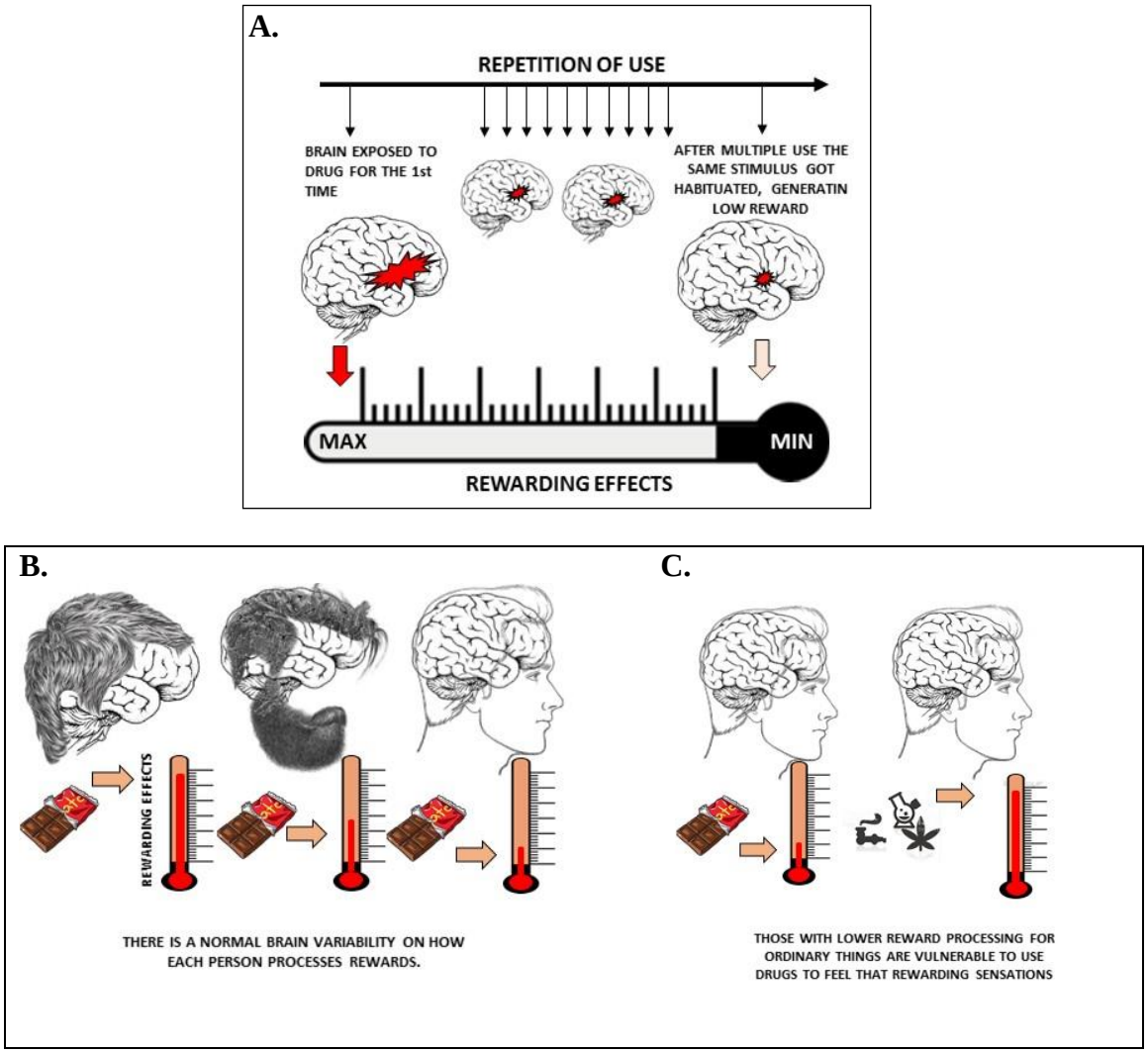

Figure 1. Brain addiction theories—hedonic adaptation and reward deficiency. Based on theories from Solomon and Corbit (1974) and Blum et al. (1996), respectively.

Figure 1.A shows hedonic adaptation or opponent-process theory, in which a person develops reduced rewarding-reaction to the same stimulus across repetitive use. Figure 1.B and 1.C depict reward-deficiency theory, in which some among the general

population are less reactive to reward (1.B) and are thus more susceptible to seeking drugs to have rewarding sensations (1.C). Importantly, this last theory can accept both natural variability and plastic changes as leading to such reduced rewarding processing.

Reward deficiency theory. Reward deficiency theory, like opponent-process theory, posits that people would need to use drugs because of a pathological failure in reward response. In original theory, the authors named this reward deficiency syndrome (Blum, Cull, Braverman, & Comings, 1996). However, different from opponent-process theory, reward deficiency theory does not presume that reward deficiency has a necessarily cause to happen, such as repetitive use (although it can also occur because of that). Thus, it can be an individual trait (for example, blunted reward response) or can occur due to neuroadaptations following repeated drug use or epigenetic changes following trauma experiences. According this theory, people have compulsive and addictive behaviors to compensate for the lack of reward activity (Blum et al., 2000). This theory is most related to the beginning of drug use. Figure 1B illustrates it and differentiates it from hedonic adaptation or opponent-process theory.

Hypofrontality theory—goal-directed/motivated behaviors. Since the discovery of reductions in excitatory activity in frontal cortical areas (West & Hardy, 2006), assumptions on addiction have held that addicted people would have problems with controlling their behaviors and desires. The imbalance between controlling systems and rewards would cause goal-directed or motivated behaviors (Everitt & Wolf, 2002). This theory was initially based upon DA activity, but glutamate and other neurotransmitters became included later (Shin et al., 2016). In addition, here hypofrontality theory and goal-directed theory are combined, since both assume that people will fail to inhibit their desires because of a failure in executive control (Balleine & Dickinson, 1998).

Moreover, one important update of this theoretical background supported that if addictive behaviors start early in the lifespan, then rewarding mechanisms will "burn" developmental stages, particularly the Prefrontal Cortex (PFC) maturation. Therefore, failure to inhibit desires will cause motivated behavior, increasing the likelihood of SUD development (Ernst & Korelitz, 2009; Ernst, Pine, & Hardin, 2006; Ernst, Romeo, & Andersen, 2009). Although the effective control of goal-directed behaviors has proven to be protective, frontal dysfunction is just one piece in a bigger puzzle, since this controlling process is not exclusively related to the PFC (Corbetta & Shulman, 2002). Given this background, this theory is most focused on supporting the habituation and progression of drug use, rather than its initiation. However, the update on the theory supports that decision-making immaturity in adolescence may be a pathway for novel-seeking behaviors, which could influence initiation (Ernst et al., 2009).

Impulsivity theory. This theory posits that SUDs are related to an overall hyperactive rewarding-brain system. By this, the theory holds that when facing cues, reward systems hijack cognitive control systems most of the time, which would make the organism answer with attitudes toward rewarding behaviors. Thus, it explains not only drug-seeking but also novelty-seeking behaviors, particularly risky ones. Importantly, this theory also has support in sensitization, but differently from incentive sensitization, it posits that there is a trait characteristic of rewarding hyperactivity in SUD, rather than a sensitization to low-intensity stimuli (Bjork, Chen, Smith, & Hommer, 2010; Buckholtz et al., 2010).

Incentive-sensitization theory. The incentive-sensitization theory posits that those previously reported effects in the DA system sensitize neuronal networks that play important functions in value-attribution and salience selection. This increasing sensitization makes a classical conditioning pairing by rewarding memories with neutral stimuli (Robinson & Berridge, 1993, 2000). Such a mechanism has great adaptive function for natural rewards

(Berridge & Kringelbach, 2011; Kringelbach & Berridge, 2009), but for some people, the system becomes sensitized to drugs or gambling (Berridge & Robinson, 1998; Robinson & Berridge, 1993). Because of this, ordinary stimuli can trigger reward processing, in turn causing behavioral disruptions.

Incentive-sensitization theory assumes that this sensitization hijacks the cognitive and motor systems and causes drug-seeking behaviors (Robinson & Berridge, 1993, 2000). Consistently, studies in attentional bias have confirmed this idea, since attentional bias is a seeking behavior (implicit but driving the individual toward the drug). When participants with CUD perform dot-probe tasks (a selective attention test), for example, they have increased attention toward drug-cue stimuli (Hester, Dixon, & Garavan, 2006; Liu et al., 2011; Waters, Marhe, & Franken, 2012). In addition, in line with incentive assumptions, those CK with higher attentional bias showed higher craving (Copersino et al., 2004; Hester et al., 2006) and shorter periods for relapsing (Field & Cox, 2008; Field, Munafò, & Franken, 2009; Marhe, Luijten, van de Wetering, Smits, & Franken, 2013; Waters et al., 2012). This theory assumes a mechanism that may play roles in the habituation/initiation and progression of drug use.

Hedonic homeostatic dysregulation—a downward spiral. Concluding that most theories indeed have some consistent points, some new ideas have combined some of those assumptions into an adapted model integrating different sciences to support the initiation, adaptation, and fall into addictive disorders. This is the case of that theory postulated by Koob and Le Moal (1997) that the path for addiction has stages, which they illustrated as a downward spiral. According to the theory, the spiral has three steps: (a) anticipation, (b) binging, and (c) withdrawal (negative affect)—the endpoint is addiction. The theory has strands in social psychology, psychopathology, psychosocial dysfunction and psychobiology changes. Figure 2 has an adapted model for their model.

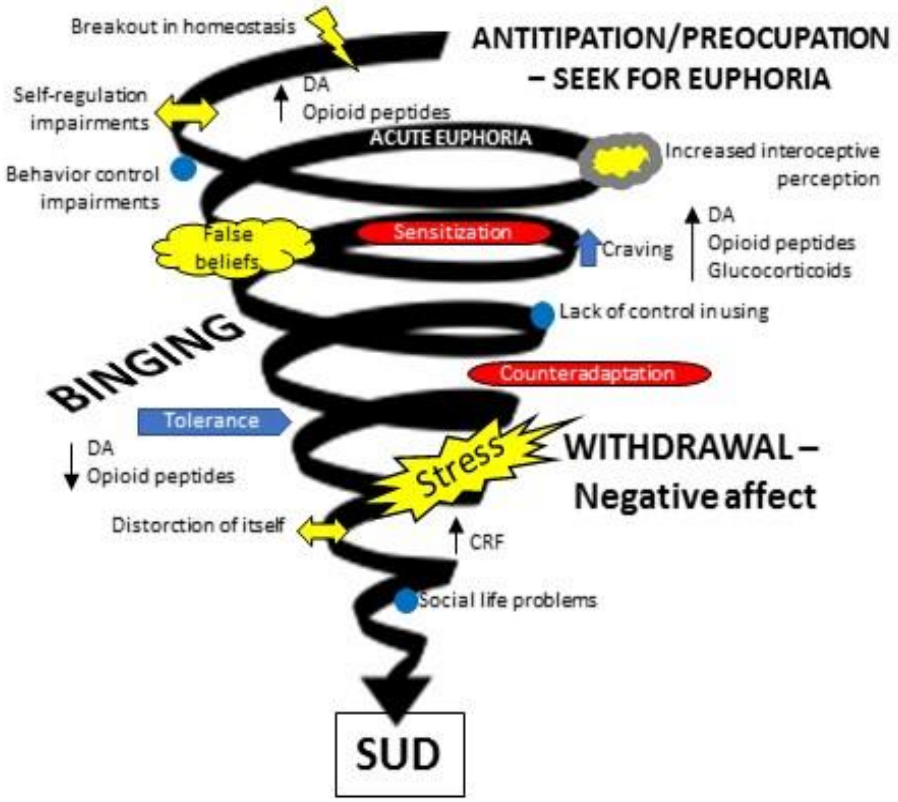

Figure 2. Addiction brain theories—hedonic homeostatic dysregulation: a downward spiral. Adapted from Koob and Le Moal (1997) [4]. The large words are the main steps of the downward spiral. Note that spiral goes progressively and homogeneous downward pathway that becomes more severe and complex-to-avoid. The small signs regard some occurrences that support the theory and came from different scientific disciplines, including social psychology (yellow), psychopathology (blue), neuropsychology (red), and neurobiology (black signs).

According to Koob and Le Moal (1997), in social psychology (and here they meant the psychology of predicting behaviors), the first drug use occurs for multiple reasons, which they did not try to explain clearly, but most important is the conceptualization following such experimental use. Then, there is a breakpoint in psychological balances, enabling the initial

[4] From "Drug Abuse: Hedonic Homeostatic Dysregulation" by G.F. Koob and M. Le Moal, 1997, *Science*, *vol. 3.* Permission from AAAS for reuse in thesis was granted. Permission for adapting the Figure from the author (G. F. Koob) was granted also, according AAAS request.

drug use and its repetition. Because of impaired self-regulation, (a) people understand that they truly feel balanced when they are on drugs, which follows (b) repetitive use in escalated amounts. After that, interoceptive increased attention and focus in dysphoria and withdrawal lead to (c) even more consumption and becomes a disorder (Koob, 2003; Koob & Le Moal, 1997).

From a psychopathological point, when drug use starts, a failure to control simple behavior makes people use more drugs than they initially expected. After that, (a) a continued desire and anxiety to use emerge, which lead to (b) excessive consumption. Moreover, (c) physical and psychological disturbances (e.g., cravings, cognitive problems, increased sleep without the drug) occur. Then, tolerance, withdrawal, and problems in everyday life start, and for which drugs are used to cope (note that these occurrences were based on the DSM-5 criteria for SUDs, with few adaptations from later reviews in the model). An SUD appears as a result. Moreover, the model for dysfunctional occurrences is not very complex, but it indicates that they would start with small impairments in decision-making with (a) urgency behaviors and sensitization. These would appear and trigger (b) more and more use. As a result, (c) a counteradaptation occurs, and that which was used to cause pleasure will begin to cause distress in its absence, requiring even more usage (Koob & Le Moal, 2008; Koob & Le Moal, 1997; Koob & Volkow, 2010; Volkow et al., 2016).

From a neurobiological perspective, initial drug use simply leads to (a) increased DA and opioid peptides. Repeated drug use, combined with initial distress when taking drugs, causes additional increases in glucocorticoids. To maintain homeostasis, (b) the individual takes higher doses. The withdrawal between consumptions causes increased (c) corticotropin-releasing factor (CRF) and reduced DA and opioid peptide activity. The result is withdrawal and the continuation of the spiral (Koob, 2010; Koob & Le Moal, 1997; Koob & Volkow, 2010). The theory is most focused on the sustained transition from initial drug use to SUDs,

but it is also considered a model for understanding the progressive deteriorations due to drug use.

A model for allostasis in addiction. Importantly, in the beginning, Koob did not find other theories to be incorrect, such as the opponent-process theory, since he indeed proposed a model with reductions in reward processing, or theories involving sensitization (Koob & Le Moal, 1997). However, he noticed that such mechanisms would have normal deviations and that some people would not experience such changes in their reward systems but in other related mechanisms (Koob, 2004). Because of this, he proposed that some allostatic changes in the stress-related systems would occur to help stabilize the reward system (Koob & Le Moal, 2001).

Allostasis is a term from stress research and refers to a biological mechanism to keep apparent stability, despite imbalances. It is a mechanism in which the organism "keeps homeostasis" by changing internal setups. Thus, an allostatic state is a situation in which there is a balance, but it is divergent from the expected healthy balance (McEwen, 1998). Koob and Moal (2001) defined how addictive disorders could use an allostatic load to stabilize reward processing but at the cost of impairing the stress system. As previously stated, along the drug use stages the secretion of glucocorticoids and CRF changes, which in a chronic fashion is suggested to cause allostatic changes, enabling the reward system to partially recover from DA system neuroadaptations.

This theory is particularly interesting because it supports the vulnerability of those with recognized stress-system dysfunction, such as in the case of childhood maltreatment (Wilson & Widom, 2009). Likewise, it would help to explain the maintenance of relapses, particularly in the face of stressful situations (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Sinha et al., 2003). An adaptation of the neurobiological and allostatic changes leading to addiction and increased vulnerability to relapse in CUD are shown in Figure 3.

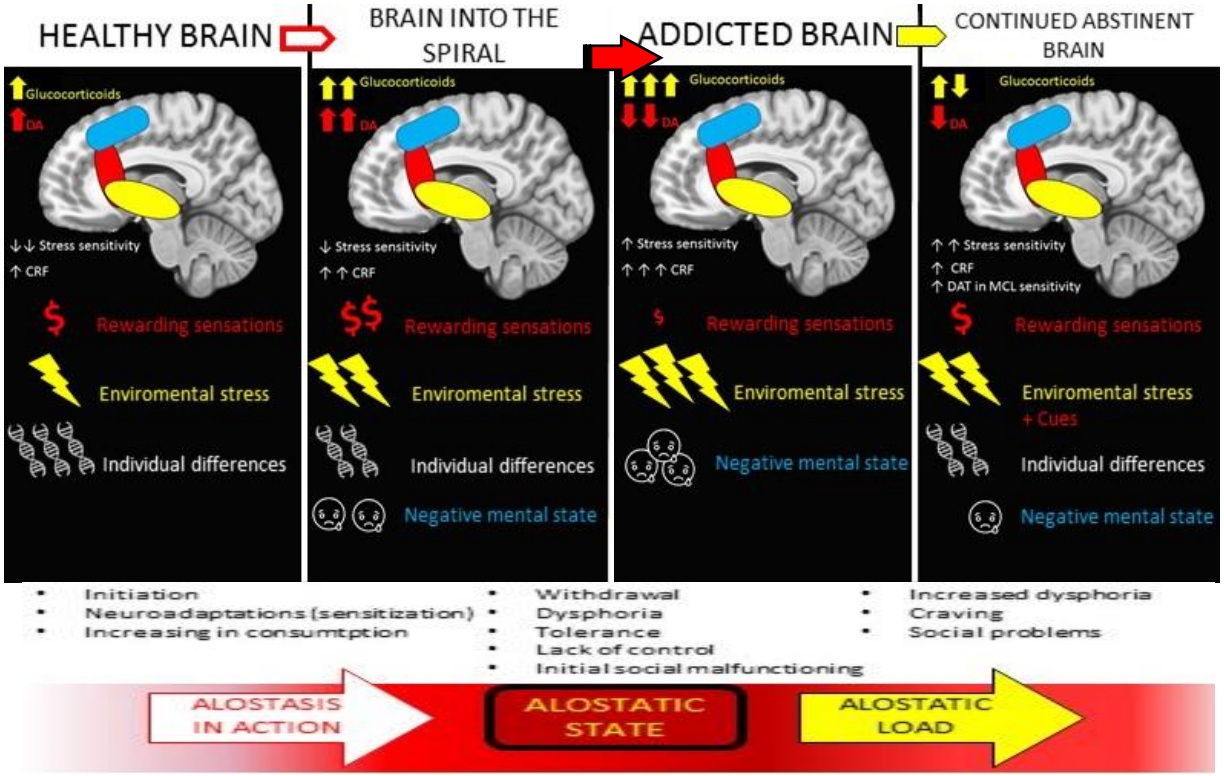

Figure 3. Addiction brain theories—allostasis in addiction: neurobiological summary. Adapted from G. F. Koob and M. Le Moal (2001) [5]. Note that the aspects highlighted in yellow are most related to the stress system, those in blue to the striatal-cortical systems, and those in red to the reward system. Changes occur across different stages of the escalation, but while the reward system returns to a similar state after abstinence, the stress system does not. Because of that, even in continued abstinence, there is a loading cargo—the allostatic load.

[5] Adapted from "Drug Addiction, Dysregulation of Reward, and Allostasis" by G. F. Koob and M. Le Moal, 2001, *Neuropsychopharmacology*, *vol. 24*, p. 113. Copyright 2018 by Springer Nature Terms and Conditions for RightsLink Permissions Springer Customer Service Centre GmbH: Springer Nature.

Self-medication hypothesis. Different from hedonic reasons, some patients report that they start using drugs to cope with problems or suffering, such as pain, depression, or anxiety. Moreover, some data indicated that patients who have SUD in co-occurrence with other psychiatric disorders have positive associations in symptoms, meaning that as depression symptoms increases, the SUD becomes more severe. Alternatively, people who do not have a SUD but do have other psychiatric disorders are at increased risk of developing a SUD. Because of that, a second but not exclusive theory proposed that some people find drugs to be an alternative to self-regulate themselves when trying to cope with their own symptoms. This is known as the self-medication hypothesis, which states that negative reinforcement is the primary rewarding effect for these people (Khantzian, 1985, 1987).

Importantly, this theory had a strong psychoanalytical background and revealed that distress, particularly those related to traumas, implies increased vulnerability to addiction, since drugs would alleviate the related symptoms (Storr, Ialongo, Anthony, & Breslau, 2007; Tull, McDermott, Gratz, Coffey, & Lejuez, 2011; Yehuda, 1999). According to this theory, depression and posttraumatic stress disorder (PTSD) are the two psychiatric comorbidities that make people most strongly susceptible to drug use for self-medication purposes (Chilcoat & Breslau, 1998; Majewska, 1996)—Figure 4 depicts an example of this.

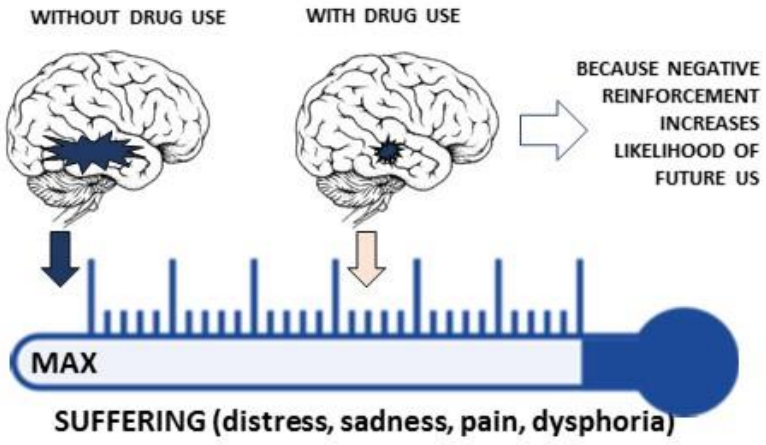

Figure 4. Addiction brain theories—Self-medication hypothesis. Based on Khantzian (1985) hypothesis.

Positive- and negative-urgency personality traits. Theories that synthesized other theories, such as the hedonic, self-medication, and reward-deficiency theories, have suggested individual traits that make individuals vulnerable. Because of observations that impulsivity behaviors follow certain experiences but also that people process experiences differently, these theories hold that some individual characteristics support distinct behaviors. Experimentally, authors (Cyders & Smith, 2008) have identified that some people show rash behaviors when excited, while others do when distressed. In addition, some people do not show such vulnerability. Thus, this theory identified that emotionally reactive people have certain personality traits named "positive" and "negative urgency" traits. Therefore, those who answer impulsively when experiencing positive affect show positive urgency; on the other hand, those who behave impulsively after negative experiences show negative urgency (Cyders & Smith, 2008). Interestingly, the theory has foundations in both behavioral and genetic evidence, since those with negative urgency show increased activation in a brain system that emerges in puberty and is associated with gene variations in serotonin transporters (Billieux, Gay, Rochat, & Van der Linden, 2010; Cyders & Smith, 2008; Dolan, Bechara, & Nathan, 2008).

Crack cocaine use as a possible age-accelerating process. The progression of crack cocaine is a remarkable issue, and the theory that crack cocaine accelerates aging is one of the most remarkable in this sense. Cocaine can cross the blood–brain barrier, and as CUD continuously causes this to occur, plasticity in the permeability of the blood-brain barrier occurs. Therefore, toxins, pathogens and leukocytes can cross the barrier easily (Kousik, Napier, & Carvey, 2012; Kubera et al., 2008). Moreover, as already stressed, the overlapping activation of the reward and stress systems leads to hypothalamus-pituitary-adrenal (HPA) axis and related activity, impacting the immune system (Fox et al., 2012; Marasco et al., 2014). These are some of the reasons why some disorders have a faster progression under

crack cocaine use, such as HIV (Baum et al., 2009; Meyer et al., 2014; Tyagi, Bukrinsky, & Simon, 2016; Wakim, Molloy, Bell, Ross, & Foxe, 2017), atherosclerosis (in addition to the obvious increase in sympathetic activity; Erwin, Hoyle, Smith, & Deliargyris, 2004); and cancer (particularly due to blunted production of antitumor chemokines; Gardner et al., 2004). In addition, some speculate that exposure to toxins and glucocorticoids accounts for reductions in cortical thickness found in CK (Andersen & Teicher, 2009; Briand & Blendy, 2010; De Kloet, 2004; Makris et al., 2008; Wakim et al., 2017).

After taking the evidence of the progressive effects caused by cocaine use and combining it with other evidence about health and aging, a theory on a faster aging progression in CUD emerged. Aging accompanies a number of changes, including higher levels of C-reactive protein, lymphocyte, and serum globulin, which are likewise reported in drug users (Reece, 2007). In addition, decreases in DA activity in the anterior cingulate cortex (ACC) and PFC are expected in typical aging (Volkow et al., 2000), which have previously been reported in crack cocaine users (Volkow et al., 1993). Similarly, oxidative stress, which is tissue damage due to excessive oxygen—in contrast to low antioxidant resources—is a normal and expected occurrence that becomes increasingly present with age (Yan, 2014). However, excessive oxidative stress can lead to disorders, some of which are age-related, including type II diabetes, cancer, and neurodegenerative disorders (Sena & Chandel, 2012). The severity of crack cocaine use is associated with higher oxidative stress (Sordi et al., 2014), and although abstinence may reduce it (Zaparte et al., 2015), it probably cannot reverse or completely normalize the oxidative stress caused by the detrimental effects of crack cocaine (Lindqvist et al., 2015). Oxidative stress and glucocorticoids are assumed to reduce telomere length—telomeres are the nucleotides at the end of chromosomes, and reductions in their length are related to aging (Lindqvist et al., 2015). Shortened telomeres among alcohol users in comparison to healthy participants (Pavanello et al., 2011) reinforce

how drugs cause faster aging. Among crack cocaine users, those with childhood trauma (a negative modulator in CUD severity) showed shortened telomeres as well (Levandowski et al., 2016).

Finally, progressions in brain changes, including gray-matter reductions in the brain (Ersche, Jones, Williams, Robbins, & Bullmore, 2012), have supported theories about how addiction accelerates aging (Bachi, Sierra, Volkow, Goldstein, & Alia-Klein, 2017; Bartzokis et al., 2000; Ersche et al., 2012; Koechl, Unger, & Fischer, 2012). It is proposed that the more quickly aging occurs due to crack cocaine use, the more severe the SUD is. Therefore, mechanisms leading to such progressive tracking are particularly relevant for producing protective interventions. The increased vulnerability to diseases from alterations in the immune system is one of the remarkable issues that the theory could help to investigate. Additionally, progressive changes in the brain may account for reduced everyday functioning, and investigation of in this concern can help to reduce the social burden related to addiction.

Complementary Section I contains a work in which my colleagues and I tested this theory: “Crack Cocaine Dependence and Aging Effect on Working Memory”. This work is published in *Revista Brasileira de Psiquiatria*. In the work, we found the working memory performance of CK-F to be similar to that of female healthy older adults (HO), giving some support for the theory.

Brain networks and systems integrating CUD mechanisms. Because interactions between multimodal pieces of information from social, internal, and induced inputs fall under behavioral changes, integrative mechanisms are important in addiction (Koob & Volkow, 2010; Sutherland, McHugh, Pariyadath, & Stein, 2012). Given this consideration, neuroscience technologies have enabled studies involving humans to include tests of interactions across neural circuits, assuming functional connectivity (FC) and efficiency of

inter- and intranetworks (Bressler & Menon, 2010; Greicius, Supekar, Menon, & Dougherty, 2009; Menon & Uddin, 2010). For a better understanding of FC and the study of systems and networks, the Complementary Section 2 of my thesis provides some basic support. It is a narrative review/chapter on the relevance of resting-state functional magnetic resonance imaging (rs-fMRI) methods for psychological sciences— *Resting-State Magnetic Resonance Imaging as a Tool for Psychological Sciences: Fundaments, Methods, Definitions and Possible Applications*.

Studies on the dynamics of the brain circuits in crack cocaine users revealed interesting patterns and provide a background for some of the theories on CUD burden and progression. In the following sections, I include some of the rs-fMRI results in crack cocaine users.

Acute effects. Early studies on rs-fMRI revealed that after cocaine use, a reduction in visual and motor networks occurs. Authors discussed this effect as a normal response to increase the blood-oxygen-level dependent (BOLD) signal in MCL pathways due to DA release following drug use (Li et al., 2000). Later discussions included the idea that the effect could be a possible relaxation of incentive salience or impulsivity-driven processing. This idea means that, following acute drug use, those attention-driven mechanisms uncouple from each other because the goal has been achieved (Sutherland et al., 2012). Giving some support for such an idea, cue-craving tasks provoke increased connectivity between these networks, and it makes sense for this FC to be reduced after reaching the objective (Garavan et al., 2000).

Trait characteristics. When investigating crack cocaine users not following acute effects, researchers tried to report trait neuronal characteristics from crack cocaine users. Studies initially focused most on MCL functioning because this is a DA pathway with a robust body of literature; additionally, theoretical statements support its dysregulation in

SUDs (Wise, 2009). Consistently, differences in FC in MCL circuitry appeared (Contreras-Rodríguez et al., 2016; Gu et al., 2010; Y. Hu, Salmeron, Gu, Stein, & Yang, 2015; Konova, Moeller, Tomasi, Volkow, & Goldstein, 2013; Liang et al., 2015; McHugh et al., 2014; McHugh, Gu, Yang, Adinoff, & Stein, 2017; Ray, Di, & Biswal, 2016; Ray, Gohel, & Biswal, 2015; Tomasi et al., 2010; Verdejo-Garcia et al., 2014; Wang et al., 2015; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011; Wisner, Patzelt, Lim, & MacDonald, 2013), but clear conclusions on increases or decreases are difficult to make due to conflicting results (Sutherland et al., 2012). Methodological aspects and bias issues, such as sex and the length time of abstinence, are some of the possible explanations for conflicts.

Moreover, the simple definition and focus on MCL pathways is subject to hindering conclusions because the method (rs-fMRI) is based on the assumption that what really matters is the exact dynamics, and thus, to restrict the investigation to one single circuit seems counterintuitive. By this token, few studies involved an in-depth look for what those MCL connections are. For example, amygdala-ACC connectivity or VTA-OFC connectivity may mean different things because both the amygdala and VTA are involved in limbic emotional processing, but the OFC encompasses attentional cognitive networks and ACC-implicit salience processing (Ma et al., 2010). Unfortunately, few discussions tried to differentiate that.

Furthermore, most studies identified limbic-related connectivity as disrupted (Cisler, James, et al., 2013; Dean, Kohno, Hellemann, & London, 2014; Gu et al., 2010; Konova, Moeller, Tomasi, & Goldstein, 2015; McHugh et al., 2014). Given the network knowledge from rs-fMRI studies (Biswal et al., 2010; Damoiseaux et al., 2006; Dosenbach et al., 2007; Fox & Greicius, 2010; Greicius et al., 2009), disruptions in limbic connectivity became more consistent for increased limbic-default mode network FC (Adinoff et al., 2003; Contreras-Rodríguez et al., 2016; Konova et al., 2015; Konova et al., 2013; Li et al., 2000). Other

results suggested sometimes the salience network (SN) to has increased FC with dorsal attention network (DAN, Cisler, Elton, et al., 2013; Ray et al., 2015), others with frontoparietal network (FPN, Camchong et al., 2011; Liang et al., 2015). According one study, SN-DAN or –FPN FC is a result of treatment status. SN-DAN is more prone to remain abstinent and SN-FPN to relapse and to have a sensory-motor response (an index of craving). Such DAN and FPN disengagement is indeed confirmed by anticorrelations in crack cocaine users (Kelly et al., 2011).

Increased trait limbic-DMN FC gives support for different theories, such as self-medication, because higher interoceptive processing may leads to enhanced perception of internal emotional states, causing emotional urgency, for example. In addition, the same evidence plus the opposition of DAN-FPN gives support for a large hyperconnectivity network, which enhances sensibility for rewards due to SN participation. Such evidence, combined with graph theory data on rs-fMRI that show that although FC increased, there is an inefficiency in the FC of crack cocaine users (Wang et al., 2015), gives support for incentive sensitization and impulsivity theories. Moreover, such uncoupling of two cognitive networks partially can give support for hypofrontalization theory. On the other hand, few results of reduced intralimbic FC (Gu et al., 2010; Hu et al., 2015) may support reward deficiency theory.

However, the studies included limitations. Among the most remarkable limitations were the different methods and patient statuses. The heterogeneity of psychiatric comorbidities and age was also a problem. Moreover, all samples were predominantly of males, which also can impact generalizations

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CHAPTER 2—Research on Sex Differences and the Need for Its Inclusion in SUD Research

The study of sex differences in SUDs has a long story, although it has not a massive body of data. Moreover, it has issues that deserve attention. Despite of that, there is support for holding differences in CUD. In the following, these points are reviewed.

A Historical Agenda for Investigation of Sex Differences in SUDs

Sex differences have been an official topic of interest in SUD research since 1975, when the National Institute on Drug Abuse (NIDA, from the United States) was prompted to carry out supporting studies on women with addiction. The initial motivation was due to a noticed trend of male-only samples (Greenfield et al., 2007; Wetherington, 2007). Later, in the mid-1980s, HIV become an epidemic, together with cocaine use. The NIDA then promoted campaigns supporting studies on female addiction and its association with HIV.

Nevertheless, the noticed imbalances did not dissolve. In response, in 1994, the National Institute of Health (NIH, also from the United States) made public a guideline for conducting scientific studies, requiring the inclusion of females and minorities, which was reedited and reinforced several times after that, including in 2017 (NIH notice number: NOT-OD-18-014). NIH reformulations demanded the NIDA to require studies to include females of all ages and not exclusively those pregnant or with HIV. In addition, they required translational studies and the investigation of existing sex differences (across all ages as well), which was reinforced in 2014 (Clayton & Collins, 2014).

Despite all this historical background, a review on sex differences identified not only imbalances but also biased reporting methods, making the problem even more complex. Males outnumbered females, and interestingly, when studies included female-only samples, this fact was commonly mentioned in the title. On the other hand, studies with male-only samples did not have such a peculiarity. At the time of this review, authors concluded that

when samples encompass a single sex, it should be clear in the paper title to avoid generalizations. Likewise, investigations on sex differences should highlight it as much as possible because it is of remarkable value (Beery & Zucker, 2011).

Similarly, in 2007, Wetherington showed how the investigation of sex differences in addiction began to grow, although at a slow pace, through the last decades. He conducted separate searches for studies on PubMed, crossing *gender differences* with (a) *drug abuse,* (b) *drug dependence,* (c) *drug addiction*, and (d) *smoking*. Figure 1 shows the picture he previously depicted in his work.

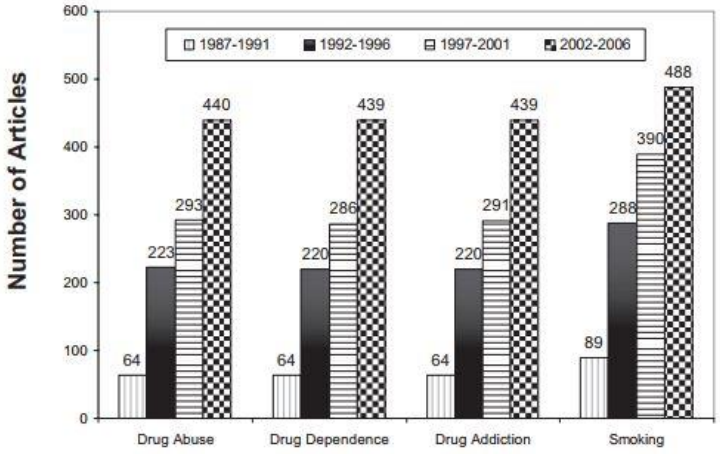

Figure 1. Evolution of gender differences in SUD research. Adapted from Wetherington, 2007 [6]. It shows the evolution of research on gender differences from 1987 until 2006. The author conducted searches on PubMed, crossing *gender differences* in four different searches with addiction topics. The revelation of a growing body of evidence, almost in a continuous progression, was noticed.

To test where the growth of the field stands, his search was reconducted. Furthermore, the reedition of the search counted with a few differences. Because of the interest in crack

[6] Adapted from "Sex-gender differences in drug abuse: A shift in the burden of proof?," by C. L. Wetherington, 2007. *Experimental and Clinical Psychopharmacology, 15,* p. 414. Copyright 2018 by American Psychology Association was granted by Copyright Clerance Center.

cocaine research, a search for *cocaine* was included. In addition, because cocaine is a specific drug, searches for *alcohol* and *cannabis* also were included. The reconduction of the search crossed the terms not with *gender differences*, as Wetherington previously did, but with *sex differences* (the next section will address the terminology and better explain the reason). The retrieved numbers of the search are in Figure 2.

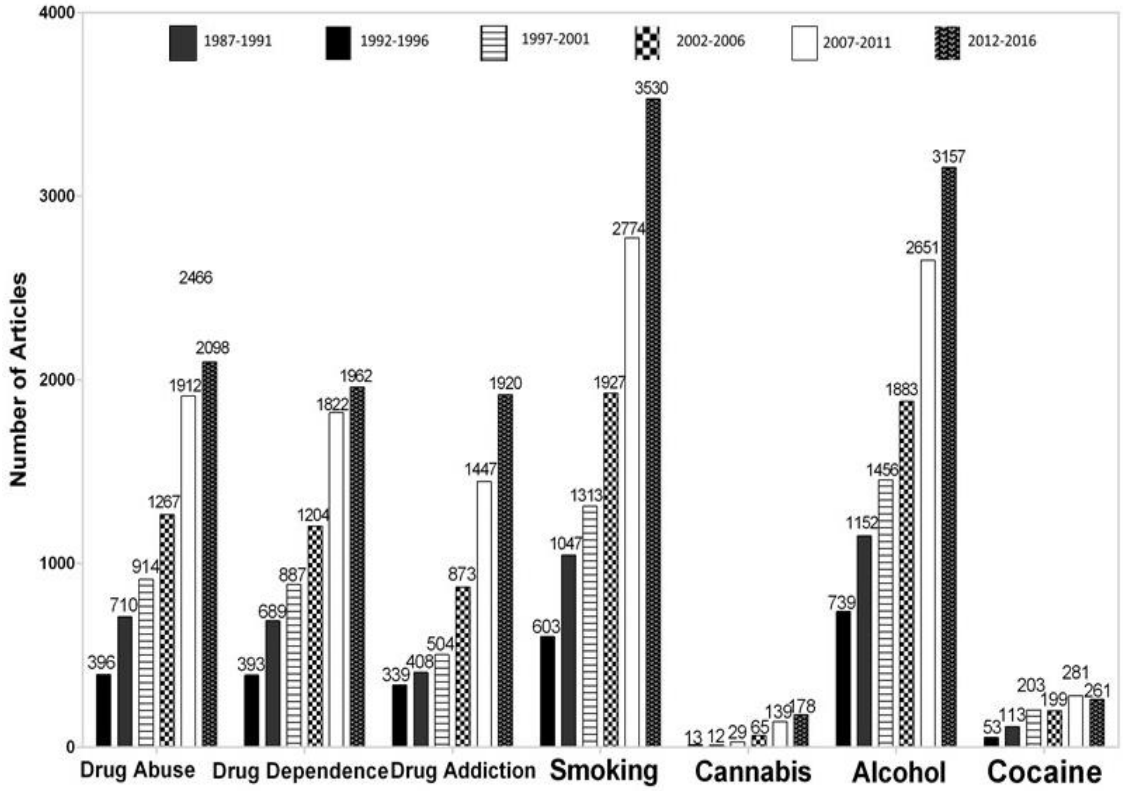

Figure 2. The continued evolution of sex differences in SUD research. The figure depicts the same search from Wetherington (2007) in PubMed. However, the reproduction includes two more periods of four years (2007–2011 and 2012–2016), used *sex differences* instead of *gender differences*, and included searches for studies on cannabis, alcohol, and cocaine.

The simple search showed that (a) the growth of the topic within SUD research continues; (b) the growth has also been noticed with cannabis, cocaine, and alcohol, with remarkable amounts for this last topic, which together with *smoking* has higher amounts of

studies; and moreover, (c) the number of works using *sex differences* is at least twice that of those using *gender differences*—revealing a terminology issue (later addressed). As a side note: for all crossing terms, cocaine was the only one that did not show increases every four years.

The Brazilian Agenda for Sex Differences Research in Addiction

In Brazil, the ANPP (Brasil, 2015) has not clearly mentioned *sex differences*, but there are specifically descriptions of the need to investigate gender differences in subsections of the document. Of note, there is a whole subsection for women's health (Subsection 8). In addition, Subsection 2 (Mental Health) mentions the need for studies on gender and likewise factors for protection, vulnerability, and prognosis in specific population groups. Furthermore, it includes the investigation of an exploratory profile of sociodemographic information. By comparing with policies in other countries, one could suggest Brazil is lacking in addressing sex differences more directly, which indeed is true. However, a disclaimer is required. Brazil is a country with a lot of cultural heterogeneity, and the inclusion of gender rather than sex may promote more cultural-related research, particularly because social arguments on this topic are emerging now in the Brazilian media.

Promoting Research on Sex Differences and Standardizing It

Different agendas restate that not only basic research but also clinical research should consider the inclusion of both sexes in studies, even if the focus was not sex differences. Experts strongly advise and reinforce the need for evidence-based hypotheses to consider sex as a mandatory variable in the equation because different outcomes can emerge (Wizemann & Pardue, 2001). Furthermore, because of bias in reports, as mentioned earlier, guidelines must reinforce the need for reporting on sex differences and specify conduct for doing so. One of these recommendation guides (Wizemann & Pardue, 2001) indicates that the lack of knowledge about the topic is not exclusively due to historical practices but also because of

mistakes and heterogeneous reporting. It begins with problems in terminology and extends to the absence of information when there are no differences. In this sense, there are some recommendations for research and progress in the field, according Wizemann and Pardue (2001):

Recommendations for Research:

- Promote research on sex at the cellular level.
- Study sex differences from womb to tomb.
- Mine cross-species information.
- Investigate natural variations.
- Expand research on sex differences in brain organization and function.
- Monitor sex differences and similarities for all human diseases that affect both sexes.

Recommendations for Addressing Barriers to Progress:

- Clarify use of the terms sex and gender.
- Support and conduct additional research on sex differences.
- Make sex-specific data more readily available.
- Determine and disclose the sex of origin of biological research materials.
- Conduct and construct longitudinal studies so that the results can be analyzed by sex.
- Identify the endocrine status of research subjects.
- Encourage and support interdisciplinary research on sex differences.
- Reduce the potential for discrimination based on identified sex differences. (p. 11)

Terminology

When studying sex differences, some conceptualizations are necessary, as confusions and misinterpretations can occur because some issues and biased research may put limitations on interpretations or even offend some people. Moreover, in sciences that have a humanity background, such mistakes are particularly problematic. In the following sections, there are some terms and conceptualizations. It is important to note that, although I tried to separate the concepts, it is not entirely possible to do so in everyday life. This thesis, unfortunately could not account for so many variables in the diversity of sex, gender, and sexual preferences. Therefore, all works of this thesis assumed a *cisgender* perspective for sex differences, a concept that is better explained next.

Making Clear Sex, Gender, and Sexual Preferences

Differences between sex, gender, and sexual preference are easy to understand, although there are confusions regarding the topic. Mainly, the approach of observation determines the meaning, that is, if the concept refers to biological, social, or attraction/mate selection characteristics. It is remarkable that there are overlapping effects across these concepts, but there is independency between them as well.

Sex. Sex refers to biological characteristics of organisms. Most organisms, even single cells, have a sex. Sex is, in general terms, binary: men and women, male and female. Sex refers to chromosomes, hormones, and specific internal and external organs (such as, obviously, the genitals; Becker et al., 2005; Greenspan et al., 2007).

Gender. For some time, gender was a synonym of sex. However, the differentiation was made necessary when some theorists noticed that some used sex as an independent variable, while others were working with it as a dependent variable. Most who used sex as an independent variable worked with sex as a consequence of biological differences, which indeed is the definition of sex (Unger, 1979). Those who used sex as a dependent variable meant the role that each person assumes in behavioral terms in the environment. Soon, a

redefinition coined this second use of the term as gender: those nonbiological characteristics that socially are attributable to males or females in the relations people have with others (Barry et al., 1957; Bem, 1984). By this token, gender regards the cultural identity of someone, which is dissociated from phenotypic characteristics (i.e., sex).

Gender can be used as a definition for a social role, which would be a *gender role*, as the way people see someone acting, so it is defined by attitudes rather than the genitals (Kessler & McKenna, 1978). Gender can also be used from the person's own perspective, meaning the way a person perceives him- or herself in the world. This perspective is referred to as *gender identity* (Bem, 1984; Greenspan et al., 2007; Rosenfield, 1982). There is a historical trajectory that continues in the present time in which people expect gender to match with biological sex. However, in fact, there is not an obvious relationship between identity and social roles (Barry et al., 1957). In terms of prevalence, most people have a gender identity that matches with their phenotypic sex, which is referred to as *cisgender*. In the United States, about 99% of the population declare to be cisgender (Flores, Herman, Gates, & Brown, 2016).

Sexual preferences. Sexual preference/orientation refers to the sexual attraction regarding a specific sex (Barry et al., 1957; Bem, 1984). Confusion sometimes occurs regarding sexual orientation and gender. Mate preference regards the emotional and sexual attraction that someone has for a given sex. Sexual orientation is independently free of gender identity or role. The characterizations in sexual preferences mostly include homo-, hetero-, bi-, or asexual (Sell, 1997; Shively & Kaplan, 1984). In this work, sexual preferences were not considered.

Sex Differences

Sex differences regard those different characteristics that males and females have in typical development. Some assume that traits that have sex differences are *dimorphic* traits, and there are authors who use the terms *masculinization* and *feminization* as descriptions of the traits of males and females, respectively (Becker et al., 2005).

Before detailing some sex differences, it is important to note that when investigating sex differences, the objective is not to detect the presence versus the absence of a specific marker/characteristic or something else. Research in sex differences is aimed to measure *how* different males and females are in certain points or if they indeed are different (Maney, 2016). Moreover, some dimorphic characteristics can be subject to modification, while others are not; research on sex differences incorporates these points as well (Becker et al., 2005).

The Existence of Sex Differences

Sex differences exist in most medical and psychological conditions. These differences include age of disease onset, specific manifestations, treatment adherence, dropout rate, and side effects. It is accepted that misinterpretations and a historical lack of policies and commitment to investigating sex differences have led to the existence of bias in certain types of knowledge nowadays (Freeman et al., 2017). For example, a study from the 1980s with a large male-only sample led to conclusions about low cardiovascular risk and a low increased risk of stroke with acetylsalicylic acid (aspirin) use (Group, 1989). Interestingly, more than 15 years later, a second study with a female sample revealed that aspirin use reduces the risk of stroke but does not affect the risk of cardiovascular problems, which suggests the existence of sex-dependent and sex-independent effects, respectively (Ridker et al., 2005). Taking this simple example into consideration, we could argue that there is a need to clarify the conditions in which sex differences do and do not exist, as this knowledge could change the clinical practice for treating many disorders. It is also interesting to note that conditions with

a very poor treatment response, such as SUD, are those that should be investigated the most in this regard (Becker, 2009, 2016; Becker & Kleinman, 2013; Becker et al., 2012).

The initial evidence, and some of the most accumulated evidence, for sex differences relates to psychological functions and abilities (Benbow & Stanley, 1980; Linn & Petersen, 1985; Voyer, Voyer, & Bryden, 1995). In this regard, studies have indicated that men have an overall better performance than women in spatial cognition tasks (Uttal et al., 2013). On the other hand, women have been shown to perform better in social cognition and episodic memory recognition in general terms (Gur et al., 2010). It is important to make clear that differences do not mean deficiencies. Moreover, there are cognitive functions that have no sex differences, and some evidence has shown that the differences that do exist may not be based on performance itself but rather on learning abilities with regard to specific functions, or they exist in the pathways activated in men's and women's brains (Halpern, 2012).

Origins of Sex differences

Sex differences may arise from different causes. For a better understand of sex differences, they must be understood in terms of determination and differentiation. *Sex determination* refers to the gonadal development and is attributable to genetic processes. *Sex differentiation* refers to the development of all other external and internal structures, not restricted to those related to the gonads, which means that most sex differences are triggered by sex-differentiation effects. It should be noted that gonadal development is attributable to a single gene from the Y-chromosome: *Sry*. The function of this gene is to trigger precursors of early gonadal bipotentials, thereby promoting testis development (McElreavey, Vilain, Abbas, Herskowitz, & Fellous, 1993; Sinclair et al., 1990), although exceptions do exist, mostly related to sex-syndromes (Sekido & Lovell-Badge, 2008; Swain, Narvaez, Burgoyne, Camerino, & Lovell-Badge, 1998).

Biologically driven-sex differences. The earliest theories held that sex differences were totally biologically determined. At that time, theories assumed that biological predisposition (Lillie, 1916) could explain both sex determination and differentiation due to chromosomic differences (Vilain & McCabe, 1998). Females have two X-chromosomes, which, due to genetic variability, can make recessive manifestations of some X-chromosome genes present only in females. Males have one X-chromosome and one Y-chromosome. A simple interpretation could therefore draw the conclusion that specific dominant genes of the Y-chromosome will only affect males (Angelopoulou, Lavranos, & Manolakou, 2006; Carruth, Reisert, & Arnold, 2002). By this token, dimorphic differences could account for the expression of genes in sex chromosomes. Indeed, animal studies have identified singular brain development in the presence of Y- and X-chromosomes in mice. However, it is not clear if all dimorphism can be directly attributed to the genes of sex-chromosomes, although it is clear that they have some role, as has been noticed since research was first conducted in this field (Rice, 1984).

In addition, biological theories of sex differences state that gonadal hormones have two main differentiation effects: one *organizational* and the other based on *activation* (Arnold & Breedlove, 1985). Organizational effects are those that are irreversible or more permanent, while activation effects refer to transitional effects occurring during exposure to certain hormones, such as ovulation in females. According to this theory, some occurrences of pervasive sex differences would be dependent on timing. This means that organizational effects occur during opportunity windows in the development period—critical periods during which changes become more likely, are more sensitive, and have enduring effects. As has been stressed already, childhood is an opportunity moment in which stressful experiences have an influence and can lead to permanent changes (McEwen, 2012; Storr et al., 2007; Weiss, Longhurst, & Mazure, 1999; Yehuda, 1999). In this regard, opportunity windows also

exist for sex hormones, which can make themselves felt a different developmental moments in time. Such moments, which include those in the gestational period, the first months after birth, and puberty, have organizational effects in the brain (Schulz, Molenda-Figueira, & Sisk, 2009; Van Etten, Neumark, & Anthony, 1999). In addition, in a following section, it will present data in which fluctuations can be seen in subjective crack cocaine effects across the menstrual cycle (Sofuoglu, Dudish-Poulsen, Nelson, Pentel, & Hatsukami, 1999); this can be defined as an activation effect, as the subjective valuation of the drug use depends on the menstrual phase.

Psychosocial, evolutionarily driven sex differences. Nevertheless, some sex differences seem to occur independently of opportunity windows, and nonbiological interpretations have also been done suggested. For example, an alternative explanation is that some experiences are so strong that they break through the opportunity windows, such as childhood maltreatment (Thompson, Kingree, & Desai, 2004). Regardless of this possible explanation, early psychology studies held that even if sex was a biologically determined characteristic, differences are not free of social bias (Shields, 1975). Moreover, along similar lines, according to an evolutionary picture, the gender roles men and women have assumed over time continue to model their behavior. Furthermore, as social disparities between men and women continue to undermine the existence of equal social opportunities, adaptations based on gender roles assumed by humanity will require a long time to reduce (Buss, 1995).

Integrative psychosocial and biological theories of sex differences. In the past, biosocial theories of sex differences combined biological and social pressures to explain physical and psychological characteristics and dimorphisms. The most famous biosocial theory in this regard is that of Money and Ehrhardt (1972). More recently, adaptations of the biosocial theory of sexual dimorphism indicated a balance between social and biological factors in determining sex differences. Sex differences, in terms of physical and

psychological outcomes, could be caused by various aspects or, more frequently, aspects that have different weights. By this token, it is possible that men do indeed have stronger spatial learning abilities compared to women as a result of the biological predisposition to the activation of this aspect. However, if a woman exercises her spatial abilities a lot, it is possible for the imbalance to disappear. However, training and biologic predisposition will have different weights in the equation (Wood & Eagly, 2002).

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CHAPTER 3: Sex Differences in crack cocaine users

Not surprisingly, sex differences that are common even in healthy conditions may interact with other mechanisms, and, in CUD, there are, likewise, specificities. Thus, here I is offered a summary of some evidence of sex differences in animals and of general sex differences in humans. In the end, although some theories of sex differences exist, questions remain, and despite the evolution of the field, these questions should be posed in future studies.

Animal Studies

The study of sex differences in crack cocaine use arose from preclinical studies. The data indicated that such dimorphisms are present in every step of drug use, from the effects of initial use to initiation to maintenance to progression and even to abstinence and relapse (Quinones-Jenab & Jenab, 2012). Moreover, experimental work with animals has supported the notion that sex differences do not entirely account for sex hormones (Hu, Crombag, Robinson, & Becker, 2004; Hu & Becker, 2003).

There is support for the notion that females have more intense rewarding effects and locomotor response in rats, which represents distinctions in the acute effects of the drug (Sircar & Kim, 1999). Conclusions, with additional data, have indicated that the initiation of drug use is also characterized by sex differences. For example, repeated cocaine administration leads to sensitization in female rats sooner than in male rats, as female animals show faster self-administration behaviors (Jackson, Robinson, & Becker, 2006; Lynch, 2008). Similarly, the progression of cocaine use and evolution of CUD is supported by evidence in studies with animals. Females have been found to evolve through *checkpoints* of self-administration more quickly; in this regard, female rats reach higher indexes in bar pressing to receive cocaine sooner than male rats (Caine et al., 2004; Kippin et al., 2005). Moreover, the conditioning to drug cues occurs more quickly in females. By using the

conditioning place preference (CPP) paradigm, data revealed that female animals experience faster conditioning than male ones (Russo et al., 2003) and that female rats can develop conditioning with lower doses than males (Zakharova, Wade, & Izenwasser, 2009). Finally, sex differences in experimental studies with animals also support the notion that the extinction of drug-seeking behaviors is more pervasive in females than in males. A total of 180 days after the drug withdrawal, males do not exhibit such behaviors whereas females do (Kerstetter, Aguilar, Parrish, & Kippin, 2008).

Most animal studies tested the ability of sex hormones to mediate or modulate sex differences in cocaine use. Although there is a strong background on this topic that will be presented next, animal studies have provided some of the best evidence for assuming that sex differences are not entirely accounted for by sex hormones in cocaine use. The effects of higher sensitization previously reported have been replicated in castrated and ovariectomized male and female rats, respectively. Results such as these support the notion that gonadal hormones do not determine sex differences (Hu & Becker, 2003; Hu et al., 2004).

Evidence of Sex differences in Human Crack Cocaine Users

Results in animal studies have promoted translational studies to test whether similar results would appear in humans. Given the subjectivity that is inherent to human beings, the results were not only validated for humans but also revealed novel data. Thus, this section provides some results related to sex differences in crack cocaine users extracted from studies with humans. For the sake of organization, we will first provide general characteristics, and after that, we will offer some observations on vulnerability, acute use, initiation/habituation, and progression.

Sociodemographic and Epidemiological Sex Differences in Crack Cocaine Users

Sex differences in crack cocaine use are easily identified by referring to numbers on the prevalence of use. Men outnumbered women in a proportion of 3:1 (Winstock et al.,

2017), meaning that, of those 17.1 million users (considering a 12-month prevalence) in 2016, 5.7 million were women (UNODOC, 2017). In addition, an observed increase in the burden of SUD in women in a 25% estimation is higher than the 19% reported in men, taking into account numbers from 2005 to 2015 (UNODOC, 2017). In Brazil, considering the estimate that 2.2% of the population had used crack cocaine in the last 12 months, the data indicated that, for men, the estimate was 6.6%, and for women, it was 1.3%. Taking only crack into consideration, use of which accounts for 2.2% of the total population, estimates for men were 3.7%, and for women, they were 0.07%. When evaluating CUD, rates for the total population were 0.6% (0.09% in males, 0.03% in females; Abdalla et al., 2014). Therefore, epidemiological numbers support the existence of sex differences in CK. Figure 1 provides the epidemiological and profile sex differences in crack cocaine users. The data is in the form of a figure rather than a table to illustrate differences in the proportion, and by means of this, to indicate that not even one of those characteristics is divided in the middle, thereby reinforcing sex differences in CK.

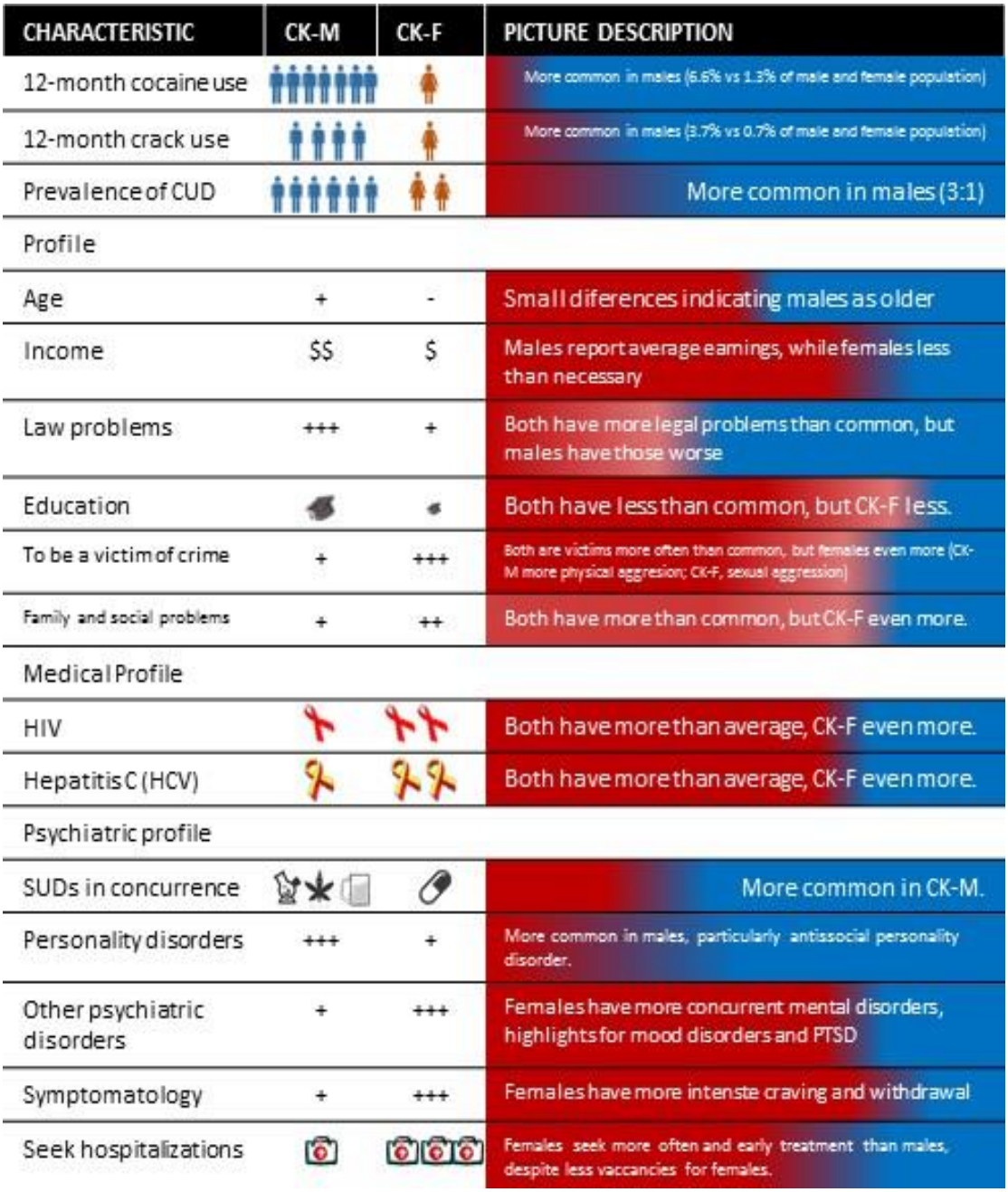

Figure 1. Summary of sex differences in the general profile of crack cocaine users. The figure combines data from studies to indicate differences. In the right column, the difference is described, and the pattern of the gradient indicates a proportion of the difference between groups of male crack cocaine users (CK-M) and groups of female crack cocaine users (CK-F). More red means more issues for CK-F; more blue means more issues for CK-M. For the sake of comparison, we assumed that the determined

outcome would be worse. For example, we use seeking hospitalizations sooner as an index of higher severity, but this could have a different interpretation; the same is true of age, in which we understood a low age to be more dangerous.

For the sociodemographic perspective, sex differences also appear. In general terms, the average Brazilian crack user (in the 12 months before the study) was: male, aged between 20 and 39 years old, with low or middle education (primary and high school), single, had a middle income, and employed. However, taking this profile into account, sex differences do appear, because females were, in general, 14–29 years old, low income, and unemployed, although the small sample size should be considered when interpreting the data (Abdalla et al., 2014). It is important to note that these data came from crack cocaine users and that some subtle differences can be seen in CUD and when evaluating participants in the treatment.

Data from CK seeking treatment indicated that males have more problems with the law, are less likely to live with a partner, and report living with other drug users more often than females (Vernaglia et al., 2017). On the other hand, women are less educated, more frequently unemployed, have lower income, report receiving less than income than is necessary to cover their own expenses, and commonly exchange sex for drugs or money (Bertoni et al., 2014; Imtiaz, Wells, & Macdonald, 2016; Vernaglia et al., 2017). Women are also more frequently victims of crime, with being raped the most common (physical violence often occurs more with males; Bertoni et al., 2014). In addition, women report more social and family problems, often involving problems caring for children (Vernaglia et al., 2017). Moreover, women are younger, which indeed matches other data suggesting that women enter into drug treatment programs earlier than men (Najavits & Lester, 2008)

With these findings taken into consideration, an important issue emerges: women seek treatment for CUD sooner than men. Unfortunately, while the proportion of women using

cocaine is three times less than men, data indicate that when estimating drug users in treatment, the proportion is 5:1 (Winstock et al., 2017). This finding contrasts not only with prevalence numbers but also with the data of this thesis, which indicate that women have more severe crack cocaine courses. In particular, it may match telescoping theory (see in the next of this chapter) and is probably perpetuated by societal contexts, such as those indicating vulnerability (see in a following section of this chapter).

Medical profile. Sex differences in medical conditions among crack cocaine users require special attention, as there are many manifestations that add burden to CUD. For example, recent data has indicated that in crack cocaine users, more DALYs (disability-adjusted life years, a metrics used by the World Health Organization (WHO) to compare the burden of diseases) relate to hepatitis C than to HIV nowadays (UNODOC, 2017). On this issue, reports have indicated that females have higher rates of HIV (Bertoni et al., 2014; Vernaglia et al., 2017) hepatitis C (HCV) infections (Macías et al., 2008) in comparison to males, although investigations inside Brazilian prisons did not find differences for HCV (Puga et al., 2017).

Psychiatric disorders are another issue that need to be taken into account. Some studies in the past reported no sex differences in the severity of CUD but a considerable difference in psychiatric disorders (Najavits & Lester, 2008). Nevertheless, other studies, especially after DSM-5, have defined the associated psychiatric issues as a part of the CUD severity or at least as being counted as part of the severity (Becker, 2016; Fattore, Melis, Fadda, & Fratta, 2014; Imtiaz et al., 2016; Pedraz et al., 2015).

Regardless of the concept used to determine severity, male and female crack users show differences in the prevalence of concurrent psychiatric disorders. Concurrent SUDs with CUD are more common in men (Falck et al., 2004; Minutillo et al., 2016; Pedraz et al., 2015), and likewise, personality disorders (Falck et al., 2004; Narvaez et al., 2014). On the

other hand, women show higher rates of most other mental disorders (Falck et al., 2004; McCance-Katz, Carroll, & Rounsaville, 1999; Najavits & Lester, 2008; Pope et al., 2011; Wong, Badger, Sigmon, & Higgins, 2002).

Sex differences Before Using, While Using, in the Initiation, in the Progression, and More

Crack cocaine use is suggested to has sex differences that influence the acute effects of crack cocaine use, the initiation and habituation, and the progression of drug use after the development of CUD. The body of evidence is strong enough to support a theory of this topic. Table 1 gives a summary of these sex differences.

Table 1

Summary of Findings on Sex Differences across Different Drug Use Stages

	CK-M	**CK-F**	**References**
Before using	Vulnerability		
Social context of drug use	↑↑↑	↓	(Becker et al., 2016; Courtwright, 2009)
Violence in drug-dealing places	↓	↓↓↓	(Becker et al., 2016; Courtwright, 2009)
Susceptibility for developing CUD after initial use	-	↑↑↑	(Reboussin & Anthony, 2006; Vsevolozhskaya & Anthony, 2016; Zilberman et al., 2003)
Moderator effects with childhood maltreatment	↑?	↑↑↑	(Hyman et al., 2008; Wilson & Widom, 2009; Francke et al., 2013)
In the beginning—acute.	Induced responses		
Euphoria	+++	+	(Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008)
Anxious	+	+++	(Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008)
Latency time (time between use and response)	+++	+-	(Lukas et al., 1996)
Duration of high	+-	++	(Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008)
Dysphoria in the withdrawal	++	+	(Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008)

Cocaine plasma concentration	+++	+	(Lukas et al., 1996)
Cardiovascular response	++	+++	(Lynch et al., 2008)
Reduced appetite	++	+++	(Lukas et al., 1996)
Initiation/habituation			
Drug use places	More likely to use		
Workplace	+++	+	(Kennedy et al., 2013)
Home	+	++	(Kennedy et al., 2013)
During leisure	+	++	(Kennedy et al., 2013)
Motives for using	Higher likelihood		
To get reward	++	+-	(Kennedy et al., 2013; Terry-Mcelrath et al., 2009)
To get out of distress	+	+++	(Kennedy et al., 2013; Terry-Mcelrath et al., 2009)
To cope with physical symptoms	+-	++	(Kennedy et al., 2013; Terry-Mcelrath et al., 2009)
To social purposes	+	+-	(Kennedy et al., 2013; Terry-Mcelrath et al., 2009)
To test self-control	+-	++	(Kennedy et al., 2013)
Conditioning	Intensity/ changes		

Drug-cueing craving	+/↑	++/↑↑	(Elman et al., 2001; Robbins et al., 1999)
Stress-cueing craving	+	+++/↑↑	(Back et al., 2005; Kennedy et al., 2013)
Craving induced by everyday distress	+	+++	(Waldrop, Back, & Brady, 2007; Waldrop, Back, & Verduin, 2007)
Attentional bias for drug cues	++	+++	(Robbins et al., 1999)
Higher subjective craving	+	++	(Elman et al., 2001)
Progression			
Days using the drug	+	++	(Kennedy et al., 2013)
Overdoses	+	++	(Soldin & Mattison, 2009)
Seek hospitalization	+	++/↑	(Vernaglia et al., 2017)
General drug use severity	++	+++	(Becker, 2016; Imtiaz et al., 2016; Liana Fattore et al., 2014; Pedraz et al., 2015)
Treatment and relapse			
Difficulty to stop using	++	+++	(Back et al., 2005)
Relapse	↑	↑↑↑	(Kosten et al., 1993; Robbins et al., 1999; Van Etten et al., 1999)
Good expectations for treatment	+++	-	(Najavits & Lester, 2008)

Susceptibility to everyday distress	+	+++	(Waldrop, Back, & Brady, 2007; Waldrop, Back, Verduin, & Brady, 2007)

Note. In the table, the number of symbols is informative about the intensity of each measure. Differences between groups of male crack cocaine users (CK-M) and female crack cocaine users (CK-F) are displayed. For vulnerability, signs indicated increased (↑) or decreased (↑); for induced responses, however, there is increased (+) or decreased (-) symptoms. For *more likely* and *higher likelihood*, measures indicate more (+) or less (-). Intensity and changes refers to higher (+) changes and how fast (↑) changes occurring.

Before: Sex differences in the vulnerability to crack cocaine use and CUD. Higher rates of males using crack cocaine and males with CUD indicate that sex differences exist in the susceptibility to crack cocaine use. Possibly the most important variable in this regard is a social one: Opportunity (Becker, McClellan, & Reed, 2016). Brain changes because of the drug are totally dependent on the environment (Uslaner et al., 2001). Cultural determination can turn drug use into a transgressive or desired behavior due to social shaping. It is easy to conclude that across most historical periods, in different countries, drug use has always been less acceptable for women than for men (Courtwright, 2009). In line with this, a Brazilian study found that men are 4.4 times more likely to experiment with crack cocaine than women (Abdalla et al., 2014). Therefore, there is a protective factor for women, which is social pressure.

In addition, most illegal drugs are only available in dangerous areas, which is another protective factor for women, because physical fragility is often seen as more attractive in women (Becker et al., 2016). Consistently, women prefer to use drugs at home and in the presence of people close to them (Badiani & Spagnolo, 2013; Kennedy, Epstein, Phillips, & Preston, 2013). Because of this, men are more susceptible in terms of environmental and social opportunities.

With regard to psychobiological susceptibility, however, women are found to be at greater risk. Among the most commonly used drugs, crack cocaine has the smallest time from first use to the development of addiction (~1–2 years; Vsevolozhskaya & Anthony, 2016). On the other hand, compared to other drugs, it is estimated that around 5% of people who try crack cocaine develop CUD. Data show that women are more vulnerable to experiencing a faster transition to CUD than men (Becker et al., 2012; Reboussin & Anthony, 2006; Van Etten et al., 1999; Vsevolozhskaya & Anthony, 2016; Zilberman, Tavares, & el-Guebaly, 2003). Moreover, proportionally, more women will develop CUD after recreational use than

men (Najavits & Lester, 2008). Taking into consideration data suggesting that 5% of people who ever use cocaine will develop CUD, we can estimate that, according to the sex-specific likelihood, it will be 3% of men and 7% of women (Vsevolozhskaya & Anthony, 2016).

Moreover, one major psychological risk factor is the history of childhood maltreatment, which increases the chance of CUD development (Andersen & Teicher, 2009) and has detrimental effects on CUD, because there is slower reduction of abstinence symptoms (Francke, Viola, Tractenberg, & Grassi-Oliveira, 2013). Interestingly, childhood maltreatment has interactions and indeed confers risks, but reports indicate that it is sex-dependent, showing effects only for females (Hyman et al., 2008; Wilson & Widom, 2009).

In the beginning: Sex differences in acute crack cocaine effects. Men and women show different responses to acute crack cocaine use. Men report more euphoria and dysphoria (Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008) and a shorter latency between use and responses (Lukas et al., 1996). Moreover, using the same dose, plasma cocaine concentrations following intranasal cocaine use are higher in males than in females (Lukas et al., 1996).

On the other hand, females feel more anxious and report a longer subjective sensation of being high (Kosten et al., 1996; Lukas et al., 1996; Lynch et al., 2008). Similarly, females have a higher cardiovascular response and more reduction of hunger than males (Lynch et al., 2008). Some assumptions posit that lower cocaine plasma concentrations in women, together with increased sympathetic activity, is evidence of sex differences in pharmacokinetics processing (Cone, 1995; Evans & Foltin, 2010).

Although results on differences in acute effects are consistent, other studies have failed to find such differences, without taking some biasing variables into consideration (Collins, Evans, Foltin, & Haney, 2007; Lukas et al., 1996; Lynch et al., 2008; Sofuoglu et al., 1999). Two intervenient points have also emerged: the administration route and, more

importantly, the menstrual cycle. Some evidence on sex differences in crack cocaine users are only true when participants report smoking it (Collins et al., 2007; Foltin & Haney, 2004). Furthermore, some studies have revealed that sex differences could be dependent on the phase of the menstrual cycle, thereby strengthening the role of sex hormones. Some indicated differences in the feeling and duration of being high are only present in the luteal or follicular phase, which would mean that the activation effects demonstrate differences (Evans, 2007). Although this point is still debatable, but the role of sex hormones continues to receive more and more attention (it will be addressed in this text soon).

Initiation/habituation. If, in animals, it is seen in the context of classical learning, as in CPP experiments, in humans, the location of use may play an important role as well. In this regard, men prefer to use in the workplace and with coworkers; women, on the other hand, prefer to use at home when doing leisure activities or when doing nothing. Women report using in the presence of their partner, strangers, and children (Kennedy et al., 2013). Given this insight, it is easy to conclude that women are more subject to develop conditioning, because drug use can lead men to be fired, while use of drugs in the home is in a *safe place* where children cannot be avoided at most times (Becker, 2016; Becker et al., 2016; Becker et al., 2017).

In line with this assumption, women are more reactive to cocaine-cues, as shown by their higher attentional bias (Robbins, Ehrman, Childress, & O'Brien, 1999) and craving following drug cues (Elman, Karlsgodt, & Gastfriend, 2001; Robbins et al., 1999) and their stress and depressive emotional states (Back, Brady, Jackson, Salstrom, & Zinzow, 2005; Kennedy et al., 2013). Thus, women are easily conditioned both to positive and negative affect triggers, which matches data suggesting that women use crack cocaine for more days in a month than men (Kennedy et al., 2013). Supporting this, women show higher subjective craving in general (Elman et al., 2001).

Progression. Advances through to problematic drug use show sex differences. Two theories support the role of sex-difference in a complementary way: *the second stepper downward spiral* and the *telescoping effect*. Differences in the progression are supported by the data for initiation and by some of the data previously collected on victimization, comorbidities, and general profiles. Moreover, women have more overdoses (Soldin & Mattison, 2009), enter drug treatments earlier (Vernaglia et al., 2017), and have higher drug use severity (Becker, 2016; Imtiaz et al., 2016; Liana Fattore et al., 2014; Pedraz et al., 2015).

A sex-dependent downward spiral—the second stepper downward spiral. As previously mentioned, one theory about the transition to CUD holds that it takes the form of a downward spiral (Koob & Le Moal, 1997), in which the first step is hedonic pursuit, anticipation, and preoccupation. When our understanding of sex differences became clearer, some authors provided an adaptation of the theory (Becker et al., 2012). It is now known that drug use can be motivated by other factors than achieving euphoria but can also be engaged in to cope with negative affects or feelings (Baker, Morse, & Sherman, 1986; Martin et al., 2014; Stacy, Newcomb, & Bentler, 1991), although some conflicting data suggest that using drugs as a form of negative reinforcement has stronger rewarding and conditioning effects (Martens et al., 2008). As women are more likely to use drugs to cope with negative affects (Kennedy et al., 2013), the second stepper downward spiral model suggests that women enter into the spiral through a second step, which is the vulnerability factor (Becker et al., 2012). Moreover, other neurobiological, social, and psychopathological differences support the notion that women move down the spiral more quickly. Figure 2 provides examples of this.

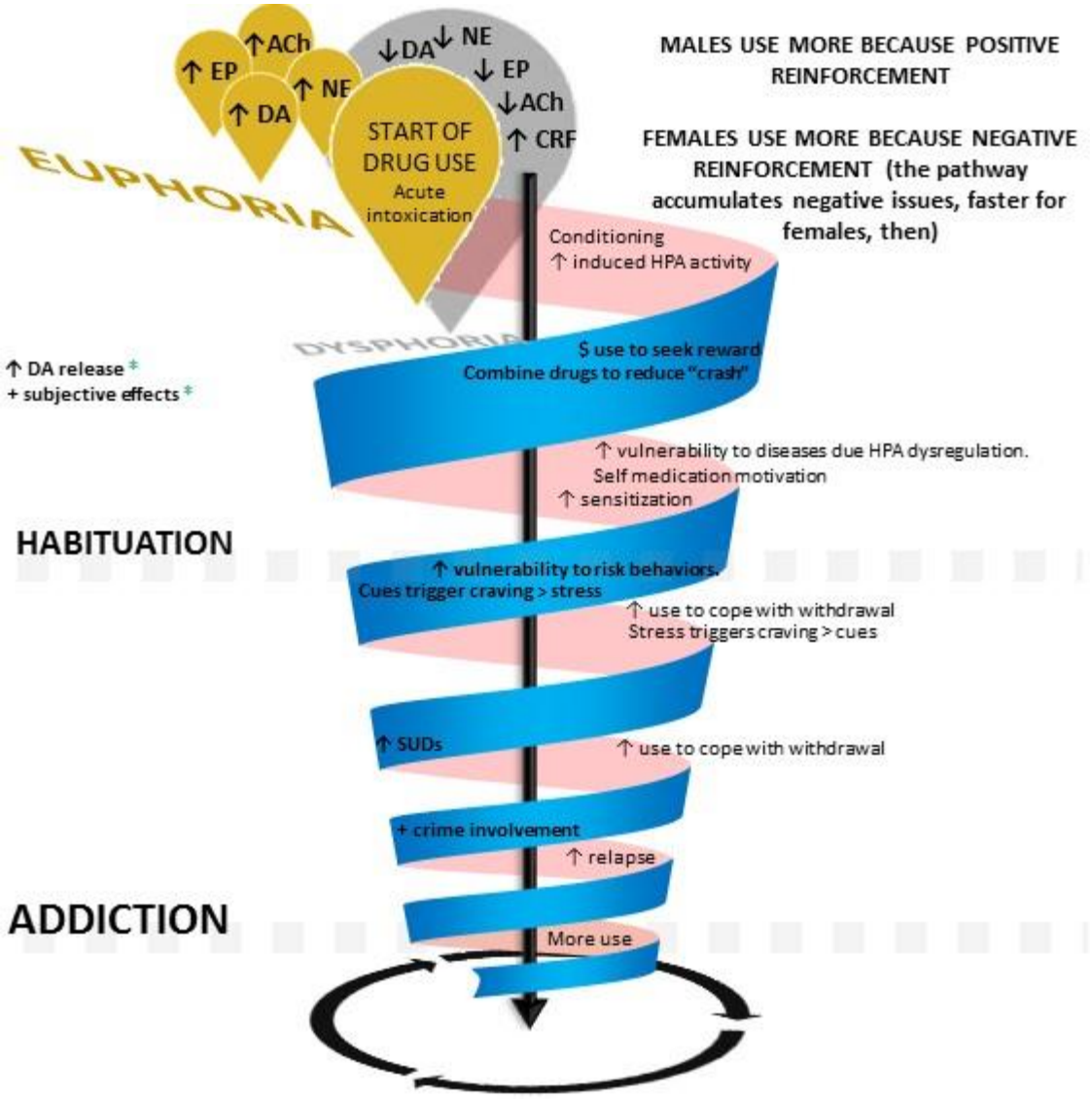

Figure 2. An addiction theory for sex differences in addiction: the second stepper downward spiral. Adapted from the theory from Becker et al. (2012). NE: norepinephrine. EP: endogenous opioids. Ach: acetylcholine. * This is dependent on the menstrual cycle.

Figure 2 illustrates that women advance more quickly down the spiral. In the model, I have not included information that is not in the source, but I have combined as much of it as I could in the same diagram. As can be seen, the start of the drug use varies based on whether the motivation is to seek a reward or reduce bad feelings. Acute use is highlighted in yellow. Acute intoxication leads to rewarding effects due to the occurrences marked in the smaller yellow shapes. After acute intoxication, breakdown effects (in gray) include rapid and

exaggerated reduction in these markers, leading to dysphoria and compensatory releasing of CRF. Repeated drug use leads to positive or negative reinforcement, which is the second most effective factor in conditioning. Reinforcement occurs due to DA release and subjective effects, which are dependent on the menstrual cycle. Across drug use stages, landmarks and differences are shown (the occurrence for males is shown in the blue part of the spiral, whereas, for females, it is shown in the pink part of the spiral). As more issues arise, the person goes through the spiral more quickly. As females use more as a result of negative reinforcement, and as more negative issues arise for females than for males, the transition to addiction is expected to occur more quickly for females.

Telescoping effect. Therefore, women have a faster initiation and progression into being habituated to drug use (Haas & Peters, 2000). When this sex-difference was noticed in alcohol dependence, it was coined the *telescoping effect* or *telescoped course* (McCance-Katz et al., 1999; Morrison, 1990; Piazza, Vrbka, & Yeager, 1989; Zilberman et al., 2003). In fact, data support the notion that women arrive before men at various landmarks along the CUD path, as they are more likely to seek hospitalization and experience an overdose than men. In addition to the sociodemographic issues indicating that women have more severe experiences than men, when CUD is already established, women also have poorer success in stopping use (Back et al., 2005), and their periods of abstinence are often shorter than men (Kosten, Gawin, Kosten, & Rounsaville, 1993; Robbins et al., 1999; Van Etten et al., 1999). As a result, there is solid support for the telescoping effect in females.

Treatment and relapsing. Much of the appeal of the sex differences agenda in research on drug use came from negative results of trials on CUD and likewise on other SUDs. By this token, even small positive results appear to be inapplicable to both males and females (Dackis et al., 2012; Klimas et al., 2012; Kosten et al., 1993; Majewska, 1996;

Malcolm et al., 2005). Some results have indicated that female crack cocaine users have more difficulty stopping use (Back et al., 2005) and that when they successfully achieve abstinence, they relapse more quickly than malese (Kosten et al., 1993; Robbins et al., 1999; Van Etten et al., 1999). On the other hand, females report better expectations of treatment than males do, which might be an alternative explanation for their earlier enrolment in supervision rather than having a more severe disorder (Najavits & Lester, 2008).

As stated in habituation mechanisms, women are more reactive to both drug cues and negative affect. In line with this, daily distress predicts positively higher cue reactivity in women than in men. This finding is particularly true for distress caused by interpersonal conflicts, which are occurrences that are more often reported by women (Waldrop, Back, & Brady, 2007; Waldrop, Back, Verduin, & Brady, 2007). Moreover, some of the interventions are less accepted by women compared to their acceptance among men (Gate, Lim, Harvey, & Hardwick, 2007; Morrissey & Harper, 2004).

Stress-related brain organization and functioning. At the brain level, there are several sex differences in crack cocaine users. Sometimes, data is informative, but it can also give rise to more questions given our actual knowledge. First, while most important organizational and functional characteristics of the reward system (including both positive and negative reinforcement systems) are similar in males and in females, attention can be given to dimorphisms in the activation and organization of these systems in relation to other brain systems and networks. How reward mechanisms are triggered and how they relate to secondary responses is of particular interest. According to the data and the background, the habituation to drug use and its progression intensify such differences (Becker et al., 2012; Becker et al., 2017).

Data collected under experimental conditions revealed that craving induced by drug cues has higher activation in some brain areas within the insula, striatum, and both the ACC

and PCC (Potenza et al., 2012); the two latter areas are related to the SN. This means that in males, areas of selective attention, emotional processing, and inhibition are activated together to a larger extent. Positron emission tomography (PET) studies have investigated this more specifically and found that in males craving triggered by cues does indeed relate to activation in the amygdala, insula, OFC, and ACC, areas related to similar functions. In female crack cocaine users, on the other hand, drug cues activated more areas in the central sulcus and other frontal areas. The conclusions of these studies indicated that craving activates more widespread brain areas in females than in males, as behavioral response is similar or even stronger, despite the brain signals being not so pronounced in the related brain areas (Kilts, Gross, Ely, & Drexler, 2004).

An interesting fact is that, given the observations of stress triggering craving, studies have looked for sex differences in the stress-craving pathways at a brain-processing level. As reward mechanisms overlap stress mechanisms in the brain, and it is well accepted that these shared areas have changes and interactions, it was not surprising that female crack cocaine users showed increased activation in reward-related areas after stress. In fact, females who use cocaine showed increased activation under stress in the same areas in which males who use cocaine showed activation under drug cueing (Potenza et al., 2012). Similar previously published results (Li et al., 2005) have suggested that coping strategies for emotional distress may have differences in males and females, which probably has the cingulate cortex as a central coordinator of the switching system. Besides having important functions in switching between multiple networks and types of information, the cingulate cortex also shows dimorphic patterns of activation/deactivation.

Regarding craving induced by both stress and drug cues, researchers have become interested in investigating which trigger is stronger, despite sex differences. Intravenous corticotrophin-releasing hormone (CRH) injections in crack cocaine users induce craving

responses, and consistently, subjective stress and craving responses are positively associated with each other (Back et al., 2010; Brady et al., 2009). This procedure also causes an increase in the heart rate and plasma cortisol levels. Between CK-M and CK-F, cortisol and heart rate are significantly higher in CK-F during such experiments. In addition, while cortisol and CRH levels show positive correlations to each other in healthy controls and CK-M, this cannot be found in CK-F. Researchers have hypothesized that, in CK-F, non-HPA stress-sensitive mechanisms cause changes due to stress exposure, which may impact subjective reactions, HPA activity, and heart rate (Brady et al., 2009). Curiously, the HPA axis of female crack cocaine users has blunted the stress response compared to males (Waldrop et al., 2010). Thus, one hypothesis suggests that some disruption in brain-stress related areas leads to hyperactivation in females that fails to activate the hypothalamus and in fact triggers MCL pathways (Gerra et al., 2009).

Could sex hormones explain all sex differences in CK? It is uncertain. Gonadal hormones modulate cocaine-induced outcomes, even though it is not clear whether this occurs partially or totally. The effects of the menstrual cycle indicate that subjective feelings are more pronounced in the follicular phase compared to the luteal phase (Evans, 2007; Lukas et al., 1996; Sofuoglu et al., 1999). Preclinical evidence suggests that estradiol, which is elevated in the follicular phase, facilitates cocaine responses (Martinez, Peterson, Meisel, & Mermelstein, 2014) and increases drug-seeking behaviors (Doncheck et al., 2017), which is not exclusive to female rats (Bagley et al., 2017). However, progesterone, which is particularly increased in the middle of the luteal phase, reduces subjective responsiveness to cocaine in women (Evans, 2007; Swalve et al., 2017; Swalve, Smethells, Zlebnik, & Carroll, 2016), although this is most noticeable when the drug is smoked (Evans, 2007). Moreover, progesterone increases social intelligence and learning (Milivojevic, Sinha, Morgan, Sofuoglu, & Fox, 2014). Given that distress due to interpersonal conflicts is particularly

likely to increase cue reactivity (Waldrop, Back, & Brady, 2007; Waldrop, Back, & Verduin, 2007), fluctuations in ovarian hormones can modulate not only cocaine pharmacokinetics but also psychological functioning related to triggering drug-seeking behaviors (Becker et al., 2017; Becker et al., 2012).

As can be seen, estrogen has facilitation proprieties for crack cocaine effects, while progesterone seems to reduce its effects (Quinones-Jenab & Jenab, 2012). Moreover, these hormones with natural fluctuations across the menstrual cycle have been found, in animal studies, to mediate interactions with other cocaine-sensitive systems, revealing activation sex differences due to the ovarian cycle. For example, estrogen mediates interactions of cocaine with endogenous peptides (Segarra et al., 2010) and likewise modulates cocaine-HPA effects (Anker & Carroll, 2010) and even DA neurotransmission, thereby increasing its release into the nucleus accumbens (NAcc) and the ventral tegmental area (VTA; Febo, Ferris, & Segarra, 2005). It also contributes to accelerating sensitization in areas such as the striatum (Hu & Becker, 2003; Peris, Decambre, Coleman-Hardee, & Simpkins, 1991). On the other hand, it has protective effects in inhibiting the combination of HIV proteins and cocaine and accelerating brain-blood barrier permeability (Turchan et al., 2001).

In line with the assumption that estrogen influences brain plasticity, it has also been found that the magnitude of pubertal estradiol during adolescence may cause organizational differences that coordinate different activation mechanisms throughout the lifespan. This suggests that in adolescence, estradiol influences motivational mechanisms rather than learning ones, which is particularly dangerous when it comes to early drug use (Perry, Westenbroek, & Becker, 2013). This is important because human data is available that supports the notion that decision making is similar in adolescents and in female crack cocaine users (Kluwe-Schiavon, Viola, Sanvicente-Vieira, Pezzi, & Grassi-Oliveira, 2016). Thus, bad choices may *burn* developmental stages. Due to increases in estradiol in puberty, concurrent

drug use may work together to create a brain organization that favors motivated behaviors (Ernst et al., 2006).

Few Models for Sex Differences in Crack Cocaine Despite Many Theories for Characteristics of Addiction

As can be seen, sex differences have been observed in crack cocaine users. However, there is a lack of studies integrating outcomes in consistent models. By this token, Becker tried to combine most theories and describe the pathways of habituation and progression of CUD in males and females (Becker et al., 2016; Becker et al., 2012). He proposed sociocultural and biological models for sex differences in crack cocaine use, but in fact, some of the most important sex differences (stress and reward relation) were not included as part of the puzzle of sex differences in addiction.

Moreover, hypotheses about plasticity and activation differences have been suggested, but there is a lack of testing of networks and biological levels in humans. In addition, the second stepper downward spiral indeed contributes to telescoping effects, but it does not include risk factors, although it has been acknowledged that they exist. Importantly, this work is not a criticism of the works of Becker and colleagues; rather, it is a compliment. They were pioneers in proposing and investigating ideas about sex differences, and the pursuit of this thesis was to join them and try to add data to the ideas they proposed.

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EMPIRICAL SECTION

CHAPTER 4: Sex Differences in Multidimensional Clinical Assessment of Crack Cocaine Users

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CHAPTER 5: Sex Differences in Intrinsic Brain Connectivity In Crack Cocaine Users

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Abstract

Cocaine use disorder (CUD) has been related to sex differences in its clinical presentation, therefore, the need for sex-oriented interventions has been suggested. This work investigated sex differences in the prevalence of concurrent mental disorders, trauma exposure, psychosocial problems and drug use severity in 1,344 participants (798 males and 546 females) with crack cocaine addiction, inpatients of a detoxification program. All participants took part in a comprehensive clinical assessment during early abstinence, including Structured Clinical Interview (SCID-I), Addiction Severity Index 6 (ASI-6) and the Childhood Trauma Questionnaire (CTQ). After correcting for multiple comparisons and controlling results for biasing variables, major differences regarding prevalence of lifetime psychiatric disorders came out, with females having higher rates of comorbidities. Traumatic past experiences also showed differences among men and women, with males reporting more childhood physical abuse, whereas females reported more sexual abuse across life, since childhood. The age of onset of crack cocaine use also showed differences, with females starting earlier. In addition, differences in the overall severity of drug use and related clinical outcomes indicated women who use crack have a more severe disorder in comparison to men. Results indicated that men and women that use crack cocaine have differences that must be considered in treatment strategies.

Keywords: sex, crack, cocaine, psychopathology, psychosocial

Sex Differences in Multidimensional Clinical Assessment of Crack Cocaine Users

Crack cocaine use disorder (CUD) has been related to sex differences in different studies (Becker, 2016; Becker, McClellan, & Reed, 2017; Degenhardt et al., 2014). In terms of epidemiology, annual cocaine use prevalence is estimated at 18.8 million users (UNODOC, 2016), being three times more prevalent among men (Abdalla et al., 2014). Among people who already use cocaine, women have an increased risk of early onset of crack consumption (Lejuez, Bornovalova, Reynolds, Daughters, & Curtin, 2007; Pope, Falck, Carlson, Leukefeld, & Booth, 2011), and they have a faster escalation from initial drug use to addiction (i.e., substance use disorder, SUD) (Stoltman, Woodcock, Lister, Greenwald, & Lundahl, 2015), an effect called "telescoping" (Piazza, Vrbka, & Yeager, 1989). Female crack users often have more social problems while males face more problems with the law (Vernaglia et al., 2017). Female crack users have higher rates of HIV (Bertoni et al., 2014) and comorbid psychiatric disorders, although personality disorders are more prevalent in males (Falck, Wang, Siegal, & Carlson, 2004).

Therefore, sex differences are not restricted to the consequences of the drug, but may also play a role in vulnerability to it. Motivations for drug use in men are more related to drug-cue exposures while women more often report drug-seeking behaviors after stress and negative emotions (Kuntsche & Müller, 2012; Potenza et al., 2012; Zilberman, Tavares, & el-Guebaly, 2003). Other sex differences regarding vulnerability to drug addiction could be related to the effects of early life stress. Childhood maltreatment, highly prevalent among cocaine users (Scheidell et al., 2017), is a predictive risk factor for addiction (Andersen & Teicher, 2009) that is found to anticipate drug use in females but not in males (Hyman et al., 2008; Wilson & Widom, 2009). Moreover, such negative events are related to increased

symptomatology in crack users, worsening withdrawal and depressive symptoms (Francke, Viola, Tractenberg, & Grassi-Oliveira, 2013).

Our main purpose was to investigate sex differences regarding mental disorder comorbidities, trauma exposure, psychosocial problems and drug use severity in patients with CUD during early abstinence.

Methods

This is a cross-sectional study designed to investigate sex differences within psychosocial characteristics of inpatient crack cocaine users during detoxification treatment. The data came from interviews and questionnaires from participants who voluntarily enrolled in one of two public detoxification inpatient programs funded by the Brazilian government in Southern Brazil. Each unit was designed to receive males or females exclusively, but at both facilities, inpatients were locked in an abstinence-controlled medical unit and followed a standardized protocol for three weeks. Patients had no access to alcohol, cigarettes, or other drugs during their hospitalization. During treatment, patients received prescribed medications for withdrawal symptoms and comorbid conditions. The Ethical Committee of the enrolled institutions approved this research, and all participants provided written informed consent.

Eligibility for this study included (a) fulfilling DSM-IV criteria for (crack) cocaine use disorder (CUD); (b) self-reporting crack as the primary drug of choice in cases of polysubstance use; (c) being 18 years old or more; (d) having no cognitive deficits compromising the ability to answer the protocol; (e) having no missing information in their files. The total sample included 1,344 participants (798 males).

The interviews mainly occurred during the second week of detoxification to avoid acute interference of symptoms in the evaluation. The assessment protocol

evaluated mental disorders, severity of substance use disorders, clinical and psychosocial characteristics and childhood trauma history. In addition, we assessed other medical conditions, legal and labor issues, social support problems and family care issues. The assessment usually took one or two sessions ranging between 30 and 60 minutes each.

Instruments

Psychiatric comorbidities. Participants were interviewed with the Structured Clinical Interview (SCID-I) (First, 1997) in order to identify mental disorders and confirm the diagnosis of CUD (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 1994). The substance use and abuse disorders module of the SCID-I was modified for this study. We considered both disorders (substance abuse and substance dependence) as a single disorder: SUD, fitting DSM-5 criteria (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force., 2013). We also organized the disorders according to the DSM-5 structure (e.g., considering trauma and/or stress-related disorders separately from anxiety disorders). We assessed lifetime and current (last 12 months) diagnoses. Because the focus of our study was specifically crack users, we proposed a subdivision in which snorted cocaine was considered separately from smoked cocaine. Thus, although formally the entire sample has the diagnosis of stimulants (cocaine) use disorder, we evaluated current or lifetime snorted cocaine use disorder, crack cocaine use disorder and other stimulants use disorder.

Drug use severity and negative life issues. Addiction severity and problems in other areas of psychosocial functioning were assessed with the Addiction Severity Index 6 (ASI-6) (Cacciola, Alterman, Habing, & McLellan, 2011; McLellan,

Cacciola, Alterman, Rikoon, & Carise, 2006). ASI-6 is a structured interview that allows investigators to assess a range of domains often affected by alcohol and drug use. We used a validated Brazilian Portuguese version (Kessler et al., 2012). The ASI-6 includes a series of detailed information including patterns of drug use, trauma history and other life issues and allows for the computation of composite scores for the severity of nine different domains that may be problematic in addiction: drug use, problems related to family, alcohol consumption, psychiatric issues, medical problems, legal issues, financial problems, lack of social support and social problems. In ASI-6, higher scores indicate more severe negative impacts in each domain. The only adaptation to the scoring system was that we considered prostitution non-formal work in accordance with Brazilian law, instead of considering prostitution a crime as the original instrument does. Thus, if a patient reported prostitution as working, it was not scored in his or her legal issues domain.

Trauma history. We assessed childhood trauma with the Brazilian version of the Childhood Trauma Questionnaire (CTQ; Grassi-Oliveira et al., 2014; Grassi-Oliveira, Stein, & Pezzi, 2006). The CTQ is a 5-point Likert-type scale with 28 items that assesses how often abuse or neglect experiences occurred while participants were children. The CTQ allows the use of continuous variables indicating the severity of different types of childhood maltreatment (emotional, physical and sexual abuse; emotional and physical neglect), but it also allows the use of cutoff scores to classify such scores according to their severity level (minimum, moderate and severe) (Bernstein et al., 2003).

The history of traumatic events occurring during adulthood also is an important variable within crack cocaine users because violence is one of the most common causes of death among this population in Brazil (Dias, Araújo, Dunn, et al.,

2011). Since the ASI-6 has specific questions regarding type of and age at different traumatic experiences, we used the information acquired in this trauma section to assess adult trauma history. We considered traumatic experiences occurring after 18 years old as adult traumatic events.

Data analyses

Initially, we computed descriptive analyses (i.e., mean, standard deviation, number of observations and percentages) considering the whole sample. We used chi-square tests with the Yates correction for continuity for categorical variables or Fisher's test when the number of observations was small. We also calculated the odds ratio (OR) for each psychiatric disorder (current and lifetime) and its 95% confidence intervals (CIs)—we assumed significant CI when values exceeded 1.00. For continuous variables, we used Student's t-test or Mann-Whitney as appropriate. Because of the size of the sample, we included also Cohen's *d* effect sizes for parametric tests and estimated *r* for those non-parametric ones to avoid Type I errors. For Cohen's *d*, we considered values of < 0.2 as "small to medium," < 0.5 as "medium to large" and <0.8 as "large" (Cohen, 1988). For *r* equivalent to *d* we considered <0.10 small, <0.24 medium and < 0.37 large (Rosenthal & Rosnow, 1984; Rosnow & Rosenthal, 1996).

It is worth mentioning that the number of observations of each variable varied considerably due to missing data or nonexistent data. For example, if a participant had never used cannabis, the data about his or her age of first cannabis use did not exist. Similarly, ASI-6 composite scores for many participants were zero because there was no chance of problems in that specific domain—for example, if a participant had no

kids, there was no ASI-6 children problems score. In these cases, we removed the participant from that specific comparison.

These previous described steps were our initial procedures, and after that, we tested data to correct for multiple comparisons and adjust for confounders. Considering the number of comparisons in our study, we corrected all *p*-values for multiple testing with a false discovery rate (FDR) test (Benjamini & Yekutieli, 2001), assuming a corrected *p*-value of 0.05 or lower. Because significant sex differences may in truth have secondary explanations and we assessed a number of possible confounding issues, we considered those group differences that remained significant after multiple analysis corrections for inclusion in adjusted models together with sociodemographic variables (even if there were no group differences). Because there was a high amount of collinearity among some variables, we selected always that variable that most encompassed the phenomenon—for example, if both actual and lifetime specific mental disorders had significant differences, we selected the lifetime one for inclusion in the model.

To calculate adjusted models, we ran logistic and linear regressions for each variable with significant sex differences after FDR corrections. We performed regression analyses by using the backward method manually. We ran repeated regressions until sex was the least predictive variable in the model. Then, we extracted the adjusted odds ratio for sex and its 95% CI, besides checking if the model also had significance. For continuous variables, we manually performed backward linear regressions repeatedly until sex was the least significant variable in the model. Then, we considered the Beta value as the predictive value for sex.

Results

Sociodemographic characteristics

Sample characteristics are shown in Table 1. The sample with available data included 1,344 participants: 798 males and 546 females. Sociodemographic comparisons revealed sex differences. Although most of the sample had self-declared as white in both groups, when we tested differences in proportions, there was a higher proportion of males who self-declared as white, while more females self-declared as black. Females more often had a stable relationship. Education level showed differences as well, although intragroup characteristics were similar: most of the sample reported their highest level of education was basic. However, differences in proportions indicated males as having more frequent intermediate or high education levels. Females also reported having more children and lower individual income than males did.

Table 1

Sociodemographic characteristics

	All (n = 1344)		Males (n = 798)		Females (n = 546)		Statistics		
	n	*M/n(SD/%)*	*n*	*M/n(SD/%)*	*n*	*M/n(SD/%)*	$X^2/t/U$	*p*	Corrected *p* value
Sociodemographic									
Age (years)	1319	32.328 (10.75)	784	32.405 (11.66)	535	33.0505 (8.62)	1.162[a]	0.245	0.340
Income ($)	1026	313.97 (484.26)	657	347.79 (454.75)	369	254.57 (528.53)	- 6.803[c]	<0.001	<0.001
Ethnicity (%)									
White	1336	637 (47.7)	699	418 (52.7)	637	219 (40.3)	19.801[b]	<0.001	<0.001
Black	1336	379 (28.4)	699	188 (23.7)	637	191 (32.2)	20.858[b]	<0.001	<0.001
Other	1336	319 (23.9)	699	187 (23.6)	637	132 (24.3)	0.094 [b]	0.794	0.841
Partner status (%)									

Married/ living with a partner	1267	389 (31.0)	787	227 (28.8)	469	162 (34.5)	4.463 [b]	0.037	0.061
Widowed	1267	61 (4.9)	787	44 (5.6)	469	17 (3.6)	2.458 [b]	0.136	0.226
Divorced/Separated	1267	36 (2.9)	787	21 (2.7)	469	15 (3.2)	0.296 [b]	0.603	0.697
Number of Children	1258	1.88 (1.96)	752	1.45 (1.73)	506	2.51 (2.10)	10.767[c]	<0.001	<0.001
Education level (%)									
Basic	1319	863 (65.4)	795	500 (62.9)	524	363 (69.3)	5.686 [b]	0.018	0.039
Intermediate	1319	385 (29.2)	795	255 (32.1)	524	130 (24.8)	8.068 [b]	0.004	0.010
High	1319	53 (4.0)	795	40 (5)	524	13 (2.5)	5.327 [b]	0.022	0.046

Note. [a] t-test value. [b] Pearson Chi-Square. [c] Mann-Whitney Standardized Z.

Drug use characteristics

Using ASI-6 sections for drug and alcohol use, we found sex differences in substance use characteristics (see Table 2). Regarding the age of first use, there were sex differences for alcohol, sedatives, inhalants and crack. Males reported first use of alcohol and inhalants at a younger age than females; females reported a younger age of first use of sedatives and crack. Years of use also showed sex differences, but there were no sex differences in length of time of crack use. Males reported more years of use for alcohol, cannabis and stimulants other than cocaine/crack, and this last with a large effect size. Females reported more years of use for tobacco, hallucinogens and opiates other than heroin. Although there were no sex differences for the number of hospitalizations for drug use, females had more detoxification hospitalizations and a younger age of first drug use treatment, both results with medium and large effect sizes, respectively.

Table 2

Drug Use Characteristics and ASI Scores For Drugs and Alcohol

	All		Men		Women		Statistics			
	n	*M/n(SD/%)*	*n*	*M/n(SD/%)*	*n*	*M/n(SD/%)*	*t/U*	*p*	Corrected *p* value	Effect size
Crack										
Age of first use	1147	22.07 (8.29)	494	24.16 (8.43)	653	19.31 (7.23)	-10.454[a]	<0.001	<0.001	-0.308 [d]
Years of use	1032	7.21 (5.83)	557	6.86 (5.50)	475	7.21 (5.83)	-1.003 [b]	0.316	0.458	-0.065
Alcohol										
Age of first use	1090	14.82 (4.01)	629	14.46 (3.55)	461	15.31 (4.53)	-3.372 [b]	0.001	0.002	-0.208 [c]
Years of use	583	11.35 (9.7)	379	13.08 (10.34)	204	8.09 (7.59)	-3.704 [a]	<0.001	<0.001	-0.153 [c]
Tobacco										
Age of first use	1087	13.15 (5.39)	614	13.10 (5.52)	473	13.21 (5.23)	-0.328 [b]	0.743	0.808	-0.020

Years of use	1068	17.05 (9.15)	598	16.58 (9.91)	470	17.62 (8.13)	4.008 [a]	<0.001	<0.001	0.122 [c]
Cannabis										
Age of first use	1088	15.10 (4.31)	627	14.99 (4.3)	461	15.24 (4.21)	-0.950 [b]	0.342	0.482	-0.058
Years of use	1080	10.81 (8.19)	617	11.11 (8.63)	463	10.37 (7.46)	-2.928 [a]	0.003	0.008	-0.089 [c]
Powder cocaine										
Age of first use	1058	17.97 (5.59)	613	17.97 (5.10)	445	17.96 (6.21)	0.009 [b]	0.993	0.999	0.001
Years of use	1047	8.73 (6.99)	611	8.92 (7.55)	436	8.47 (6.14)	0.415 [b]	0.678	0.754	0.065
Stimulants different than cocaine/crack										
Age of first use	145	21.45 (7.93)	98	21.80 (8.30)	47	20.72 (7.11)	0.768 [b]	0.444	0.561	0.139
Years of use	126	5.97 (5.64)	94	6.61 (5.81)	32	4.09 (4.71)	-2.912 [a]	0.004	0.014	-0.259 [e]
Sedatives										
Age of first use	374	23.22 (11.77)	220	24.95 (9.37)	154	20.75 (14.19)	-2.597 [a]	0.009	0.020	-0.134 [c]
Years of use	335	6.30 (7.11)	216	6.78 (8.03)	119	5.53 (5.26)	0.383 [b]	0.702	0.774	0.184

Hallucinogens										
Age of first use	181	20.91 (6.17)	128	21.24 (6.44)	53	20.13 (5.43)	1.102 [b]	0.272	0.406	0.186
Years of use	178	3.89 (4.55)	125	4.27 (5.02)	53	2.50 (1.60)	2.006 [b]	0.046	0.089	0.475 [c]
Inhalants										
Age of first use	511	16.91 (6.14)	301	16.25 (4.94)	210	17.85 (7.45)	-2.714 [b]	0.007	0.020	-0.253 [c]
Years of use	506	4.36 (5.40)	295	4.88 (5.96)	211	3.76 (4.61)	0.377 [b]	0.706	0.774	0.210 [c]
Heroin										
Age of first use	32	20.90 (8.29)	24	21.70 (9.25)	8	18.50 (3.81)	0.945 [b]	0.352	0.491	0.452 [c]
Years of use	32	2.22 (1.92)	24	2.28 (2.21)	8	2.00 (0)	0.286 [b]	0.777	0.833	0.179
Other opiates than heroin										
Age of first use	63	25.74 (9.42)	50	25.74 (10.07)	13	25.76 (6.64)	-0.010 [b]	0.992	0.999	-0.002
Years of use	19	4.16 (2.7)	9	2.5 (2.13)	10	5.50 (2.41)	2.737 [a]	0.006	0.015	0.214 [c]
Treatment indexes										
Number of hospitalizations for drug use	1064	5.38 (6.74)	532	5.67 (7.53)	532	5.03 (5.62)	1.526 [b]	0.127	0.213	-0.130

Detoxification hospitalization	1033	3.27 (4.92)	567	2.63 (5.12)	466	4.04 (4.55)	10.178 [a]	<0.001	<0.001	0.316 [d]
Age of first drug use treatment	995	24.74 (9.38)	530	25.69 (9.07)	465	23.64 (9.61)	-3.175 [a]	0.001	0.002	-0.308 [e]

Note. In cases of t-test, effect size reported refers to Cohen's *d*; and in cases of Mann-Whitney, to *r* equivalent to *d*. [a] Mann-Whitney Standardized Z. [b] t-test value. [c] small effect size. [d] medium effect size. [e] large effect size.

Negative life issues

Sex differences appeared in different life issues and are shown in Table 3. Regarding housing, females had been homeless more often. Regarding medical issues, HIV and other medical conditions were more prevalent in females. The former had a significant 95% CI (2.46–4.98). Regarding employment, females had higher rates of unemployment and more often worked in non-formal occupations in comparison to males. Among females, the most common non-formal work was prostitution: 18.6% referred to having worked in prostitution (not including cases in which they had exchanged sex for drugs) while 17.5% referred to other non-formal occupations. Among males, 2.3% referred to having worked in prostitution. Regarding legal problems, males had higher proportions of previous arrests, reinforced by a significant 95% CI (0.35–0.66). In social life, females reported having fewer close friends, likewise having less contact with close friends (95% CI = 0.58–0.96) and siblings (95% CI = 0.49–0.82) in the last 30 days. At the same time, males had less contact with a partner in the last 30 days (95% CI = 1.42–2.31). Besides that, in terms of interpersonal conflicts with close people, males reported higher proportions of fights or arguments than females did in the last 30 days, which also was significant at 95% CI (0.44–0.72). History of suicide also showed sex differences: females more often had a history of suicide attempts, either any time in the life course or in the last 30 days, but only a lifetime history of suicide attempts remained significant at 95% CI (1.53–2.42).

Table 3

Sex-differences in negative life issues related to drug use and trauma

	Men		Women		Statistics			
	n	*M/n(SD/%)*	*n*	*M/n(SD/%)*	X^2/ *t/Z*	*p*	*Corrected p value*	*Effect size or OR*
Housing issues (%)								
Homeless in lifetime	796	314 (39.4)	516	227 (53.7)	22.618 [a]	<0.001	<0.001	1.778
Homeless in the last 6 months	496	212 (26.6)	441	161 (38.1)	16.988 [a]	<0.001	<0.001	1.693
Homeless in last 30 days	796	145 (18.2)	423	132 (31.2)	26.541 [a]	<0.001	<0.001	2.037
Medical Issues (%)								
HIV	794	53 (6.7)	520	104 (20.0)	53.239 [a]	<0.001	<0.001	3.504
Other Serious Medical Condition Different than HIV	775	379 (48.9)	504	287 (56.9)	7.912 [a]	0.005	0.001	1.382
Employment issues								

Employment (not working %)	791	361 (45.6)	522	253 (48.5)	1.011 [a]	0.337	0.479	1.120
Not formal employment (%)	791	115 (14.5)	522	165 (31.6)	54.620 [a]	<0.001	<0.001	2.71
Legal Problems								
Already Arrested (%)	764	294 (38.5)	520	129 (24.8)	26.188 [a]	<0.001	<0.001	0.527
Social life								
Number of close friends	756	2.01 (3.33)	520	1.35 (3.19)	-4.280 [c]	<0.001	<0.001	0.202 [d]
Interactions in last month								
In touch with a partner (%)	632	330 (52.2)	489	325 (66.5)	23.038 [a]	<0.001	<0.001	1.814
In touch with a sibling (%)	632	498 (78.8)	483	338 (70.0)	11.347 [a]	0.001	0.002	0.627
In touch with close friends (%)	628	256 (40.8)	490	167 (34.1)	5.226 [a]	0.025	0.046	0.751
Fight with close people (%)	754	563 (74.7)	518	324 (62.5)	24.532 [a]	<0.001	<0.001	0.522
Suicide (%)								
Suicide attempt in life	743	259 (34.9)	512	260 (50.8)	31.034 [a]	<0.001	<0.001	1.928
Suicide attempt in last 30 days	742	81 (10.9)	512	124 (24.2)	38.029 [a]	<0.001	<0.001	2.601
Trauma History (%)								

Physical harassment	621	275 (44.3)	473	152 (32.1)	16.651 [a]	<0.001	<0.001	0.596
Witnessed a hard crime	625	466 (74.6)	474	285 (60.1)	25.952 [a]	<0.001	<0.001	0.515
Sexual harassment	624	55 (8.8)	473	223 (47.1)	208.95 [a]	<0.001	0.001	9.228
Raped as an adult	617	35 (5.7)	467	59 (12.6)	16.264 [a]	<0.001	0.001	2.405
Childhood Trauma	474		498					
Total CTQ score	474	47.71 (16.44)	498	49.99 (19.53)	-1.969 [c]	0.049	0.094	-0.126 [d]
Physical Neglect								
Score		8.81 (3.62)		8.84 (4.09)	-0.142 [c]	0.887	0.911	-0.007
Emotional Neglect								
Score		10.43 (4.76)		11.57 (5.85)	2.204 [c]	0.028	0.056	-0.213 [d]
Moderate (%)		89 (18.8)		153 (30.7)	18.536 [a]	<0.001	<0.001	1.918
Severe (%)		46 (9.7)		92 (18.5)	15.330 [a]	<0.001	0.001	2.108
Sexual Abuse								
Score		6.51 (3.60)		8.02 (4.98)	-5.405 [b]	<0.001	<0.001	-0.347 [e]
Light (%)		127 (26.8)		205 (41.2)	21.668 [a]	<0.001	<0.001	1.912

Moderate (%)	81 (17.1)	160 (32.1)	28.659 [a]	<0.001	<0.001	2.297
Severe (%)	38 (31.4)	83 (16.7)	15.887 [a]	<0.001	<0.001	2.295
Physical Abuse						
Score	10.39 (5.39)	9.62 (5.23)	-2,556 [c]	0.011	0.025	0.144 [d]
Light (%)	272 (57.4)	249 (50.0)	5.031 [a]	0.025	0.045	0.743
Severe (%)	142 (30.0)	114 (22.9)	5.891 [a]	0.015	0.046	0.694
Emotional Abuse						
Score	11.552 (5.23)	11.92 (5.61)	-1.066 [c]	0.287	0.420	-0.067

Note. In cases of t-test, effect size reported refers to Cohen's *d*; and in cases of Mann-Whitney, to *r* equivalent to *d*. For categorical variables where chi-square or Fisher's exact test were used, the OR is reported. For CTQ, total score and scores for each subscale are shown. Data displayed on presence/absence of specific types of trauma is shown only for significant differences. [a] chi-square or Fisher's exact test. [b] Mann-Whitney Standardized Z. [c] t-test value. [d] small effect size. [e] medium effect size. [f] large effect size.

Trauma. Descriptive data for childhood and adult history of traumas is in Table 3.

Childhood maltreatment. Using the CTQ continuous scores, sex differences indicated males had more intense histories of physical abuse while females had higher scores for sexual abuse—only the last difference had a large effect size. When comparing presence/absence of each specific childhood trauma assessed by the CTQ using cutoffs for intensity, the proportion of males with more frequent histories of physical abuse remained significant for light (95% CI = 0.57–0.95) and severe (95% CI = 0.52–0.92) intensities. Females had more frequent histories of sexual abuse regardless of the intensity, but 95% CI remained significant only for moderate (95% CI = 1.69–3.11) and severe (95% CI = 1.52–3.44). In addition to these differences, females showed more moderate (95% CI = 1.42–2.58) and severe (95% CI = 1.44–3.08) emotional neglect than males.

Adult history of trauma. By using the trauma section of the ASI-6, we investigated adult history of trauma in the sample. Sex differences indicated that in adulthood, males more often suffered physical harassment and witnessed a hard crime. Females more often suffered sexual crimes, reporting higher rates of sexual harassment and rape during adulthood, with 95% CI supporting both (1.75–4.19 and 6.03–10.97, respectively). Among those participants who suffered some type of sexual crime, 77.6% also experienced sexual aggression during childhood.

Psychiatric comorbidities

A total of 991 participants answered the SCID-I. Table 4 shows the total estimated prevalence as well as the prevalence of each disorder assessed in each group and the respective comparisons. Figures 1 and 2 show forest plots based on

ORs and 95% CIs with unadjusted values for current and lifetime psychiatry comorbidities, respectively (values are displayed in Supplementary Table 1). Females had more mental disorders than males when substance use disorders were not taken into account. When comparing individual groups of current disorders, males had higher prevalence only for alcohol use disorder. Females, on the other hand, had higher estimates for any trauma and/or stress-related disorder, post-traumatic stress disorder, any anxiety disorder and powder cocaine use disorder. More differences appeared if we considered lifetime comorbid disorders. Males showed more hallucinogen use disorder, panic with agoraphobia and mood-induced disorders. Females had more any trauma and/or stress-related disorder, post-traumatic stress disorder, anxiety disorder, brief psychotic disorder, dysthymia, major depressive disorder, obsessive-compulsive disorder and anxiety-induced disorders. Moreover, females also had more specific phobia, any bipolar disorder and bipolar disorder type I.

Table 4

Sex differences in psychiatric comorbidities with Crack Cocaine Use Disorder

	All (n=991)	Men (n=468)	Women (n=523)	X^2	p	Corrected *p* value
	n (%)	n (%)	n (%)			
Any Psychiatric Disorder Additional to CUD (Current)	875 (88.3)	408 (87.2)	467 (89.3)	1.067	0.323	0.464
Any Psychiatric Disorder Additional to CUD (Lifetime)	957 (96.6)	454 (97)	503 (96.6)	0.517	0.491	0.600
Any Psychiatric Disorder Different than Substance Use (Current)	646 (65.2)	265 (56.6)	381 (72.8)	28.651	<0.001	<0.001
Any Psychiatric Disorder Different than Substance Use (Lifetime)	728 (73.5)	294 (62.8)	434 (83)	51.501	<0.001	<0.001
Substance use disorders						
Any substance use disorder (Current)	737 (74.4)	361 (77.1)	376 (71.9)	3.563	0.068	0.124
Any substance use disorder (Lifetime)	914 (92.2)	438 (93.6)	476 (91)	2.288	0.154	0.253
Alcohol (Current)	402 (40.6)	247 (52.8)	155 (29.6)	54.859	<0.001	<0.001
Alcohol (Lifetime)	566 (57.1)	287 (61.3)	279 (53.3)	6.419	0.012	0.030

Powder cocaine (Current)	373 (37.6)	147 (31.4)	226 (43.2)	14.657	<0.001	<0.001
Powder cocaine (Lifetime)	662 (66.8)	301 (64.3)	361 (69)	2.469	0.121	0.205
Cannabis (Current)	330 (33.3)	149 (31.8)	181 (34.6)	0.853	0.380	.511
Cannabis (Lifetime)	628 (63.4)	283 (60.5)	345 (66)	3.231	0.075	0.135
Inhalants (Current)	27 (2.7)	8 (1.7)	19 (3.6)	3.448	0.078	0.139
Inhalants (Lifetime)	158 (15.9)	67 (14.3)	91 (17.4)	1.752	0.193	0.297
Sedatives (Current)	134 (13.5)	60 (12.8)	74 (14.1)	0.373	0.577	0.677
Sedatives (Lifetime)	179 (18.1)	88 (18.8)	91 (17.4)	0.329	0.620	0.711
Stimulants different than cocaine (Current)	20 (2)	8 (1.7)	12 (2.3)	0.428	0.652	0.742
Stimulants different than cocaine (Lifetime)	69 (7)	30 (6.4)	39 (7.5)	0.418	0.535	0.638
Hallucinogens (Current)	6 (0.6)	4 (0.9)	2 (0.4)		0.430[a]	0.553
Hallucinogens (Lifetime)	24 (2.4)	17 (3.6)	7 (1.3)	5.50	0.022	0.046
Schizophrenia and Related Disorders						
Schizophrenia	12 (1.2)	4 (0.9)	8 (1.5)	0.941	0.394	0.525
Schizoaffective disorder	5 (0.4)	2 (0.4)	3 (0.6)		1.000[a]	0.999

Schizofreniform disorder	1 (0.1)	1 (0.2)	0			
Brief Psychotic Episode (Current)	15 (1.5)	0	15 (2.9)			
Brief Psychotic Episode (Lifetime)	26 (2.6)	6 (1.3)	20 (3.8)	6.247	0.016	0.035
Bipolar and Related Disorders						
Any Bipolar disorder	75 (7.6)	22 (4.7)	53 (10.1)	10.422	0.002	0.005
Bipolar Type I	38 (3.8)	9 (1.9)	29 (5.5)	8.786	0.004	0.010
Bipolar Type I in a hypo or maniac episode	2 (0.2)	0	2 (0.4)			
Bipolar Type I in a mixed episode	16 (1.6)	2 (0.4)	14 (2.7)	7.868	0.005	0.012
Bipolar Type I in a depressive episode	12 (1.2)	5 (1.1)	7 (1.3)	0.151	0.777	0.833
Bipolar Type II	37 (3.7)	13 (2.8)	24 (4.6)	2.254	0.179	0.284
Bipolar Type II in a hypomanic episode	6 (0.6)	1 (0.2)	5 (1)		0.222[a]	0.335
Bipolar Type II in a mixed episode	16 (1.6)	3 (0.6)	13 (2.5)	5.291	0.023	0.047
Bipolar Type II in a depressive episode	11 (1.1)	7 (1.5)	4 (0.8)	1.202	0.366	0.506
Depressive Disorders						
Major Depressive Disorder (Current)	130 (13.1)	54 (11.5)	76 (14.5)	1.941	0.187	0.291

Major Depressive Disorder (Lifetime)	207 (20.9)	71 (15.2)	136 (26)	17.540	<0.001	<0.001
Dysthymia (Current)	12 (1.2)	7 (1.5)	5 (1)	0.601	0.564	0.667
Dysthymia (Lifetime)	39 (3.9)	10 (2.1)	29 (5.5)	7.589	0.008	0.018
Anxiety Disorders						
Any Anxiety Disorder (Current)	372 (37.5)	151 (32.3)	221 (42.3)	10.515	0.001	0.002
Any Anxiety Disorder (Lifetime)	453 (45.7)	181 (38.7)	272 (52)	17.691	<0.001	<0.001
Any Panic Disorder (Current)	37 (3.7)	18 (3.8)	19 (3.6)	0.031	0.868	0.898
Any Panic Disorder (Lifetime)	54 (5.4)	25 (5.3)	29 (5.5)	0.020	0.999	0.999
Panic Disorder With Agoraphobia (Current)	17 (1.7)	12 (2.6)	5 (1)	3.788	0.083	0.144
Panic Disorder With Agoraphobia (Lifetime)	24 (2.4)	17 (3.6)	7 (1.3)	5.500	0.022	0.046
Panic Disorder Without Agoraphobia (Current)	20 (2.0)	6 (1.3)	14 (2.7)	2.430	0.173	0.278
Panic Disorder Without Agoraphobia (Lifetime)	30 (3.0)	8 (1.7)	22 (4.2)	5.246	0.025	0.050
Social Anxiety (Current)	98 (9.9)	41 (8.8)	57 (10.9)	1.267	0.287	0.420
Social Anxiety (Lifetime)	162 (16.3)	65 (13.9)	97 (18.5)	3.919	0.480	0.592
Specific Phobia (Current/Lifetime)	200 (20.2)	64 (13.7)	136 (26)	23.305	<0.001	<0.001

Generalized Anxiety Disorder (Current)	138 (13.9)	70 (15)	68 (13)	0.788	0.408	0.539
Generalized Anxiety Disorder (Lifetime)	222 (22.4)	96 (20.5)	126 (24.1)	1.820	0.195	0.297
Trauma and Stress-Related Disorders						
Any Trauma and/or Stress-Related Disorder (Current)	134 (13.5)	28 (6)	106 (20.3)	43.101	<0.001	<0.001
Any Trauma and/or Stress-Related Disorder (Lifetime)	178 (18)	45 (9.6)	133 (25.4)	41.922	<0.001	<0.001
Post-Traumatic Stress Disorder (Current)	131 (13.2)	27 (5.8)	104 (19.9)	42.902	<0.001	<0.001
Post-Traumatic Stress Disorder (Lifetime)	175 (17.7)	44 (9.4)	131 (17.7)	41.582	<0.001	<0.001
Adjustment Disorder (Current)	5 (0.5)	1 (0.2)	4 (0.8)		0.378[a]	0.511
Adjustment Disorder (Lifetime)	5 (0.5)	1 (0.2)	4 (0.8)		0.378[a]	0.511
Eating Disorders						
Any Eating Disorder (Current)	14 (1.4)	3 (0.6)	11 (2.1)	3.792	0.061	0.115
Any Eating Disorder (Lifetime)	22 (2.1)	11 (2.4)	11 (2.1)	0.070	0.832	0.867
Anorexia (Current)	9 (0.9)	3 (0.6)	6 (1.1)		0.512[a]	0.616
Anorexia (Lifetime)	15 (1.5)	9 (1.9)	6 (1.1)	0.997	0.436	0.556
Bulimia (Current)	9 (0.9)	2 (0.4)	7 (1.3)		0.184[a]	0.289

Bulimia (Lifetime)	15 (1.5)	8 (1.7)	7 (1.3)	0.228	0.796	0.841
Obsessive-Compulsive Disorders						
Obsessive-Compulsive Disorder (Current)	69 (7)	34 (7.3)	35 (6.7)	0.125	0.803	0.842
Obsessive-Compulsive Disorder (Lifetime)	134 (13.5)	45 (9.6)	89 (17)	11.572	0.001	0.002
Substance-Induced Disorders						
Any Substance-Induced Disorder (Current)	297 (30)	130 (27.8)	167 (31.9)	2.030	0.165	0.268
Any Substance-Induced Disorder (Lifetime)	377 (38)	191 (40.8)	186 (35.6)	2.886	0.101	0.173
Psychotic-Induced Disorder (Current)	33 (3.3)	14 (3)	19 (3.6)	0.316	0.600	0.697
Psychotic-Induced Disorder (Lifetime)	54 (5.4)	27 (5.8)	27 (5.2)	0.176	0.677	0.754
Mood-Induced Disorders (Current)	242 (24.4)	111 (23.7)	131 (25)	0.237	0.657	0.742
Mood-Induced Disorders (Lifetime)	302 (30.5)	169 (36.1)	133 (25.4)	13.299	<0.001	<0.001
Anxiety-Induced Disorders (Current)	70 (7.1)	26 (5.6)	44 (8.4)	3.072	0.083	0.144
Anxiety-Induced Disorders (Lifetime)	97 (9.8)	35 (7.5)	62 (11.9)	5.356	0.024	0.049

Note. [a] Fisher's exact test.

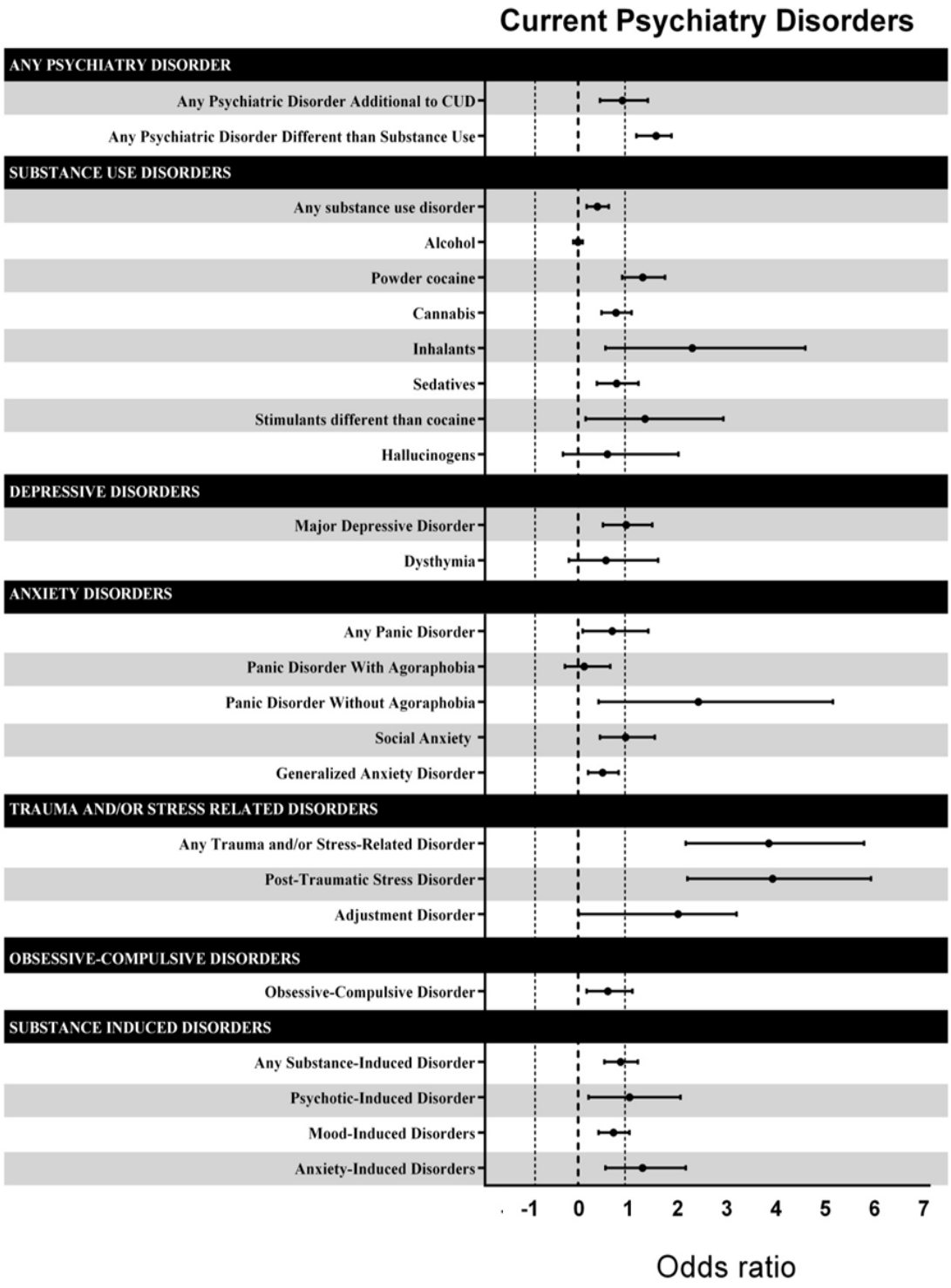

Figure 1. Forrest plot with the *ORs* for current concurrent psychiatric disorder. Data in the picture uses the mean OR, the central dot of each line, and the 95% CI. Males was the reference group, meaning as far from the midline, higher the risk for females.

Values under the zero means higher risk for males. For consideration of statistically significant, results should have a 95% CI that exceeded 1.0.

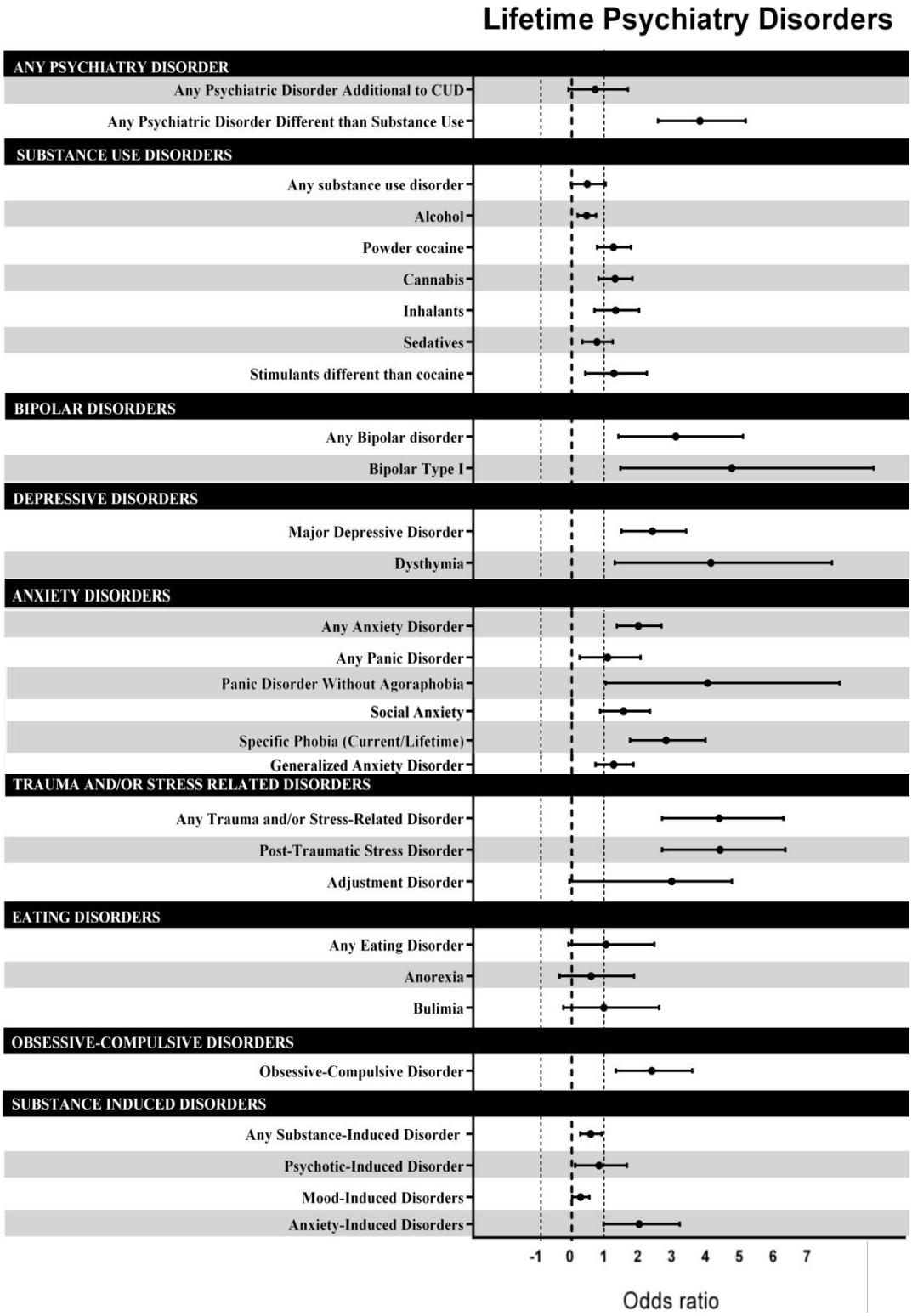

Figure 2. Forrest plot with the *ORs* for lifetime psychiatric disorder. Data in the picture uses the mean OR, the central dot of each line, and the 95% CI. Males was the reference group, meaning as far from the midline, higher the risk for females.

Values under the zero means higher risk for males. For consideration of statistically significant, results should have a 95% CI that exceeded 1.0.

ASI-6 composite scores

We found significant sex differences in seven of the nine ASI-6 individual composite scores, but not all had effect sizes different than small. Figure 3 shows a comparison of ASI-6 scores (full details of the values are shown in Supplementary Table 2). The results that survived corrections and remained with at least medium effect size were restricted to indications of overall drug use severity in females (ASI-6 Drugs score). In addition, data showed worse psychosocial functioning of females, particularly related to child care (ASI-6 Children Problems score), emotional suffering (ASI-6 Psychological Problems score), employment problems (ASI-6 Employment Problems score) and Social Support Problems (ASI-6 Social Support score).

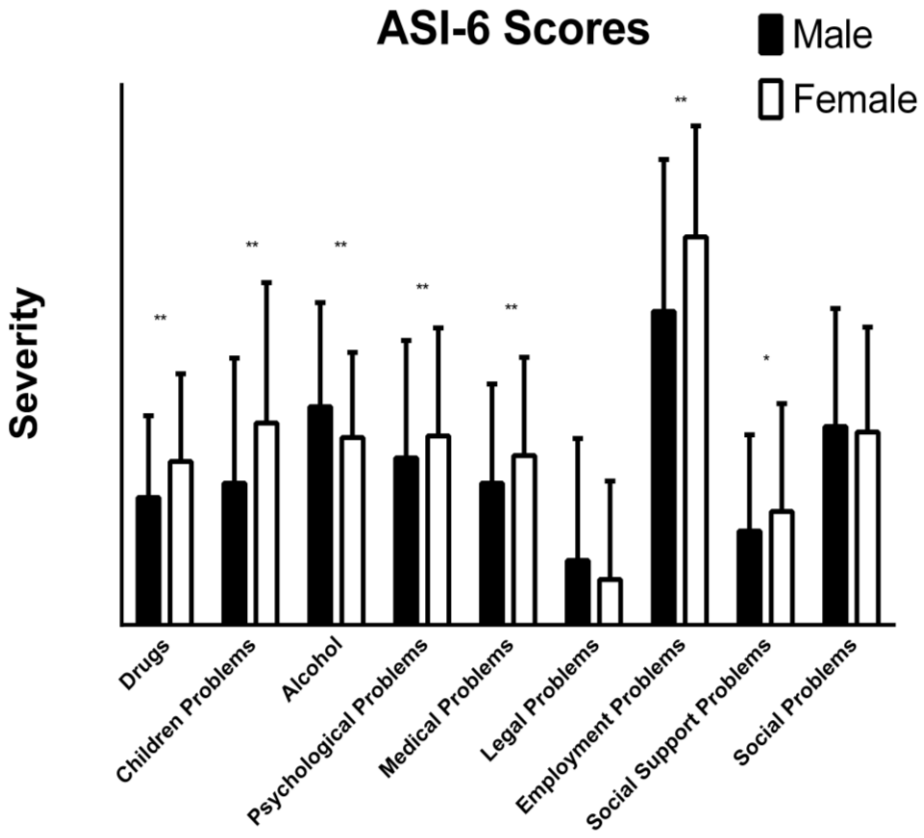

Figure 3. Differences in ASI-6 Scores – CUD severity.

* $p < 0.05$; ** $p < 0.001$.

Adjusted results

Given the heterogeneity of different outcomes, it is important to note that we tested the predictive values of sex for each specific variable by using regression models. We tested all those comparisons that had significant sex differences after multiple comparisons correction. Detailed information of adjusted values can be found in the supplementary tables. Among the results were drug use characteristics (Supplementary Table 3), negative life issues (Supplementary Table 4), comorbidities with CUD (Supplementary Table 1) and ASI-6 scores (Supplementary Table 5) that survived adjustments and remained, pointing out sex as a significant predictive variable with significant 95% CI.

For females, the age of first crack use was earlier than for males. Similarly, despite small effect sizes, years of alcohol use showed differences indicating males to have a longer time of using.

In negative life issues, most of the previous results remained significant, indicating a sex effect on reported results. Females had been homeless more often in the previous six months prior to hospitalization. Women had higher rates of HIV infection as well as different non-psychiatric disorders. Males had more arrests than females. Social life showed sex differences regarding the most common people to support crack users who are hospitalized for detoxification. Males had more close friends and reported having been in touch with an adult sibling in the month prior to hospitalization while females more frequently had been in touch with a partner. Males had been involved in more recent fights/arguments with close people than females. Descriptively, both groups suffered high rates of traumatic events, but more males reported having suffered physical harassment and witnessing hard crimes while females more often had suffered sexual harassment. Regarding childhood trauma, all previously reported differences survived adjustments, with males reporting to have suffered more physical abuse and females more sexual abuse and emotional neglect.

After adjustments, sex differences remained with predictive effect for psychiatric comorbidities with CUD. Males had higher estimates and risk for comorbid current hallucinogens use disorder and panic disorder with agoraphobia. Females had higher estimates for any current or lifetime psychiatric disorder different than drug use disorders, having the highest predictive values for trauma and stress-related disorders, including both current and lifetime PTSD. Predictive higher risks among females also survived for lifetime brief psychotic disorders, major depressive

disorder, any anxiety disorder, obsessive compulsive disorder and anxiety-induced disorders in addition to any bipolar disorder, particularly type I and specific phobia.

ASI-6 composite scores after adjustments remained significant in Drugs, Children Problems, Employment Problems and Social Support scores, showing females as more impacted in these domains of psychosocial functioning. The comparison between ASI-6 Alcohol scores remained significant, indicating more severity related to drinking among males.

Discussion

In this work we found sex differences in the severity of problems in a sample of crack users who were voluntarily admitted to a detoxification hospitalization. Our findings indicate and reinforce previous findings that among those with CUD, males and females suffer with different consequences of drug use (Bertoni et al., 2014; Elman, Karlsgodt, & Gastfriend, 2001; Fox & Sinha, 2009; Lejuez et al., 2007; Najavits & Lester, 2008; Vernaglia et al., 2017). Our findings also support different trajectories for the course of drug use for men and women (Bertoni et al., 2014; Hicks et al., 2007; Minutillo et al., 2016). These findings are relevant for targeting better interventions, identifying specific major problems in males and females who use crack to address primarily the most common issues. In addition, prevention strategies and policies can be improved, and future directions in research also need to be acknowledged (Evans, 2007).

Among the sex differences revealed in our study, some probably relate to issues that occurred before any drug use, which may have influenced the path for drug use disorder together with genetic factors (Becker, Perry, & Westenbroek, 2012; Bobzean, DeNobrega, & Perrotti, 2014). One difference in this sense was the lifetime

prevalence of psychiatric disorders—although current prevalence of comorbidities also showed differences, most of the survival ones were lifetime disorders. Indeed, comorbidities with CUD were expected to be more common among females than males (Falck et al., 2004; Pope et al., 2011), which makes mandatory the observation of comorbidities among crack users. Special attention needs to be paid to trauma and/or stress-related disorders in female health services, since this was one of the major results in our study. In addition, it is worth stating that as most of the differences are not in the current status, it is possible to suggest partial confirmation to the self-medication hypothesis (Khantzian, 1985) for CUD development in females (Chilcoat & Breslau, 1998) . By a similar token, it also matches with other theories that assume that females are more prone to use drugs to cope with negative emotional states (Kuntsche & Müller, 2012). Such results, combined with previous data, point to the need for primary mental health care, especially for females, as a way to target the avoidance of problematic crack use later in life.

Other sex differences that may contribute to the emergence of drug use refer to childhood maltreatment, which impacts males and females differently (Wilson & Widom, 2009). Among crack users, women reported higher rates of sexual abuse while men reported more physical abuse. Although global estimates of childhood maltreatment are not conclusive about sex differences in the prevalence of such experiences (Viola et al., 2016), there are data in line with our findings (Edinburgh, Saewyc, & Levitt, 2006; Thompson, Kingree, & Desai, 2004). These results stress that the relationship between early negative experiences and crack use still need better understanding, and it needs to consider sex-specific effects (Hyman et al., 2008).

Sex differences also appear when crack is used. Different ages at first use were found for crack, which is consistent with already documented data on urban

drug users (Lejuez et al., 2007; Pope et al., 2011). Because we found no differences in ages of first use for other substance, and we also found females to have an increased severity of drug use, we consider that our data support the "telescoping effect" (Piazza et al., 1989) in crack users.

Social support and the quality of relation networks are important predictors of treatment success in SUD (McKay et al., 2013; McMahon, 2001). Sex differences in crack inpatients were found, particularly regarding the composition of social networks. Among females, partners were the most common people in touch in the month prior to hospitalization while men had more friends and siblings in touch. Both groups reported to have some kind of fight or argument in the month before the hospitalization, with males reporting it more often than females. However, it is noteworthy to consider that for females, fights or arguments had critical potential for ending a stable relationship with a partner and probably made them fall apart without a social support network. Considering that motivations for drug use have sex differences (Kuntsche & Müller, 2012), and that for females the major reason to use drugs is to cope with negative feelings, the composition of the social network may be evaluated regarding how strong they are and if even in hard times it can support the patient's needs. In addition, there is a high chance that there are sex differences in the prevalence of drug use among the partners of crack users who are hospitalized. That means that even for females who more often have a partner, it is not necessarily a protective factor because the partner could also be a user. Unfortunately, in this work we did not assess this issue.

Regarding those issues that may be of critical importance due to the most negative outcomes associated with them, if we take into account the two already documented most common causes of death in crack users (i.e., HIV complications and

violence victimization) (Dias, Araújo, Dunn, et al., 2011), sex differences also appear. For violence victimization there is some equilibrium, men most often having physical assaults and women sexual harassment. Differently, HIV infection is remarkably more common among females, as are other clinical disorders. This is in line with previous data (Bertoni et al., 2014; Vernaglia et al., 2017) and makes clear the need for complete medical attention for users, particularly females.

Sex differences in inpatients for crack detoxification are widespread, which is clear when one takes into account the different domains assessed by the ASI-6. Across nine domains of the scale, sex differences appeared in five. Results survived at a considerable level even after corrections and adjustments. In accordance with these results, there are differences in behaviors related to social engagement, risks, employment and drug use. All differences reinforce current literature and that appropriate interventions are also needed: for males, probably avoiding problematic legal behaviors and the use of other substances; for females, a more complex picture emerges due to the problems in more areas of life. In addition, the age at which preventive strategies are used needs to be different for men and women because of differences in the age of first use. Such a more challenging approach for females is in line with data indicating females are more resistant to engaging in treatment (Greenfield et al., 2007).

Our results provide evidence that must be considered in future interventions, research and policies; however, it has some limitations. Generalizations are tentative because our data came from participants from a single city. Future multicenter studies can help in this sense. By a similar token, gender differences require attention. Our work assumed a cisgender/heterosexual perspective, but due to sociocultural interferences and gender stereotyping, sexual orientation has an impact on

psychological status (Marshal et al., 2008) that we did not address but future research should. Although trained psychologists and psychiatrists made the clinical assessments, the evaluations required the collaboration and precision of participants. Their psychological condition during hospitalization and even the unclear starting point of the symptoms makes diagnosis difficult. Particularly, some diagnoses were very hard to define because the beginning of drug use was unknown. Clinical rounds were done to minimize such problems, but the nature of the phenomenon is clearly hard to define. Besides that, both facilities were for primary drug users, meaning that there are drug users that because more severe psychological problems in other domains probably would go to other facilities and were not investigated here.

Another important point that requires care in the interpretation of our results is that we did not investigate street users; we focused on users who were suffering and voluntarily sought help. This explains why our sample has a profile different from that of previous works, including ethnicity and age (Bertoni et al., 2014; Duailibi, Ribeiro, & Laranjeira, 2008; Guimarães, Santos, Freitas, & Araujo, 2008). Our sample had more Caucasians and older people. The difference in age is simple to understand because there is a trajectory until a user seeks treatment. Unfortunately, skin color may be a predictor of social inequalities or early death, more common among black users (Dias, Araújo, Dunn, et al., 2011; Dias, Araújo, & Laranjeira, 2011). By this token, the trajectory of drug use showed differences among sexes, and it is of importance in future preventive strategies.

These data add important evidence for maintaining that CUD manifests in a sex-specific manner. Thus, there is a rationale for specific policies aimed at this population since patients have different needs (Becker, 2016; Becker et al., 2017; Lejuez et al., 2007; Minutillo et al., 2016). Future directions in research are required

as already indicated (Becker et al., 2012; Fattore & Melis, 2016). The careful reporting of sex differences is mandatory in research on crack cocaine, even though the study does not address it. The widespread differences found here, in accordance with previous data, support that crack use has a singular impact on each sex, so interventions and policies addressing crack use likewise need to have this specificity

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Supplementary Table 1

Sex-differences in drug characteristics of crack users adjusted

	Beta	*p*	*95% CI*
Crack			
Age of first use	-0.272	<0.001[a] **	-0.36 ; -0.22
Alcohol			
Age of first use	0.078	0.005[b] **	-0.05 ; 0.34
Years of use	-0.268	<0.001[b] **	-0.36; -0.07
Tobacco			
Years of use	0.022	0.552[c] **	-0.25 ; 0.21
Cannabis			
Years of use	-0.774	0.440 [d] *	-0.94 ; -0.60
Stimulants different than cocaine/crack			
Years of use	-0.090	0.687 [e]	-0.76 ; 0.40
Sedatives			
Age of first use	-0.059	0.287 [f]	-0.61 ; 0.32
Inhalants			
Age of first use	0.112	0.034 [g] **	-0.05 ; 0.31
Other opiates than heroin			
Years of use	0.567	0.014 [h]	0.84 ; 0.07
Detoxification hospitalizations	0.027	0.564 [i]	-0.21 ; 0.14
Age of first drug use treatment	-0.053	0.085 [j] **	-0.29 ; 0.13

Note. Linear regressions using the backward model manually to compute repeatedly models until sex become the least significant predictive variable in the model were

run. The Beta value reported is the Expected (B) value for sex in the model. The p value reported is the significance level for sex in the adjusted model and the 95% CI regards the standardized 95% CI for sex, not for entire model. * the constant of the model remained significant at the last step with a $p < 0.05$. ** the constant of the model remained significant at the last step with a $p < 0.001$. [a] Adjusted model remained with three variables with stronger or equivalent prediction as compared to sex: age, ASI-6 Social Support and age of first drug use treatment. [b] Adjusted model remained with one variable with stronger or equivalent prediction as compared to sex: age. [c] Adjusted model remained with 14 variables with stronger or equivalent prediction as compared to sex: age, ethnicity; marital status; individual income; previous homeless situation in life; ASI-6 Problems with Children; Psychological Problems; Employment Problems; Physical Abuse CTQ score; any lifetime Anxiety Disorder; any lifetime PTSD and related disorder; any lifetime Substance Induced Disorder, lifetime Dysthymia and lifetime Alcohol Use Disorder. [d] Adjusted model remained with nine variables with stronger or equivalent prediction as compared to sex: age, ethnicity; education level; previous homeless situation in life; Sexual Abuse CTQ score; ASI-6 Children Problems score; number of detoxification hospitalizations; any lifetime Anxiety Disorder and current Powder Cocaine Use Disorder. [e] Adjusted model remained with 16 variables with stronger or equivalent prediction as compared to sex: age; ethnicity; individual income; ASI-6 Drugs, Medical Problems, Employment Problems, and Social Support Problems Scores; Sexual Abuse CTQ score; sexual abuse in adulthood; age of first drug use treatment; lifetime Brief Psychotic Disorder; any lifetime Anxiety Disorder; any lifetime PTSD and related disorder; any Bipolar Disorder; Major Depressive Disorder; Dysthymia and lifetime Alcohol Use Disorder. [f] Adjusted model remained with four variables

with stronger or equivalent prediction as compared to sex: age; age of first drug use treatment; lifetime Brief Psychotic Disorder and Dysthymia. [g] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: age of first drug use treatment and any lifetime Anxiety Disorder. [h] Adjusted model remained with 13 variables with stronger or equivalent prediction as compared to sex: age, education level; marital status; previous homeless situation in life; individual income; history of suicide attempt in life; ASI-6 Drugs, Children Problems and Medical Scores; age of drug use treatment; any lifetime Anxiety Disorder; lifetime PTSD and related disorder and current Powder Cocaine Use Disorder. [i] Adjusted model remained only with sex. [j] Adjusted model remained with five variables with stronger or equivalent prediction as compared to sex: age; education level; ASI-6 Drugs Score; number of detoxification hospitalizations and Dysthymia.

Supplementary Table 2

Adjusted Results for Sex-Differences in Negative life issues

	OR or *Beta*	*p* for sex	Standardized 95% *CI*
Housing issues			
Homeless in lifetime	0.826	0.407 [a]	0.52 ; 1.29
Homeless in the last 6 months	1.693	< 0.001 [b] **	1.31 ; 2.17
Homeless in last 30 days	0.921	0.733 [c]	0.57-1.47
Medical Issues			
HIV	3.214	<0.001 [d] **	2.24 ; 4.59
Other Serious Medical Condition	1.400	0.023 [e] *	1.04 ; 1.87
Different than HIV			
Employment issues			
Not formal employment	0.892	0.624 [a]*	0.56 ; 1.40
Legal Problems			
Already Arrested	0.490	<0.001 [b] **	0.35 ; 0.66
Social life			
Number of close friends	-0.108	<0.001 [f] **	-0.32 ; 0.32
Interactions in the last month			
In touch with a partner	2.166	<0.001 [g] **	1.67 ; 2.80
In touch with a sibling	0.522	<0.001 [h] **	0.39 ; 0.68
In touch with close friends	0.751	0.022 [b] **	0.58 ; 0.96
Fight with close people	0.490	<0.001 [i] **	0.38 ; 0.63
Trauma History			
Physical harassment	0.528	<0.001 [d] **	0.41 ; 0.67

Witnessed a hard crime	0.491	<0.001 [d] **	0.38 ; 0.62
Sexual harassment	6.971	<0.001 [j] **	4.73 ; 10.26
Raped as an adult	1.684	0.095 [k] *	0.91 ; 3.10
Childhood Trauma			
Sexual Abuse score	0.152	<0.001 [l] **	-0.01 ; 0.30
Sexual Abuse light cutoff	0.688	0.048 [l] *	0.47 ; 0.99
Sexual Abuse moderate cutoff	0.352	<0.001 [m] **	0.24 ; 0.50
Sexual Abuse severe cutoff	0.526	0.017 [n] *	0.31 ; 0.89
Physical Abuse score	-0.124	<0.001 [o] **	-0.22 ; -0.01
Physical Abuse light cutoff	1.625	<0.001 [p] **	1.24 ; 2.11
Physical Abuse severe cutoff	1.974	<0.001 [p] **	1.43 ; 2.71
Emotional Neglect moderate cutoff	0.486	<0.001 [q] **	0.35 ; 0.67
Emotional Neglect severe cutoff	0.402	<0.001 [p] **	0.27 ; 0.59
Suicide attempt in life	1.088	0.677 [r]	0.73 ; 1.61
Suicide attempt in last 30 days	0.754	0.203 [s] **	0.48 ; 1.16

Note. [a] Adjusted model remained with 15 variables with stronger or equivalent prediction as compared to sex: age; ethnicity; individual income; physical abuse CTQ score; number of detoxification hospitalizations; ASI-6 Drugs, Children Problems, Medical Problems, Employment Problems and Social Support Problems Scores; any lifetime PTSD and/or related Disorder; any lifetime Substance Induced Disorder; lifetime Alcohol Use Disorder; some Bipolar Disorder and Current Powder Cocaine Use Disorder. [b] Adjusted model remained only with sex. [c] Adjusted model remained with 17 variables with stronger or equivalent prediction as compared to sex: age; marital status; education level; individual income; sexual abuse CTQ score; sexual harassment in adulthood; ASI-6 Drugs, Children Problems, Medical Problems, Employment Problems

and Social Support Problems Scores; any lifetime PTSD and/or related Disorder; lifetime Alcohol Use Disorder; some Bipolar Disorder; lifetime Major Depressive Disorder and Current Powder Cocaine Use Disorder. [d] Adjusted model remained with one variables with stronger or equivalent prediction as compared to sex: ASI-6 Medical Problems Score. [e] Adjusted model remained with three variables with stronger or equivalent prediction as compared to sex: age; ASI-6 Medical Problems Score and some Bipolar Disorder. [f] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: Physical Abuse CTQ score and any lifetime PTSD and/or related Disorder. [g] Adjusted model remained with one variables with stronger or equivalent prediction as compared to sex: ASI-6 Employment Problems Score. [h] Adjusted model remained with one variables with stronger or equivalent prediction as compared to sex: ASI-6 Social Support Problems Score. [i] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: age and ASI-6 Psychological Problems Score. [j] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: sexual abuse CTQ score and ASI-6 Psychological Problems Score. [k] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: sexual abuse and physical abuse CTQ scores. [l] Adjusted model remained with six variables with stronger or equivalent prediction as compared to sex: Physical abuse CTQ score; sexual abuse in adulthood; ASI-6 Drugs and Employment Problems Score; some lifetime PTSD and/or related Disorder; current Powder Cocaine Use Disorder. [m] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: Physical abuse CTQ score and sexual abuse in adulthood. [n] Adjusted model remained with four variables with stronger or equivalent prediction as compared to sex: Physical abuse CTQ score; sexual abuse in adulthood; some lifetime PTSD and/or related Disorders; some

Substance Induced Disorder. [o] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: Sexual abuse CTQ score and ASI-6 Social Support Problems Score. [p] Adjusted model remained with one variables with stronger or equivalent prediction as compared to sex: Sexual abuse CTQ score. [q] Adjusted model remained with four variables with stronger or equivalent prediction as compared to sex: Physical abuse CTQ score; sexual abuse in adulthood; some lifetime PTSD and/or related Disorders; some Substance Induced Disorder. [r] Adjusted model remained with 12 variables with stronger or equivalent prediction as compared to sex: age; individual income; number of detoxification treatments; sexual abuse and physical abuse CTQ score; ASI-6 Children Problems and Psychological Problems Scores; some lifetime Substance Induced Disorder; lifetime Major Depression Disorder; lifetime Alcohol Use Disorder; some Bipolar Disorder; Current Powder Cocaine Disorder. [s] Adjusted model remained with five variables with stronger or equivalent prediction as compared to sex: ASI-6 Psychological Problems and Medical Problems Scores; some lifetime PTSD related Disorder; lifetime Dysthymia.

Supplementary Table 3

Differences in psychiatric comorbidities with Cocaine(crack) Use Disorders.

	Unadjusted Values		Adjusted Values		
	OR	*95% CI*	*OR*	*P for sex OR*	*95% CI*
Any Psychiatric Disorder Different than Substance Use (Current)	2.055	1.57 ; 2.28	2.055	<0.001 [a] *	1.57 ; 2.68
Any Psychiatric Disorder Different than Substance Use (Lifetime)	2.886	2.14 ; 3.87	2.886	<0.001 [a] **	2.14 ; 3.87
Substance use disorders					
Alcohol (Current)	0.377	0.29 ; 0.48	0.861	0.448 [b]	0.58 ; 1.26
Alcohol (Lifetime)	0.721	0.56 ; 0.92	0.827	0.214 [c] **	0.61 ; 1.11
Powder cocaine (Current)	1.662	1.28 ; 2.15	1.064	0.854 [d]	0.55 ; 2.05
Hallucinogens (Current)	0.553	0.445	0.288	0.008 [e] *	0.11 ; 0.72
Schizophrenia and Related Disorders					
Brief Psychotic Episode (Lifetime)	3.062	1.21 ; 7.69	2.970	0.029 [a] *	1.11 ; 7.88
Bipolar and Related Disorders					

Any Bipolar disorder	2.286	1.36 ; 3.82	2.286	0.002 [a] *	1.36 ; 3.82
Bipolar Type I	2.994	1.40 ; 6.39	2.994	0.005 [a] **	1.40 ; 6.39
Bipolar Type I in a mixed episode			6.409	0.014 [a] **	1.44 ; 28.34
Bipolar Type II in a mixed episode			4.173	0.031 [f] **	1.14 ; 15.26
Depressive Disorders					
Major Depressive Disorder (Lifetime)	1.965	1.42 ; 2.70	1.896	<0.001 [a] **	1.36 ; 2.63
Dysthymia (Lifetime)	2.689	1.29 ; 5.57	2.217	0.059 [g] **	0.97 ; 5.06
Anxiety Disorders					
Any Anxiety Disorder (Current)	1.536	1.84 ; 1.99	1.377	0.056 [h] *	0.99 ; 1.91
Any Anxiety Disorder (Lifetime)	1.718	1.33 ; 2.21	1.648	0.003 [i]	1.18 ; 2.30
Panic Disorder With Agoraphobia (Lifetime)			0.213	0.002 [j]	0.08 ; 0.55
Panic Disorder Without Agoraphobia (Lifetime)	0.360	0.14 ; 0.87	2.229	0.066 [k]	0.95 ; 5.23
Specific Phobia (Current)/(Lifetime)	2.218	1.59 ; 3.08	2.054	<0.001 [l]	1.45 ; 2.90
Trauma and Stress-Related Disorders					
Any Trauma and/or Stress-Related Disorder (Current)	3.995	2.57 ; 6.18	3.112	<0.001 [m] **	1.91 ; 5.05

Any Trauma and/or Stress-Related Disorder (Lifetime)	3.206	2.22 ; 4.61	3.000	<0.001 [n] **	1.96 ; 4.57
Post-Traumatic Stress Disorder (Current)	4.054	2.60 ; 6.32	3.145	<0.001 [m] **	1.92 ; 5.14
Post-Traumatic Stress Disorder (Lifetime)	3.220	2.22 ; 4.65	2.813	<0.001 [m] **	1.85 ; 4.26
Obsessive-Compulsive Disorders					
Obsessive-Compulsive Disorder (Lifetime)	1.928	1.31 ; 2.82	1.558	0.029 [o]	1.04 ; 2.32
Substance-Induced Disorders					
Mood-Induced Disorders (Lifetime)	0.603	0.45 ; 0.79	0.578	<0.001 [p]	0.43 ; 0.77
Anxiety-Induced Disorders (Lifetime)	1.664	1.07 ; 2.57	1.646	0.029 [q]	1.05 ; 2.57

Note. *ORs* and *95% CI* of unadjusted significant variables reported in the Figure 1 are reported as Unadjusted Values. Adjustments were computed with logistic regressions using the backward model manually to compute repeatedly models until sex become the least significant predictive variable in the model were run. The OR for sex in the model was extracted and is shown in the Adjusted OR. The p value reported in Adjusted Values refers to the significance level for sex in the adjusted model and the 95% CI regards the 95% CI for sex, not for entire model. * the constant of the model remained significant at the last step with a $p < 0.05$. ** the constant of the model remained significant at the last step with a $p < 0.001$. [a] Adjusted model remained only with sex. [b] Adjusted model remained with 10 variables with stronger or equivalent prediction as compared to

sex: age; education level; ethnicity; ASI-6 Medical Problems and Family Social Support Scores, Sexual Abuse and Physical Abuse CTQ scores; previous homeless situation in life; any lifetime Substance Induced Disorder; and Current Powder Cocaine Use Disorder.[c] Adjusted model remained with seven variables with stronger or equivalent prediction as compared to sex: age; ethnicity; ASI-6 Psychological Problems and Medical Problems Scores; any Bipolar Disorder and current Powder Cocaine Use Disorder. [d] Adjusted model remained with eleven variables with stronger or equivalent prediction as compared to sex: age; ethnicity; education level; physical abuse CTQ score; sexual harassment in adulthood; lifetime Major Depressive Disorder; any lifetime Anxiety Disorder; current Obsessive Compulsive Disorder; any lifetime Substance Induced Disorder; lifetime Alcohol Use Disorder; age of first cannabis use. [e] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: sexual abuse CTQ score and ASI-6 Drugs score. [f] Adjusted model remained with one variables with stronger or equivalent prediction as compared to sex: ASI-6 Psychological Problems Score. [g] Adjusted model remained with five variables with stronger or equivalent prediction as compared to sex: ASI-6 Psychological Problems Score; age of first drug use treatment; lifetime Major depressive Disorder; any lifetime Trauma and/or Stress Disorder and current Powder Cocaine Use Disorder. [h] Adjusted model remained with five variables with stronger or equivalent prediction as compared to sex: number of detoxification hospitalizations; age of first drug use treatment; any lifetime Trauma and/or Stress Disorder; current Obsessive Compulsive Disorder and lifetime Major Depressive Disorder. [i] Adjusted model remained

with five variables with stronger or equivalent prediction as compared to sex: number of detoxification hospitalizations; age of first drug use treatment; ASI-6 Drugs Score; any lifetime Trauma and/or Stress Disorder and current Obsessive Compulsive Disorder. [j] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: any lifetime Trauma and/or Stress Disorder and any Bipolar Disorder. [k] Adjusted model remained with four variables with stronger or equivalent prediction as compared to sex: ASI-6 Medical Problems Score; lifetime Brief Psychotic Episode; lifetime Major Depressive Disorder and lifetime Dysthymia. [l] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: any lifetime Trauma and/or Stress Disorder and current Obsessive Compulsive Disorder. [m] Adjusted model remained with three variables with stronger or equivalent prediction as compared to sex: sexual abuse CTQ Score; ASI-6 Psychological Problems and any lifetime Anxiety Disorder. [n] Adjusted model remained with four variables with stronger or equivalent prediction as compared to sex: sexual abuse CTQ Score; ASI-6 Psychological Problems; any lifetime Anxiety Disorder and current Obsessive Compulsive Disorder. [o] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: any lifetime Anxiety Disorder and any Bipolar Disorder. [p] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: ASI-6 Drugs Score and any lifetime Trauma and/or Stress Disorder. [q] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: any lifetime Trauma and/or Stress Disorder and lifetime Major Depression.

Supplementary Table 4

ASI-6 Composite Scores Unadjusted and Adjusted

	Men		Women		Statistics						
					Unadjusted Values					Adjusted Values	
	n	*M (SD)*	*n*	*M (SD)*	*U*	*p*	*Corrected p value*	*Effect size*	*Beta*	*p*	*95% CI*
ASI-6 Scores											
Drugs	653	52.42 (5.56)	495	54.88 (5.97)	201.95	< 0.001	< 0.001	0.214 [a]	0.208	<0.001[c]	0.12; 0.34
Alcohol	653	51.01 (10.67)	495	48.48 (9.02)	142.10	< 0.001	< 0.001	0.104 [b]	-0.187	<0.00l [d] **	-0.08; -0.25
Children	615	51.01 (9.02)	447	59.59 (10.64)	190.83	< 0.001	< 0.001	0.381 [a]	0.321	<0.001 [e] **	0.27 ; 0.40
Problems											
Psychological	643	49.10 (10.92)	493	51.95 (8.12)	197.09	< 0.001	< 0.001	0.209 [b]	0.007	0.782 [f] **	- 0.12 ; 0.16
Problems											

Medical Problems	653	47.97 (9.26)	492	50.67 (9.02)	189.52	< 0.001	< 0.001	0.154 [a]	-0.057	0.158 [g]	-0.23 ; 0.14
Legal Problems	653	50.72 (7.35)	491	52.65 (7.30)	185.28	< 0.001	< 0.001	0.150 [a]	- 0.104	<0.001 [h] **	-0.15 : 0.12
Employment problems	653	35.96 (6.23)	495	39.25 (4.18)	213.90	< 0.001	< 0.001	0.287 [b]	0.297	<0.001 [i] **	0.16 ; 0.42
Social Support Problems	633	38.12 (8.44)	489	41.02 (8.65)	183.68	< 0.001	< 0.001	0.161 [a]	0.146	<0.001 [j]	0.06 ; 0.28
Social Problems	633	55.68 (9.49)	491	54.92 (8.94)	147.55	0.145	0.221	0.043	-	-	-

Note. As all data were non-parametric we used Mann-Whitney. Corrected p value is also shown and the effect size is presented in *r* equivalent to Cohen's *d*. For adjusted values, linear regressions using the backward model manually to compute repeatedly models until sex become the least significant predictive variable in the model were run. The Beta value reported is the Expected (B) value for sex in the model. The p value reported is the significance level for sex in the adjusted model and the 95% CI regards the standardized 95% CI for sex, not for entire model. * the constant of the model remained significant at the last step with a $p < 0.05$. ** the constant of the model remained significant at the last step with a $p <$

0.001. [a] medium effect size. [b] small effect size. [c]Adjusted model remained with five variables with stronger or equivalent prediction as compared to sex: age, ASI-6 Psychological Problems and Medical Problems; previous homeless situation in life and current Powder Cocaine Use Disorder. [d] Adjusted model remained with one variable with stronger or equivalent prediction as compared to sex: age. [e] Adjusted model remained only with sex. [f] Adjusted model remained with six variables with stronger or equivalent prediction as compared to sex: education level; ASI-6 Drugs, Children Problems and Medical Problems Scores; lifetime Alcohol Use Disorder and history of suicide attempt in life [g] Adjusted model remained with 11 variables with stronger or equivalent prediction as compared to sex: age; education level; sexual abuse CTQ score; previous homeless situation in life; ASI-6 Drugs, Children Problems, Psychological Problems and Social Support Problems Scores; current OCD; any anxiety disorder lifetime and lifetime Alcohol Use Disorders. [h] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: ASI-6 Drugs and Alcohol scores. [i] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: individual income and previous homeless situation in life. [j] Adjusted model remained with two variables with stronger or equivalent prediction as compared to sex: ASI-6 Medical Problems Score and previous homeless situation in life.

Supplementary Table 5

ASI-6 Composite Scores

	Men		Women		Statistics			
	n	*M (SD)*	*n*	*M (SD)*	*U*	*p*	Corrected *p* value	*Effect size*
ASI-6 Scores								
Drugs	653	52.42 (5.56)	495	54.88 (5.97)	201.95	< 0.001	< 0.001	0.214 [b]
Alcohol	653	51.01 (10.67)	495	48.48 (9.02)	142.10	< 0.001	< 0.001	0.104 [a]
Children Problems	615	51.01 (9.02)	447	59.59 (10.64)	190.83	< 0.001	< 0.001	0.381 [b]
Psychological Problems	643	49.10 (10.92)	493	51.95 (8.12)	197.09	< 0.001	< 0.001	0.209 [b]
Medical Problems	653	47.97 (9.26)	492	50.67 (9.02)	189.52	< 0.001	< 0.001	0.154 [a]
Legal Problems	653	50.72 (7.35)	491	52.65 (7.30)	185.28	< 0.001	< 0.001	0.150 [a]
Employment problems	653	35.96 (6.23)	495	39.25 (4.18)	213.90	< 0.001	< 0.001	0.287 [b]
Social Support Problems	633	38.12 (8.44)	489	41.02 (8.65)	183.68	< 0.001	< 0.001	0.161[a]
Social Problems	633	55.68 (9.49)	491	54.92 (8.94)	147.55	0.145	0.221	0.043

Note. As all data were non-parametric we used Mann-Whitney. Corrected p value is also shown and the effect size is presented in *r* equivalent to Cohen's *d*. [a] small effect size. [b] medium effect size. [c] large effect size.

CHAPTER 5

Sex Differences in Intrinsic Brain Connectivity in Crack Cocaine Users

Breno Sanvicente-Vieira, Pedro Eugênio Ferreira, Nathalia Bianchini Esper, Leonardo Rothmann, Alexandre Rosa Franco, Rodrigo Grassi-Oliveira

Abstract

Crack cocaine use disorder exhibits sex differences in the course of the disease. As this is a brain disorder that involves changes in intrinsic brain connectivity, we investigated the existence of sex differences among crack cocaine users in this regard. We used a data-driven method in which 20 male crack cocaine users (CK-M) and 20 female crack cocaine users (CK-F), in addition to 20 healthy male controls (HC-M) and 20 healthy female controls (HC-F), undertook a resting-state functional magnetic resonance imaging exam (rs-fMRI). Investigating the functional connectivity (FC), an initial comparison on regional homogeneity (ReHo) identified areas with sex differences within CK groups. Areas of peak-activation differences become seeds in a seed-based method for investigating whole-brain FC. We compared the CK groups to themselves and to their respective-sex control groups. The CK-M showed higher ReHo than did CK-F for eight brain areas in various cortical networks, the paralimbic system, and the bilateral claustrum. For most seeds in seed-based FC, a similar pattern indicated that male CK-M had higher inter- and intra-network FC than did CK-F. Some such differences indicated that, in comparison to the respective-sex control groups, CK-M had higher FC, and CK-F had lower FC. The results also suggested that crack cocaine promotes changes in opposite directions for men and women. The contrasting FCs within the networks related to inhibition, multimodal information processing, and emotional response indicate that crack cocaine has sex-specific consequences in brain functioning – and consequently, in everyday functioning. Thus, there is a support for considering crack cocaine use disorder as two distinct brain disorders for males and females; it thus may require sex-specific interventions and in-depth investigation for each condition.

Keywords: cocaine, intrinsic brain connectivity, sex differences; substance use and related disorders; rs-fMRI.

Sex Differences in Intrinsic Brain Connectivity in Crack Cocaine Users

Crack cocaine use disorder (CUD) is a chronic, relapsing brain disorder (Dackis & O'Brien, 2001; Koob & Volkow, 2010; Volkow, Koob, & McLellan, 2016). The neurobiological changes that occur due to drug use (Lucantonio, Stalnaker, Shaham, Niv, & Schoenbaum, 2012; Nestler, 2004, 2005) include molecular (Corominas-Roso et al., 2012) and gene-expression (Bannon et al., 2014) differences, accelerated brain atrophy (Ersche, Jones, Williams, Robbins, & Bullmore, 2012), cellular senescence (Levandowski et al., 2016), and cognitive decline (Sanvicente-Vieira, Kommers-Molina, De Nardi, Francke, & Grassi-Oliveira, 2016), according to comparisons with healthy control groups (HCs). In addition, crack cocaine users, in comparison to HCs, have shown altered brain activity in cognitive and emotional tasks (Prisciandaro, McRae-Clark, Myrick, Henderson, & Brady, 2014; Verdejo-Garcia et al., 2014). These changes are reflected in decision-making (Cunha, Bechara, de Andrade, & Nicastri, 2011; Kluwe-Schiavon, Viola, Sanvicente-Vieira, Pezzi, & Grassi-Oliveira, 2016) and in social (Kemmis, Hall, Kingston, & Morgan, 2007; Sanvicente-Vieira, Kluwe-Schiavon, Corcoran, & Grassi-Oliveira, 2017) and emotional (Back et al., 2010; Hulka, Preller, Vonmoos, Broicher, & Quednow, 2013) processing, which are impairments that result in clinical (Falck, Wang, Siegal, & Carlson, 2004), legal (Shannon et al., 2008), psychological (Chaplin et al., 2010; el-Bassel et al., 1996), and professional issues (Dias, Ribeiro, Dunn, Sesso, & Laranjeira, 2008; Najavits & Lester, 2008) in everyday life. However, CUD outcomes are mediated and modulated by individual characteristics, including medical concurrences (e.g., HIV, Dias et al., 2011; Keutmann et al., 2017; Meyer et al., 2014), psychiatric disorders (Gossop, Manning, & Ridge, 2006), past experiences (e.g., childhood maltreatment, Francke, Viola, Tractenberg, & Grassi-Oliveira, 2013), and genetic factors (Rovaris et al., 2017). Among individual differences, sex has been an increasing priority for research because the data

has supported several sex differences in addictive disorders (Becker, 2016; Becker, McClellan, & Reed, 2016; Becker, McClellan, & Reed, 2017; Becker, Perry, & Westenbroek, 2012; Bobzean, DeNobrega, & Perrotti, 2014; Fattore & Melis, 2016).

It has been shown that males are at least 4.4 times more likely than females to use crack cocaine in the last 12 months (Abdalla et al., 2014). On the other hand, negative outcomes are more severe in female crack cocaine users than in male crack cocaine users (Bertoni et al., 2014; Elman, Karlsgodt, & Gastfriend, 2001; Falck et al., 2004; Keutmann et al., 2017; Lejuez, Bornovalova, Reynolds, Daughters, & Curtin, 2007; Najavits & Lester, 2008; Vernaglia, Vieira, & Cruz, 2015; Vernaglia et al., 2017; Wagner & Anthony, 2007), including higher-intensity subjective cravings (Elman et al., 2001), higher drug consumption (Bertoni et al., 2014), and stronger comorbidities (Falck et al., 2004). In addition, males are less likely to be victims of violence (odds ratio = 0.48, indicating that to be a male is more relative to protect than being female). Females also escalate faster from recreational to pathological crack cocaine use (Vsevolozhskaya & Anthony, 2016), an effect known as the *telescoping effect* (Haas & Peters, 2000; Piazza, Vrbka, & Yeager, 1989). Initial theories on this subject suggested that these sex differences were supported by sex hormones, as menstrual-cycle phases, cue-reactivity (Back et al., 2010; H. C. Fox, Sofuoglu, Morgan, Tuit, & Sinha, 2013; Swalve, Smethells, Zlebnik, & Carroll, 2016), and drug-seeking behaviors (Doncheck et al., 2017; Fox et al., 2013; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Swalve et al., 2016) show oscillations. Moreover, acute crack cocaine use also modulates physical (Fox, Jackson, & Sinha, 2009; Fox & Sinha, 2009) and psychological responses (Evans, 2007; Fox et al., 2013). Indeed, hormones influence the stress system in specific ways (Bobzean et al., 2014; Merz & Wolf, 2017). The stress and reward circuits overlap within mesocorticolimbic (MCL) brain areas and are hyperactive in crack cocaine users

(compared to healthy controls), according to cognitive and stress experiments using functional magnetic resonance imaging (fMRI) (Childress et al., 1999; Li, Kosten, & Sinha, 2005; McHugh et al., 2014; Potenza et al., 2012; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011). The MCL brain pathway has shown sex differences in crack cocaine users; females show increased activation within this area under stress, and males show increased activation under drug cueing (Li et al., 2005; Potenza et al., 2012). Compared to drug cueing, distress is a stronger trigger for craving and drug-seeking behaviors such as motor urgency (Back et al., 2010; Sinha et al., 2006; Waldrop et al., 2010). Thus, stress predicts earlier relapses (Sinha et al., 2006), which is in line with the increased vulnerability showed by female crack cocaine users (Fox et al., 2013; Potenza et al., 2012; Tull, McDermott, Gratz, Coffey, & Lejuez, 2011; Waldrop et al., 2010).

Even in nondemanding conditions such as in a resting-state fMRI (rs-fMRI), crack cocaine users have MCL hyperactivity, which supports the assumption that this is a trait characteristic in crack cocaine users (Contreras-Rodríguez et al., 2016; Konova, Moeller, Tomasi, Volkow, & Goldstein, 2013; Ray, Di, & Biswal, 2016). The rs-fMRI method is innovative and promising because it eliminates or reduces many of the limitations involved in task-evoked methods (Fox & Greicius, 2010; Koob & Le Moal, 2008; Majewska, 1996; Robinson & Berridge, 1993) and because it allows for investigations of intrinsic brain connectivity through the acquisition of the blood-oxygen-level-dependent (BOLD) data in an fMRI session without using an evoked task (Biswal, Yetkin, Haughton, & Hyde, 1995; Biswal, Van Kylen, & Hyde, 1997). The rs-fMRI data for crack cocaine users provide supporting evidence that the limbic system is engaged with widespread cortical areas, including the default mode network (DMN, Damoiseaux et al., 2006; Greicius, Supekar, Menon, & Dougherty, 2009), which is related to autobiographical memory, social cognition, consciousness, and awareness (Greicius et al., 2009; Spreng, Mar, & Kim, 2009).

Hence, changes in intrinsic brain connectivity may be more strongly coupled with emotional and reward processing in crack cocaine users than in healthy controls (Sutherland, McHugh, Pariyadath, & Stein, 2012).

Crack cocaine users exhibit increased functional connectivity (FC) in MCL pathways, which also include areas within other networks that are related particularly to inhibition and to multimodal information integration, such as the fronto-parietal network (FPN), the sensory-motor network (SMN), the dorsal attention network (DAN), and the salience network (SN) (Childress et al., 1999; Li et al., 2005; McHugh et al., 2014; Potenza et al., 2012; Wilcox et al., 2011) – although there are contrasting reports (Gu et al., 2010; Kelly et al., 2011). One hypothesis is that large-scale inter-networks, which have increased FC across competing networks, are susceptible to the exaggerated responses of some nodes (Contreras-Rodríguez et al., 2016). Repetitive excitatory activity rewards related brain areas (e.g., the MCL pathways), which become over-responsive; this is consistent with stress- and cue-induced studies (Li et al., 2005; Potenza et al., 2012; Sinha et al., 2006). In accordance with these findings, sensitization theories (Robinson & Berridge, 1993) hold that overexcitability and conditioning are continuously active, causing emotionally driven networks to suppress emotionally inhibitory ones due to overlapping functioning and thus leading to incentives for drug-seeking behavior (Barrós-Loscertales et al., 2011; Contreras-Rodríguez et al., 2016; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Thus, in decision-making scenarios, the SN probably experiences over-activation, which causes bias in information processing in favor of reward-related memories and stimuli (Parkes & Balleine, 2013). However, during the various drug use phases, intrinsic brain connectivity can show fluctuations. Recent cocaine use (<3 days) causes lower interhemispheric FC in the FPN (McHugh et al., 2014; McHugh, Gu, Yang, Adinoff, & Stein, 2017) in crack cocaine users when compared to the results for healthy controls. Strong

FC in the MCL pathway and the intra-network FPN predict earlier relapses, the former negatively (McHugh et al., 2014) and the latter positively (McHugh et al., 2017). Along these lines, continued inhibition demand relates to reduced inhibitory activity in the FPN (Barrós-Loscertales et al., 2011). Studies of nicotine dependence have addressed sex differences in addictive disorders using rs-fMRI. Their results indicated that females have stronger overall network coupling when at rest (Wetherill, Jagannathan, Shin, & Franklin, 2014).

In healthy controls, sex differences in rs-fMRI are not consistent, but most data indicate that females have higher FPN intra-network FC than males (Hjelmervik, Hausmann, Osnes, Westerhausen, & Specht, 2014). For females, FPN also increases inter-network FC in addition to intra-network SMN FC (Allen et al., 2011), although there are contrasting results (Filippi et al., 2013). Moreover, there is some support for sex differences in functional lateralization, with males predominantly recruiting the right hemisphere (Tomasi & Volkow, 2012). Both phenotypic sex and sex hormones influence rs-fMRI results. During the menstrual cycle, cognitive networks in the frontal areas show increased inter-network FC, which also occurs in SMN but which is less pronounced in DMN (Weis, Hodgetts, & Hausmann, 2017), although, again, there is conflicting data (Hjelmervik et al., 2014). Sex and mental disorders are not the only factors that have specific effects in rs-fMRI. Individual characteristics can have sex-specific effects on rs-fMRI, including sexual preferences (Hu et al., 2014), subclinical symptoms (e.g., depressive symptoms, Wang, Hermens, Hickie, & Lagopoulos, 2012), and childhood maltreatment (Philip et al., 2014). Due to this, studies have provided data for specific effects among drug users (Dean, Kohno, Hellemann, & London, 2014), including crack cocaine (Gawrysiak et al., 2017).

The objective of this work was to explore sex differences among crack cocaine users in terms of intrinsic brain connectivity. The main hypothesis was that users had sex differences. As

the current literature shows, the negative outcomes are worse in females than in males, so we expected the increases in FC within MCL brain areas to be higher in female crack cocaine users. In addition, we hypothesized that some of these sex differences would represent changes from the healthy control groups. Given the indications that crack cocaine users have increased FC in MCL pathways and networks, we presumed that the same effect would be predominant across crack cocaine user groups in comparison to their respective-sex HC. A secondary objective related to the exploratory investigation of differential associations between changes in intrinsic brain activity and some core variables: years of crack cocaine use, abstinence symptoms, and drug use severity. We expected some associations to be in opposite directions for men and women and for others to be the same. We hoped to conclude that sex-specific changes in rs-fMRI would have different weights in the CUD progression.

Methods

Participants

Eighty participants took part in this cross-sectional study – a group of 40 crack cocaine users (CK) and a 40 HC. We recruited the CK participants from public drug-treatment facilities in the local area. During hospitalization, they followed a crack cocaine detoxification protocol. As inpatients, they were in an abstinence-controlled situation with no access to any kind of drugs, including alcohol and cigarettes. We recruited voluntary HC participants from the community through local advertisements. Two CK groups comprised the clinical group: a male group (CK-M, n = 20) and a female group (CK-F, n = 20). As reference groups, we also had male (HC-M, n = 20) and female (HC-F, n = 20) HC groups.

For inclusion, all participants had to (a) be right-handed, (b) self-declare as being of low or middle socioeconomic status, (c) be 18-50 years old, (d) have completed at least middle school

(>8 years of formal education) in Brazil, and (e) have an IQ > 80. Additionally, (f) the CK participants should have tested positive for cocaine in a urine screening test during the first three days of hospitalization (indicating that there had been less than one week since their last cocaine consumption). They also (g) should have a primary mental-disorder diagnosis of CUD, and (h) their preferred means of cocaine consumption should be by smoking a rock (i.e., crack), as the route of use is related to differential consequences (Kiluk, Babuscio, Nich, & Carroll, 2013), which are particularly modulated by sex-hormones (Evans & Foltin, 2006). Aside from restrictions related to MRI procedures, the exclusion criteria included the presence of neurologic disorders, HIV, or syphilis. For the last two, the participants took a fast-track blood exam. For the CK groups, concurrent severe mental disorders were also an exclusion criterion; we accepted only patients who had depressive and anxiety disorders, who lacked severe symptoms or other substance use disorders, and for whom crack cocaine was the first-choice drug. For the HC groups, the exclusion criteria also included any mental disorder aside from tobacco use disorders. The HC participants should not have used any prescribed psychiatric medications in the last six months and should not have drunk alcohol in the week prior the exam. All participants should have tested negative for cocaine, cannabis, amphetamines, opioids, and benzodiazepines in a urine screening on the day of the MRI exam. The ethics committees from the institutions involved in the study approved this work, and all participants gave informed consent before beginning the procedures.

The recruitment and sample composition followed some important steps. This study stemmed from a larger, unpublished work that investigated externalization symptoms among male crack cocaine users. Thus, the initial CK-M sample comprised 40 participants. Based on their clinical profiles and the study's matching objectives, we recruited the CK-F and HC groups. Due to problems with acquisition (e.g., excessive motion and claustrophobia), we scanned 23 CK-F

participants, 22 male HCs and 21 female HCs. Among the 40 CK-M participants, three had excessive motion during the exam, so we excluded them as well. For the remaining 37, based on IQ, age, and years of education, we chose the CK-M participants who best matched the members of the other groups.

Measures

Presence/absence of mental disorders, including the confirmation of CUD for CK groups and exclusions were assessed by *The Structured Clinical Interview for DSM-IV Axis I Disorders* (SCID-V, First, Williams, Karg, & Spitzer, 2015). IQ was assessed with the *Wechsler Abbreviated Scale of Intelligence-II* (WASI-II), which gives an IQ score in two areas: vocabulary and matrices (Wechsler, 2011). Because even subclinical symptoms can impact and bias intrinsic brain connectivity (Wang et al., 2012), on the day of the fMRI exam, we assessed depressive symptoms using a self-assessment measure – the Beck Depression Inventory-II (BDI-II, Beck, Steer, Ball, & Ranieri, 1996). We investigated symptoms related to crack cocaine abstinence with the Cocaine Selective Scale Assessment (CSSA, Kampman et al., 1998) which considers various symptoms related to abstinence of at least 24 hours. It uses a 0-7 visual analog scale, and the sum of all items are used to compute a total score. Participants took the CSSA on the day of the MRI exam.

All participants also completed an interview regarding other medical conditions and sociodemographic characteristics. To better characterize the CK sample and to investigate the severity of drug use, the participants completed the Addiction Severity Index (ASI-6), which is an interview that evaluates drug use and the related negative psychosocial outcomes. The ASI-6 allows for the computation of composite scores of negative impact in nine domains: drugs, alcohol, family/children, psychiatric symptoms, medical issues, legal problems, employment, social support, and social problems. Higher scores mean more severe problems (Cacciola, Alterman,

Habing, & McLellan, 2011; Kessler et al., 2012; McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006).

We also assessed childhood maltreatment history with the Childhood Trauma Questionnaire (CTQ, Bernstein et al., 2003), as childhood maltreatment is documented to have sex-dependent effects on cocaine users (Scheidell et al., 2017). The CTQ is a self-answered 5-point Likert-type questionnaire with 28 items and is used to evaluate the severity of negative life experiences. The results include a global score and subscores for various types of maltreatment. Standard cutoffs can be used to classification the presence or absence of each type of maltreatment (Grassi-Oliveira et al., 2014).

Procedures

As soon as each crack cocaine user entered the drug-treatment facility and fulfilled the inclusion criteria, we invited him or her to participate in the study. After one week of hospitalization, professional psychiatrists interviewed each participant using the SCID-V, and psychologists gave them the WASI subtests to test their IQs; on the day of the cognitive assessment, medications were suspended for 24 hours. Participants also answered the ASI-6 during the second week of hospitalization and underwent an MRI exam between the eighth and 15th day of hospitalization.

The HCs were invited to participate once they expressed voluntary interest and fulfilled the inclusion criteria. Afterward, we scheduled two assessment sessions for each prior to the exam. In each ~1-hour session, the participants answered the same questions that the CKs did. We scheduled the MRI exams after finishing all these assessments.

On the day of their MRI exams, all participants had to test negative for drugs in a urine screening. Moreover, the participants had to answer the BDI-II questions. The CK participants

also completed the CSSA. For the CK participants, all psychiatric medications were suspended for 36 hours prior to the exam.

Imaging data acquisition. Data were collected on a GE HDxt 3T scanner using an eight-channel radio-frequency head coil. At the beginning of the scanning session, a single, high-resolution T1-weighted anatomic image was collected (echo time = 2.18 ms; repetition time = 6.1 ms; flip angle = 11°; number of excitations = 1; slice thickness = 1 mm; field of view = 256 mm; resolution = 256 × 256). The rs-fMRI exams were conducted while participants held still and looked at a white cross centered on a black screen; participants were instructed to try not to think about anything. As a result, 210 echo-planar images were acquired using a single-shot, gradient-echo planar-pulse sequence (echo time = 30 ms; repetition time = 2000 ms; flip angle = 90°; field of view = 240 mm; matrix size = 64 × 64). Twenty-nine interleaved, sagittal, 4.4-mm thick slices were selected to provide whole-brain coverage (at a plane resolution of 3.75×3.75 mm^2). The first three volumes were subsequently eliminated to account for T1 equilibrium effects, leaving 207 images.

Preprocessing of the fMRI data. All preprocessing and statistical analyses were carried out using the Analysis of Functional NeuroImages (Cox, 1996) toolbox. The preprocessing was performed using the afni_proc.py function, which includes slice-time and motion corrections (Sladky et al., 2011). The motion-corrected fMRI images were coregistered with the individual anatomical images (T1) (Ashburner & Friston, 1997). The T1 images were segmented into gray matter, white matter, and cerebrospinal fluid; they were then spatially normalized using a nonlinear registration to a standard space (the MNI152 template) (Ashburner & Friston, 2005). Using the same registration parameters as used for the T1 images, the fMRI images were registered to the MNI152 space and then smoothed using a 6-mm FWHM Gaussian filter. Censoring was performed

on all time points that had motion of more than 0.3 mm. Nuisance regression was performed using the average time-sequence signal of the white matter and cerebrospinal fluid, as well as with the six motion parameters (Jo, Saad, Simmons, Milbury, & Cox, 2010). Residuals were then used to calculate the FC measures.

Data analysis

Group characteristics. Analyses of variance (ANOVAs) in a 2 × 2 design compared groups for sociodemographic, childhood maltreatment, and depression factors. For the CK-M and CK-F groups, the drug use characteristics and abstinence were computed using independent two-sample t-tests.

Motion. We used a one-way ANOVA to assess the differences in average head motion between the groups. We used this analysis method because the main differences in our objectives were those between CK-Ms and CK-Fs. Secondarily, in the case of significant differences, we investigated specific group-by-group differences for further control.

Regional homogeneity. To investigate crack-use and sex differences in intrinsic brain connectivity, we combined two methods. First, we aimed to select seed areas with group differences in regional homogeneity (ReHo), which assesses the synchrony in BOLD fluctuations within clusters of voxels (Liu et al., 2010). We calculated ReHo for each subject using a 27-voxel neighborhood. We computed a 2 × 2 (Group × Sex) ANCOVA with 3dMVM (Chen, Adleman, Saad, Leibenluft, & Cox, 2014) for comparing ReHo across groups. Based on the comparisons of sample characteristics, we included depressive symptoms (from BDI-II scores) and childhood maltreatment (from CTQ total scores) as covariates due to their significant group differences. We investigated specific effects through post hoc two-sample t-tests with depressive symptoms and childhood trauma as covariates.

Seed-based FC. The second step consisted in the investigation of differences in FC. We used a seed-based method to investigate sex differences in the seed-based FC. We extracted the time-series fluctuations of the BOLD signal within the seed (also called the region of interest; ROI) during the rs-fMRI. We then created a connectivity map by calculating the correlation between the seed's time-series and that of all the brain's voxels (Biswal et al., 1997). Subsequently, we transformed the r-score into z using Fisher's method for creating FC maps. Although seed-based FC is a well-accepted method, it is limited by the arbitrary seed selection. As the method is exploratory *per se*, inconsistent determination of seeds could bias the results and reduce their relevance for the conditions investigated (Cole, Smith, & Beckmann, 2010). To cope with this problem, we used a data-driven method in which we defined the seeds based on an a priori analysis (Tomasi & Volkow, 2011; Yan et al., 2013). Thus, we defined the seeds based on the peak differences in connectivity relative to the ReHo statistical analysis and created them with a 6-mm radius (Yan et al., 2013).

Because our aim was to investigate sex differences among crack cocaine users, we defined as the seeds those areas with significant differences between CK-M and CK-F in the post hoc analyses (MNI152 coordinates for the eight seeds were defined after ReHo analyses, for this reason). We kept the HC groups in the analyses as reference groups so as to identify possible deviations in the CK groups relative to their sex-matched HC groups. We created connectivity maps for each seed and compared all groups using ANCOVAs, with the four groups as factors. Further post hoc tests explored specific group differences, in which we focused mainly on contrast between sexes among CK groups and secondarily on the contrasts between users and controls for each sex. For all this analysis, we assumed a voxel threshold of $p < 0.001$ and used multiple-comparison corrections for an *alpha* value of 0.05, as defined by 3dClustSim (Cox, Chen, Glen,

Reynolds, & Taylor, 2017). We also included average head motion as a covariate within the group analyses.

Correlation analyses. We used Pearson correlations to explore the influence of brain FC changes through the course of drug use. These correlations included the Fisher z-transformed FC values, which we placed in clusters that showed significant differences among groups; we also selected variables related to CUD (years of cocaine use, abstinence symptoms, and severity of drug use).

Results

Sample characteristics

Demographic and clinical characteristics are shown in Table 1. Across the four groups, only two measures had significant differences: the CTQ and BDI-II scores, both of which showed a main group effect. The CK groups had more severe histories of childhood maltreatment and more depressive symptoms than did the sex-matched HC groups. Due to these differences, we included BDI-II and CTQ scores as covariates in all comparative analyses of brain functioning. Regular tobacco use was also more common among the CK groups than among the HC groups, which was as expected.

Table 1

Sample Characteristics.

	CK-M (n=20)		CK-F (n=20)		HC-M (n=20)		HC-F (n=20)		Statistics	*p*
	M/n	*SD/%*	*M/n*	*SD/%*	*M/n*	*SD/%*	*M/n*	*SD/%*		
Sociodemographic										
Age (years)	30.90	6.41	33.6	6.81	31.20	8.69	30.20	5.66	F (2, 77)=0.894	0.448
Income ($)	770.96	281.78	700.80	264.12	851.61	394.57	802.58	362.96	F (2, 77) = 1.102	0.338
Years of study	9.85	2.36	9.85	2.51	10.25	1.80	10.00	2.12	H (3, 77) = 2.144	0.543
Ethnicity (white/n, %)	13	65	10	50	13	65	9	45	r = 2.590	0.459
IQ	97.60	7.37	95.25	8.69	99.20	8.27	98.85	7.40	F (2,77) = 1.367	0.261
CTQ score	45.45	18.28	47.20	16.21	32.45	9.25	34.25	10.60	F (2, 77) = 9.951[a]	<0.001
Psychiatric										
Depressive symptoms	10.05	5.61	11.90	8.16	7.20	6.80	6.70	5.40	F (2,77) = 3.925[b]	0.024
No comorbidity (n, %)	10	50	8	40	-	-	-	-	r = 0.404	0.751
Depressive disorders	5	25	3	15	-	-	-	-	r = 0.625	0.695
Anxiety disorders	5	25	5	25	-	-	-	-	r =0.000	1.000

ASI-6 Scores										
Drugs	50.05	5.67	52.95	4.08	-	-	-	-	*t* (2, 38) = -1.854	0.072
Alcohol	49.40	8.78	50.20	7.98	-	-	-	-	*t* (2, 38) = -0.301	0.765
Family/Child	54.05	10.17	52.85	9.11	-	-	-	-	*U* = 198.50	0.957
Psychiatric	52.05	7.91	48.35	7.37	-	-	-	-	*t* (2, 38) = 1.530	0.134
Medical	38.60	4.79	42.42	7.87	-	-	-	-	*t* (2, 38) = - 1.843	0.75
Legal	53.15	7.03	49.00	5.48	-	-	-	-	*U* = 135.00	0.047
Employment	39.30	3.13	39.75	3.07	-	-	-	-	*U* = 218.50	0.601
Family Social Support	40.55	8.98	51.60	13.47	-	-	-	-	*t* (2, 38) = - 3.051	0.004
Family Social Problem	50.65	6.27	50.90	11.21	-	-	-	-	*t* (2, 38) = -0.087	0.931
CSSA										
Cocaine/crack abstinence symptoms (CSSA score)	15.80	8.12	23.35	8.38	-	-	-	-	*t* (2, 38) = -2.892	0.006
Drug Use										
Characteristics										
Regular smoker (n, %)	14	70	18	90	9	45	8	40	$r = 13.641^{c}$	0.003

Age of first Alcohol Use	13.45	2.52	14.40	1.87	-	-	-	t (2, 38) = -1.352	0.185
Years of regular alcohol use (19/12)[d]	6.42	6.92	6.23	9.103	-	-	-	U = 95.500	0.459
Age of first cannabis use (20/19) [d]	13.95	2.50	14.89	1.41	-	-	-	t (2, 37)= - 1.442	0.154
Years of regular cannabis use (19/11) [d]	9.79	7.78	12.09	3.96	-	-	-	t (2, 28) = - 0.910	0.293
Age of first cocaine/crack use	19.60	6.09	22.50	8.12	-	-	-	t (2, 38) = -1.277	0.209
Years of regular cocaine/crack use	10.55	5.24	8.95	6.091	-	-	-	t (2, 38) = 0.890	0.579

Note. [a] Post-hoc analyses showed a main effect of crack $F(1, 77)=19.334$, $p < 0.001$. No other differences were found. [b] Post-hoc analyses showed a main effect of crack $F(1, 77)= 7.739$, $p = 0.007$. No other differences were found. [c] Independent chi-square analyses showed CK groups with significant more tobacco regular use than HC groups (r=11.850, $p = 0.001$). No other differences were found. [d] Number of participants included in the comparison were different than number of included participants in each group. The number of included participants is shown for CK-M/CK-F.

Within the CK groups, we found significant differences in drug use characteristics. Cocaine or crack abstinence symptoms were higher for the CK-F group than for the CK-M group, which is in accordance with the literature (Elman et al., 2001). In addition, among the ASI-6 scores, there were differences in terms of legal and family social support. For the former, CK-Ms had more problems, but for the latter, CK-Fs had more problems.

Motion

A one-way ANOVA showed significant differences in average head motion between groups, $F(1, 79) = 5.787$, $p < 0.001$. The post hoc independent-sample t-tests showed statistically significant differences only between female CKs and HCs, $t(1, 38) = 3.389$, $p < 0.01$; the remaining groups had no other statistically significant differences. Hence, all analyses comparing female CKs and HCs in terms of intrinsic brain functioning included average head motion as an additional covariate.

ReHo

Four significant areas involving ReHo differences appeared to reveal an exclusive sex effect. Relative to females, males showed higher ReHo in one sensory-motor area (the right postcentral gyrus) and in other cortical areas in the temporal lobule (e.g., the right medial temporal gyrus, rMTG) and frontal areas (e.g., the right superior frontal gyrus, SFG; and left medial frontal gyrus lMFG). Supplementary Figure 1 and Supplementary Table 1 show ReHo comparisons in terms of main effects and sex. Despite the lack of interaction effects, our main interest was in sex differences within CK, so we computed post hoc analyses. The differences between CK-Ms and CK-Fs indicated that the sex differences between the CK groups could have driven sex effects in the whole sample. The results pointed to the CK-M as having higher ReHo within the sensory-motor areas (right postcentral gyrus and left precentral gyrus), the frontal lobule (bilateral SFG),

the temporal lobule (rMTG), the bilateral right parahippocampal gyrus (PHG), and the bilateral claustrum. In all the ReHo results, CK-M had higher local connectivity than did CK-F.

Extracting ReHo values within those areas with differences between CK-M and CK-F, post hoc analyses showed that, among females, CK had lower ReHo scores than HC in both sensory-motor areas in the right claustrum. Among males, CK had higher ReHo scores than did HC in the rMTG, lSFG, and claustrum. Figure 1 and Supplementary Table 1 give details on the regions and the differences in ReHo across the four groups.

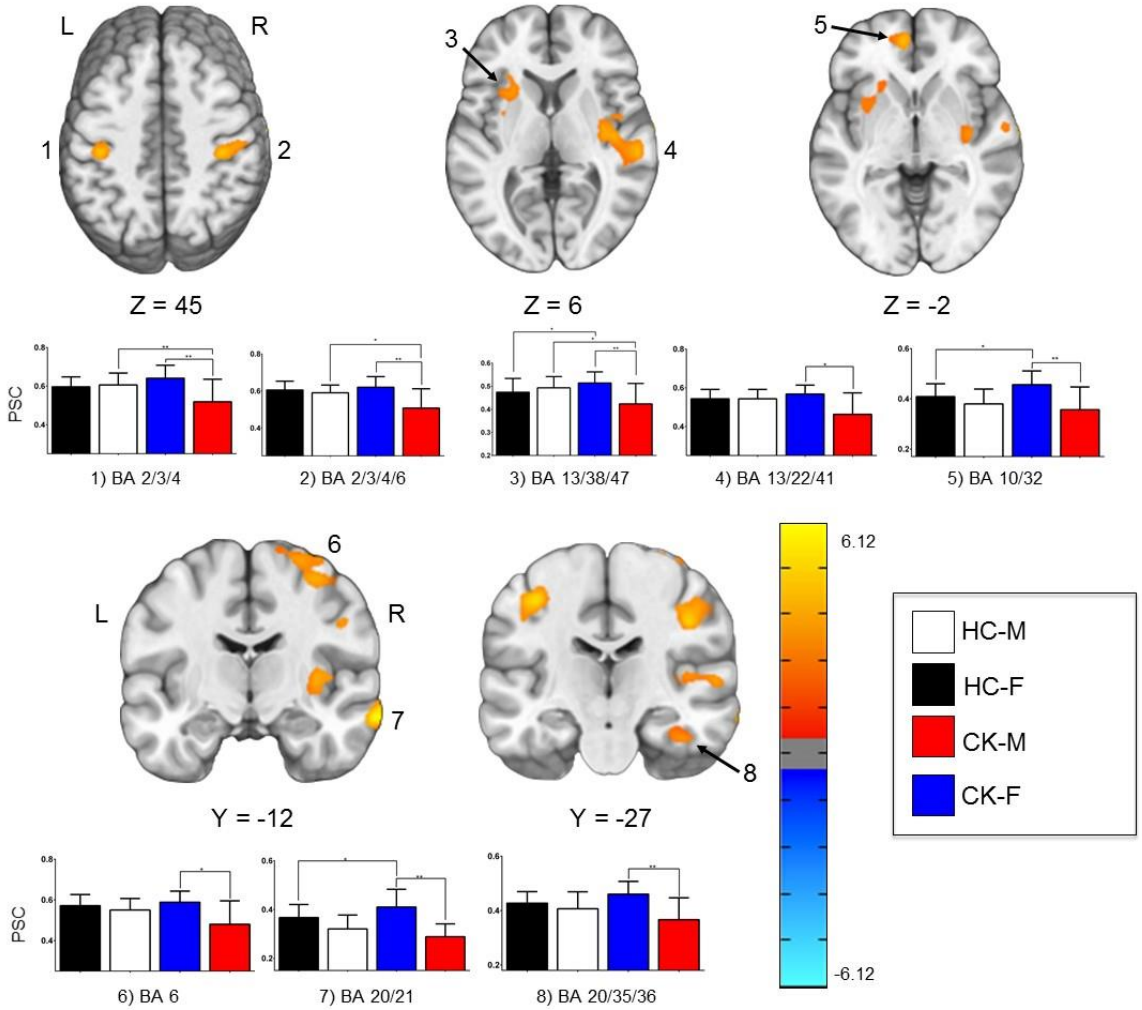

Figure 1. Sex differences in ReHo among CK groups. Figure shows regions with significant ReHo differences across four groups in post-hoc analyses. Displayed images came from

CK-M *versus* CK-F contrast. BA: Broadmann Areas. PSC: Percent signal change. Areas are identified with numbers: 1(Left Precentral Gyrus); 2 (Right Postcentral Gyrus); 3 (Left Claustrum); 4 (Right Claustrum); 5 (Left Superior Frontal Gyrus); 6 (Right Superior Frontal Gyrus); 7 (Right Middle Temporal Gyrus); 8 (Right Parahippocampal Gyrus). * p <0.05; ** p <0.001.

Seed-based FC

Using the MNI152 coordinates that refer to peak ReHo differences between CK-M and CK-F as seeds (as detailed in Supplementary Table 1 and depicted in Figure 1), we computed FC maps for each group and each seed. Afterward, we performed comparative analyses. The FC results showed several sex and group effects, as detailed in Supplementary Table 2; all other group-by-group results were in line with the study's objectives. The most significant differences were between CK-M and CK-F, which matches our objectives in this work (see Table 2).

Table 2

Sex-differences in FC of crack cocaine users

	Areas with altered FC	**CS**	**Peak MNI coordinate**			**Contrast**
Sub-system ROI	**Peak connectivity area and adjacencies**	**(μL)**	**x**	**y**	**z**	
Sensory-motor FC						
Right postcentral gyrus						
	Left precentral gyrus and rMFG	6120.4	-31.5	-12.2	55.8	CK-M > CK-F
	lSFG and lMFG	2824.8	-35	36.8	38.2	CK-M > CK-F
	rSFG and rMFG	2225.6	24.5	40.2	24.2	CK-M > CK-F
	rMFG and right precentral gyrus	11684.4	24.5	-8.8	69.8	CK-M > CK-F
	Left cingulate; medial frontal frontal gyrus	28419.2	-3.5	-1.8	45.2	CK-M > CK-F
	Right superior parietal lobule; precuneus; cuneus; and superior parietal lobule	2568	35	36.8	38.2	CK-M > CK-F
	lITG; lMTG; left middle occiptal; and fusiform gyrus	1968.8	-59.5	-54.2	-7.2	CK-M > CK-F
	rIPL	4793.6	42	-43.8	55.8	CK-M > CK-F

Left insula; postcentral and transverse temporal gyrus	3723.6	-49	-26.2	17.2	CK-M > CK-F
Left precentral gyrus					
Right postcentral gyrus and rIPL	2439.6	38.5	-26.2	41.8	CK-M > CK-F
Left postcentral gyrus	4836.4	-38.5	-22.8	48.8	CK-M > CK-F
lMFG and left cingulate gyrus	3552.4	-7	-8.8	52.2	CK-M > CK-F
rMTG; rSTG; right angular gyrus	4922	49	-50.8	6.8	CK-M > CK-F
SFG FC					
lSFG					
rMTG Right supramarginal gyrus	2953.2	45.5	-57.8	20.8	CK-M > CK-F
rSTG and rMTG	3894.8	56	-29.8	6.8	CK-M > CK-F
rSFG and rMFG	2782	21	36.8	48.8	CK-M > CK-F
Left precuneus and cingulate gyrus	3252.8	-21	-43.8	31.2	CK-M > CK-F
lIPL Left superior parietal lobules; precuneus; and left angular gyrus	3937.6	-35	-64.8	38.2	CK-M > CK-F
Right paracentral lobule and precuneus	2354	3.5	-40.2	59.2	CK-M > CK-F
rSFG					

	Left postcentral and precentral gyrus	9416	-45.5	-19.2	31.2	CK-M > CK-F
	Right postcentral gyrus	3167.2	42	-29.8	45.2	CK-M > CK-F
	Bilateral cingulate and left medial frontal gyrus	2953.2	0	-8.8	48.8	CK-M > CK-F
	Right precuneus and cuneus	1968.8	21	-78.8	34.8	CK-M > CK-F
RPHG FC						
rPHG						
	lMFG; lSFG	3338.4	-24.5	5.2	45.2	CK-M > CK-F
	rSFG and rMFG	2268.4	23	15	49	CK-M > CK-F
	Right precentral and postcentral gyrus; rIPL	5863.6	56	-22.8	38.2	CK-M > CK-F
	Right fusiform gyrus and culmen	2482.4	42	-40.2	-24.8	CK-M > CK-F
Claustral						
FC						
Right claustrum						
	Right postcentral gyrus and right precentral gyrus	8388.8	49	-29.8	34.8	CK-M > CK-F
	Left precentral gyrus	2568	-1.8	27.8	-45.5	CK-M > CK-F
	Right insula; postcentral; rSTG; rMTG	8774	49	-26.2	20.8	CK-M > CK-F

Left insula; postcentral and lSTG	4237.2	-45.5	-26.2	17.2	CK-M > CK-F
Right precuneus; cuneus and posterior cingulate	4237.2	10.5	-71.8	20.8	CK-M > CK-F
Bilateral cingulate gyrus	7104.8	0	12.2	41.8	CK-M > CK-F
rPHG and rMTG; caudate tail	3210	38.5	-40.2	-7.2	CK-M < CK-F
Left striatum (caudate) and ACC	2140	-11	24	12	CK-M < CK-F
Left claustrum					
rIPL and right postcentral gyrus	3252.8	63	-29.8	31.2	CK-M > CK-F

Note. CS: cluster size; ACC: Anterior cingulate cortex; rMTG: right middle temporal gyrus; lTG: left middle temporal gyrus; rIFG: right inferior frontal gyrus; rMFG: right middle frontal gyrus; rSTG: right superior temporal gyrus lSTG: left superior temporal gyrus; rMFG: right middle frontal gyrus; lMFG: left middle frontal gyrus; rIPL: right inferior parietal lobule; lIPL: left inferior parietal lobule; rSFG: right superior frontal gyrus; lSFG: left superior frontal gyrus; lITG: left inferior temporal gyrus; rPHG: right parahippocampal gyrus.

Correlation analysis

Based on the significant sex differences in FC among the CK, we tested associations between raw FC values and addiction severity (ASI-6 drugs score), abstinence symptoms (CSSA total score), and years of cocaine use. Due to sex differences among the CK groups, we tested correlations separately for each group. The rSFG-left postcentral and -right precuneus connections correlated positively with addiction severity, both in CK-M and in CK-F. For CK-M, a MCL FC (rPHG-lMFG) positively correlated with years of cocaine use. For CK-F, claustro-right precuneus FC had a negative correlation with years of cocaine use; similarly, claustro-striatal FC (left caudate) was negatively correlated with abstinence symptoms. In addition, CK-F had positive correlations between abstinence symptoms and the FC of both the right claustrum-rSFG and -lMFG connections. Figure 2 shows the associations between changes in FC and drug use features for CK-M and CK-F.

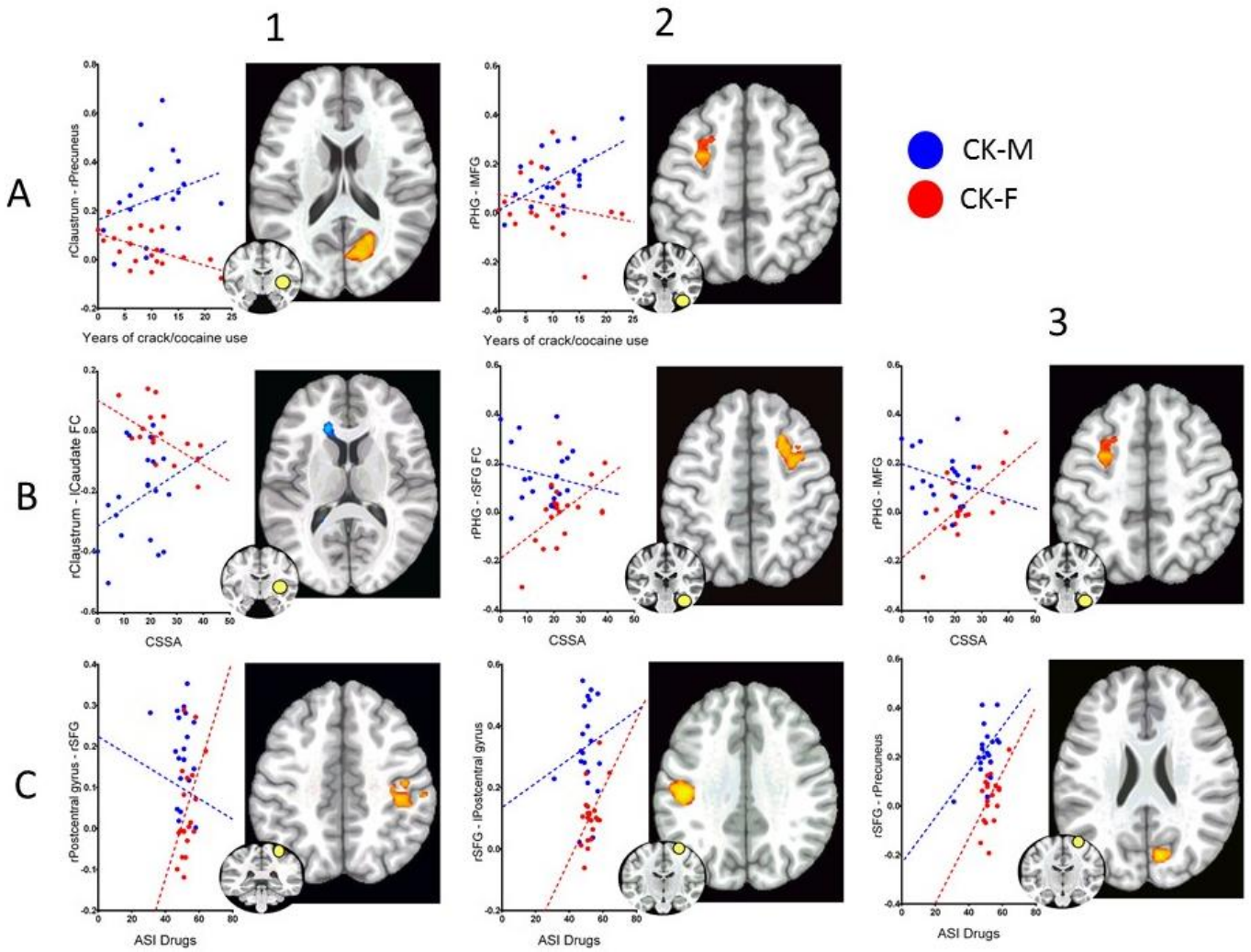

Figure 2. Associations between changes in FC and drug use features for CK-M and CK-F. The small circle with a coronal image refers the seed location and the larger picture with an axial image refers to the peak

correlational area with FC. Row A shows Pearson correlations with years of cocaine/crack use. Correlations between it and and rClaustrum-rPrecuneus FC (for CK-M, r = 0.258, p = 0.273; for CK-F, r = -0.553, p = 0.011) is in A1; and rPHG-lMFG (for CK-M, r = 0.555, p = 0.011; for CK-F, r = -0.222, p = 0.348) is in A2. Row B shows correlations with CSSA total score, as a measure of abstinence symptoms. Correlations between it and rClaustrum-lCaudate FC (for CK-M, r = 0.300, p = 0.198; for CK-F, r = -0.496, p = 0.026) is in B1; rPHG-rSFG FC (for CK-M, r = 0.017, p = 0.943; for CK-F, r = 0.527, p = 0.017) is in B2; and rPHG-lMFG (for CK-M, r = -0.128, p = 0.591; for CK-F, r = 0.638, p = 0.002) is in B3. Row C shows correlations with ASI Drugs total score, as a measure of drug use severity. Correlations between it and rPostcentral gyrus-rSFG FC (for CK-M, r = - 0.177, p = 0.454; for CK-F, r = 0.479, p = 0.033) is in C1; rSFG-lPostcentral FC (for CK-M, r = 0.421, p = 0.065; for CK-F, r = 0.506, p = 0.023) is in C2; and rsFG-rPrecuneus (for CK-M, r = 0.487, p = 0.029; for CK-F, r = 0.462, p = 0.040) is in C3.

Discussion

Sex differences in rs-fMRI results of crack cocaine users, as reported in this work, confirmed the sex differences in intrinsic brain connectivity of crack cocaine users. Using a data-driven method, we first compared local FC using ReHo. We used the significant sex differences within the CK groups as ROIs to investigate whole-brain FC. Results for both ReHo and FC supported the conclusion that female crack cocaine users have overall lower intrinsic brain connectivity than male crack cocaine users have. The differences between each CK group and its respective-sex HC group indicated sex-specific effects. For males, crack effects seem to lead to increasing FC, while for females, these effects lead to decreasing FC. The sex differences in CK groups involved areas and networks that are mainly related to inhibitory, sensory-motor, and multimodal integrative functions. In addition, FC correlated with career drug use characteristics and consistently correlated with existing sex-difference assumptions, many of which were in different directions for men and women.

Despite the lack of an interaction effect in the ReHo analyses, which showed only sex effects, it became clear from post hoc results that the CK groups drove those sex effects. The results also supported sex differences within the CK groups, as reinforced by the FC data, with CK-M having predominantly higher FC than CK-F. Moreover, the results for FC dealt with regions that comprise both distinct and overlapping networks. Thus, conclusions could be drawn regarding large-scale FC differences, with CK-M having higher FCs than CK-F. Interestingly, in other healthy control studies, although the results are debatable (Filippi et al., 2013; Hjelmervik et al., 2014; Satterthwaite et al., 2014), sex differences have indicated that females have higher measures in the motor and control networks (Hjelmervik et al., 2014; Weis et al., 2017). These results are in contrast with our findings among crack cocaine users, as SFG, for example, encompasses FPN,

which is in turn related to implicit cognitive processes (Ptak, 2012). These results may indicate that crack cocaine has sex-specific effects that reprogram natural and stable sex differences in intrinsic brain functioning.

Although we confirmed our main hypothesis regarding the sex differences in crack cocaine users, contrary to both our expectations and the results of previous studies (Contreras-Rodríguez et al., 2015; Contreras-Rodríguez et al., 2016; Gu et al., 2010; Y. Hu, Salmeron, Gu, Stein, & Yang, 2015; Konova et al., 2013; Verdejo-Garcia et al., 2014; Wisner et al., 2013), there was little evidence of crack cocaine effects. An obvious explanation relates to sex differences, as those past studies had heterogeneous sex samples, but ours had a homogenous sample, which could have affected the results, as male and female crack cocaine users seem to have differential effects from crack cocaine use. Considering the results for males only, we partially replicated previous studies (Contreras-Rodríguez et al., 2016; Y. Hu et al., 2015; Konova et al., 2013). As the claustrum has projections within the limbic system (Beneyto & Prieto, 2001), our results could support CKs having higher corticolimbic and cortico-cortical FC than controls, as shown in previous studies (Contreras-Rodríguez et al., 2016; Y. Hu et al., 2015; Konova et al., 2013). In addition, these studies reported a positive association between the number of months of peak cocaine use and MCL FC (Contreras-Rodríguez et al., 2016), which also matches with our findings. CK-M had a positive association between the FC of the PHG-lMFG network and years of crack cocaine use. The PHG belongs to the limbic system (more precisely, to the paralimbic system) and is involved in emotional-processing integration and network linkage with the hippocampal formation. The MFG comprises both the DAN and the ventral attention network (VAN). The DAN affects cognitive control, including explicit inhibition; for this reason, as well as its negative correlations with DMN, some call it the executive control network (Dosenbach, Fair, Cohen, Schlaggar, &

Petersen, 2008; M. D. Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The VAN, which has links with the SN, relates to internal attention processing, and the MFG is presumed to aid in switching between these two networks (Dosenbach et al., 2008). Thus, corticolimbic FC in limbic-DAN/VAN probably implies a limbic takeover of the DAN/VAN functions, which may explain the presence of emotionally driven, goal-directed behaviors in addictive disorders (Horvitz, 2000; Sesack & Grace, 2010). However, this result relates only to males, and one could question how problems in female crack cocaine users can be explained. Indeed, the differences between male and female crack cocaine users involve unexpected behavior, as we predicted higher measures for CK-F than CK-M given former well-recognized more pronounced impairments. In the following, we present female crack cocaine users, among whom it is not the taking over, but the isolation of emotional processing that, when combined with multimodal integration disruptions, leads to quicker declines and worse outcomes.

FPN also relates to switching, but it mediates the switching between DMN and DAN (Cole, Repovš, & Anticevic, 2014; Gao & Lin, 2012). Results have indicated that CK-M have higher inter- and intra-network FC than CK-F for both SMN and FPN. The right postcentral and left precentral gyrus are components of the SMN (Rosazza & Minati, 2011), although they (along with the SFG) are also included in the FPN sometimes (Ptak, 2012). Using these networks, we found lower ReHo in CK-F than in CK-M for FPN and SMN; these results also appeared in the FC analysis. It is possible that female crack cocaine users have less implicit inhibitory activity, as both FPN and SMN participate in suppressing implicit and automatic behaviors (Hu, Ide, Zhang, & Li, 2016). Reduced implicit inhibition increases craving sensibility (Field, Marhe, & Franken, 2013), which is a core clinical sex difference among crack cocaine users (Elman et al., 2001). Moreover, as FPN, DAN, and VAN are all inhibitory networks, they overlap to each other regarding

interference. Similarly, FPN overlaps DMN and some MCL pathways, including the hippocampus and its adjacencies. Thus, the hypothesis is that the FPN integrates and mediates conflicting networks, possibly working in feedback control (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). For example, researchers addressing the cognitive mechanisms of pain have identified both the FC of both intra-network FPN and FPN-DMN as positively predicting pain anticipation (Kong et al., 2013). One could interpret the higher FC of male crack cocaine users (in comparison to female crack cocaine users) in the SFG-MFG, -postcentral areas, and -precuneus connections, as well as in PHG-SFG as being due to FPN-DAN, -SMN, and –DMN, as well as limbic-FPN. The former group of connections may be more likely to predict harmful consequences of risky behavior. It is possible that the increased FC within these networks promotes better multimodal information integration and provides more energy for switching between functions (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). Thus, CK-M's higher FC (relative to CK-F) could indicate a resilient mechanism; however, this topic requires a better functional understanding.

CK-F had lower ReHo and FC measures for SMN than either the opposite-sex group of users or the sex-matched control group, indicating that the CK-F reductions within this network were related to progressive drug use. CK-Fs had reduced FC for the right postcentral-left precentral gyrus connection, which means decreased FC in the SMN. Inter-network FC indicated that the CK-F had decreased FC for SMN-bilateral MFG within rSFG and MTG, thus representing reduced SMN-DAN and –SFG connections. Such results can support a loss in cognitive control and an increase in motor urgency (van Maanen, Fontanesi, Hawkins, & Forstmann, 2016), but these are also supported by the higher right postcentral-caudate FC in the SMN-striatum for female crack cocaine users relative to female healthy controls. Moreover, as disruptions in the SMN represent both changes from a healthy state and sex differences within crack cocaine users, these disruptions

may be indications of telescoping effects that push females more quickly toward addiction (Morrison, 1990; Stoltman, Woodcock, Lister, Greenwald, & Lundahl, 2015). Normal aging leads to reduced SMN ReHo and reduced intra-network FC (Wu et al., 2007), and drug use may cause aging acceleration (Ersche et al., 2012; Levandowski et al., 2016; Sanvicente-Vieira et al., 2016). Thus, the female crack user changes in the SMN could be a manifestation of this phenomenon, as females are susceptible to telescoping effects (Haas & Peters, 2000; Stoltman et al., 2015). An increase in similar measures and in the same areas among males would be contradictory; however, male crack cocaine users and healthy controls did not differ in these comparisons. Thus, crack cocaine probably has a singular influence over the SMN of females, leading to little power, perhaps at undetectable levels, in male motor areas; however, we can guess that it would only be a matter of time for this group. Additionally, it is worth noting that the motor areas, the basal ganglia and its adjacencies (including the claustrum), and the striatum are all particularly susceptible to disruptions in the neurotransmission system, mainly dopamine (DA). Imbalances in DA activity due to hyper-regulation have age-related consequences in terms of motor skills (Seidler et al., 2010). As DA effects on neurobiological circuits of crack cocaine users become more recognized (Horvitz, 2000), sex-hormones such as estradiol are likewise becoming known for boosting the release of DA (Shams, Sanio, Quinlan, & Brake, 2016). Thus, one could hold that DA hyper-modulation is one etiologic pathway for accelerated SMN disruptions in addicted females.

CK-F showed lower FC related to the PHG, which leads to changes in their DMN FC, which is another age-related effect (Andrews-Hanna et al., 2007). Hippocampal formation requires the PHG and is a key piece in the DMN subsystem, which controls and creates autobiographical scenes (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). The FC of PHG-DMN bridges the hippocampal formation to the DMN; when it malfunctions, the hippocampus is isolated

from the DMN (Ward et al., 2014), causing memory-encoding impairments and the loss of gray matter in elders (Putcha et al., 2011). Such outcomes are also associated with the length of crack cocaine use (Ersche et al., 2012). Positive associations in CK-M between FC for PHG-DMN and years of crack cocaine use reinforces that there are differential effects for males and females, as shown in our work. In contrast, the PHG-DMN and -FPN connections were each positively associated with abstinence symptoms in CK-F. These results indicate that, because female crack cocaine users have reduced MCL FC, the increased engagement of this pathway brings aversive symptoms. Thus, the FC mechanisms of the brain, which could prevent the advances of addiction, seem to in fact cause aversive symptoms in females, probably making them more susceptible to relapse (as a means of avoiding distress).

Moreover, sex hormones have been shown to have a role in PHG activity in psychiatric disorders (Kindler et al., 2015), the public data for which are consistent with our results. The PHG is sensitive to cues (Ko et al., 2013), and limbic activity such as this is an emotional response marker; this includes cravings. Cravings and limbic activity have sex differences in crack cocaine users (Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005; Contreras-Rodríguez et al., 2016; Fox & Sinha, 2009). As CK-M had higher PHG ReHo than CK-F, one could conclude males have more cravings; however, our results on CSSA did not indicate this. The integration of multimodal stimuli and FC in CK-M could explain the absence of increased cravings, despite the higher PHG activity. CK-M also had higher ReHo in non-PHG areas that include controlling networks such as the FPN. The FC of PHG, with areas related to inhibitory control, was associated with successful strategies for inhibiting cravings in cigarette smokers (Ono et al., 2017), for example. Thus, the FC inter-network patterns in male crack cocaine users could counterbalance emotional activity such as that regarding PHG-FPN.

Taken together, our results indicated that female crack cocaine users had lower intrinsic brain functioning than did male crack cocaine users. This can be interpreted as an adaptive mechanism that allows females to deal with increased functioning in responsive states (Zalesky, Fornito, Cocchi, Gollo, & Breakspear, 2014); this can occur for many reasons, as sex-hormone modulation sometimes boosts brain responses (Ambrose-Lanci, Sterling, & Van Bockstaele, 2010; Back, Brady, Jackson, Salstrom, & Zinzow, 2005; Bagley et al., 2017). Fluctuations in intrinsic brain activity are an optimization mechanism that aids in dealing with usual responses (Zalesky et al., 2014). The overall reductions, which are most remarkable in the networks related to inhibitory functions, are consistent with the sex differences found in previous task-demanded fMRI studies. Under stress, CK-F have shown higher hyperactivity in MCL areas than CK-M (Li et al., 2005; Potenza et al., 2012). As female crack cocaine users are likely used to responding to everyday stress, one potential balancing mechanism would be a widespread reduction in intrinsic brain functioning when at rest. Males consistently show higher activity in similar pathways under cue-induced conditions (Potenza et al., 2012). In females, as compared to males, cravings triggered by cocaine cues are related to more widespread activations through the FPN, SN, DMN, and sensory-motor areas, as found in a positron emission tomography study (Kilts, Gross, Ely, & Drexler, 2004). In addition, a previous rs-fMRI study on sex differences in people with addictive disorders showed that, among those who smoked cigarettes, females had overall higher intrinsic brain functioning than males (Wetherill et al., 2014), which supports the hypothesis that female crack cocaine users have increased functioning in demanding reward conditions.

It is possible that these sex differences in intrinsic brain functioning and the related responsive differences to certain types of stressors play critical roles in the observed clinical differences between men and women who use crack cocaine. In fact, drug users have a known

drug-cue sensibility (Moeller et al., 2009) and have high rates of everyday stress (Grassi-Oliveira et al., 2012). Although both stress- and cue-induced cravings occur (Back et al., 2010; Sinha et al., 2006), the former predicts earlier relapses (Sinha et al., 2006); there is, however, a contrasting result that shows no differences (Back et al., 2010). Despite this discordance, the evidence converges on the conclusion that the extent of the hypothalamic-pituitary-adrenal (HPA) response after a stress-triggered craving is a predictor of earlier relapses than cue triggering (Back et al., 2010; Sinha et al., 2006). Thus, the reductions in the intrinsic brain functioning of CK-F can be viewed as an adaptive mechanism for dealing with often-stressful demands. This hypothesis is supported by the higher intrinsic functioning in CK-F than in CK-M, as it is possible to succeed in reducing sex differences in clinical outcomes due to the increased severity of drug use in women (Bertoni et al., 2014; Elman et al., 2001; Vernaglia et al., 2015; Vernaglia et al., 2017).

In addition, because females are more likely than males to be motivated to use drugs because of negative emotions (Kuntsche & Müller, 2012; Potenza et al., 2012), disruptions in their intrinsic brain functioning when at rest, such as in emotion-related circuits (e.g., DMN, DAN, and MCL connections) are consistent with possible increases in response due to stimulation (Andersen & Teicher, 2009). Altered emotional-processing circuits, such as those involved in the pathways for multimodal information integration, are over-responsive in some populations, including among the victims of childhood maltreatment (Dannlowski et al., 2012), which is a common characteristic in our sample. One could say that this is not logical, given that there were no sex differences in childhood maltreatment in our CK group. However, sex differences in susceptibility to neurobiological changes among crack cocaine users can be an issue (Hyman et al., 2008), thus justifying our control of this variable in this study. In addition, the previous data indicated that emotional processing reveals behavioral impairment in crack cocaine users, particularly related to

negative affect (Kemmis et al., 2007; Preller et al., 2014; Sanvicente-Vieira et al., 2017). Thus, emotional processing – particularly for controlling the brain gatekeepers – seems disrupted in females, which likely influences the sex differences in everyday functioning.

Regardless of the conclusions regarding overall higher intrinsic brain functioning in male crack cocaine users relative to female crack cocaine users, there were some exceptions. CK-F had higher FC between the right claustrum and the reward-related areas within the striatum and the limbic system (i.e., the caudate and PHG). A previous study showed that CK-M had higher claustrum activity in a cue-induced task than in a stress-induced one. In CK-F, no such result was found (Li et al., 2005). The function of the claustrum has been questioned, with most suggesting that it participates in conscious awareness (Crick & Koch, 2005) and interoception (Schulz, 2016) by processing and integrating multimodal stimuli (Baizer, Sherwood, Noonan, & Hof, 2014; Torgerson, Irimia, Goh, & Van Horn, 2015). The claustrum is highly wired, with multiple projections to almost all cortical regions and to several subcortical ones (Torgerson et al., 2015). Because of the connectivity of the fibers from claustrum and its suggested functions, it may be a key in synchronizing FC across various networks (Orman, 2015). Claustrum connections in CK-F are related to rewarding, suggesting an interoceptive focus on reward-related feelings and memories, accompanied by a lack of integration of other stimuli. These conclusions come from reductions in FC with relevant networks that have conflicting roles. In pathological gamblers, for instance, reduced claustrum-cortical FC associated to reduced risk perception (Rømer Thomsen et al., 2013). For CK-M, higher claustrum-SMN, -FPN (e.g., related to the right IPL), -SN (e.g., related to the insula), -DMN (e.g., related to the precuneus), and -DAN (related to the ACC) connections indicated that the claustrum plays a stronger role in integrating multiple types of stimuli. Strikingly, the CK-F had negative associations between years of crack cocaine use and

particular connections, namely the claustrum-precuneus (in the DMN). In addition, for CK-F, the FC of the claustrum-FPN was negatively associated with abstinence symptoms, reinforcing that the role of integrative processing may involves the claustrum and that continuous alterations in drug use leads to pitfalls in the progression of drug use for females.

Despite our work's support of sex differences in crack cocaine users, it has several limitations that must be kept in mind when interpreting its results. We merely hypothesized that findings related to disruptions would influence inhibition, motor skills, and multimodal integration. Real-world sex differences in this regard require detailed findings. The combination of task-based fMRI with rs-fMRI can provide clearer conclusions on this topic. We used a cross-sectional method, which hinders conclusions about the causal consequences of changes from healthy conditions due to crack cocaine use. We explored drug-career characteristics and their associations with FC across areas that showed sex differences among crack cocaine users, but the areas that did not show differences could also have sex-specific effects. We also drew conclusions about networks, but in fact, we did not use independent component analysis (ICA), which would provide the best perspective; we simply drew conclusions based on the participation of networks due to FC results for single nodes, along with support from the literature. Even though we used several methods and criteria for controlling biases, we obviously failed in controlling for everything. We investigated sex differences, but gender and sexuality may also have effects. Women's menstrual cycles affect rs-fMRI (Hjelmervik et al., 2014) results, but this was not controlled for. We did not address the amount or quality of drugs consumed. In addition, although we noted the sex differences in tobacco use disorders (Beltz, Berenbaum, & Wilson, 2015), we did not control for this in our models. Probably the most important issue that we must acknowledge is regarding an important paradox: We considered that we did not have to control for the differences

in some drug use characteristics because of the absence of such differences. However, our main premise was that there are sex differences among crack cocaine users, and we agree that other drugs may have similar effects. By this token, we cannot exclude the possibility that the results may be driven by other variables that showed no sex differences but that still have sex-specific effects; these could include nicotine use and alcohol use.

Conclusions

Intrinsic brain functioning in crack cocaine users shows sex differences. Males have higher patterns in large-scale networks. Theories on addictive disorders have suggested that, because FC increases across competitive networks, an overload of information integration would make people vulnerable to rewarding-directed behaviors due to the over-responsiveness of their incentive networks and the suppression of their contrasting systems (Contreras-Rodríguez et al., 2015; Robinson & Berridge, 1993; Verdejo-Garcia et al., 2014; Volkow et al., 2011). However, females showed disruptions in the opposite fashion (i.e., large-scale decreases). Interestingly, this probably also causes problems related to inhibition, but in a different, and possibly more dangerous, way; it occurs because of two characteristics: (a) higher response amplitude and (b) lack of information integration. Differences among female crack users, such as higher responsive amplitudes, have been documented (Potenza et al., 2012), and our results showed that female crack users main differences in comparison to male crack users were related to areas often described as links or couplings between networks. Most of these areas' suggested functions are as gatekeepers (McCarthy et al., 2017; Schulz, 2016; Torgerson et al., 2015; Ward et al., 2014). In women, this probably accelerates degenerative processes and leads to a harder course of the disease, making intrinsic brain function a novel and interesting way to target therapeutics. Finally, future studies need to apply conceptual changes after considering various recent findings, including those

presented here. CUD has sex differences not only in task-demanded conditions and peripheral markers but also in intrinsic brain functioning at rest, as in the naturalistic scenario presented here without any cognitive or environmental challenge. Because addiction, including CUD, is a brain disorder (Dackis & O'Brien, 2001; Koob & Volkow, 2010; Volkow et al., 2016), and because CUD has sex differences, future researchers must consider CUD in males and females as different brain disorders. These results put the need for sex-specific interventions back on the table (Becker, 2016; Becker et al., 2016; Becker et al., 2017; Becker et al., 2012; Bobzean et al., 2014; Fattore & Melis, 2016).

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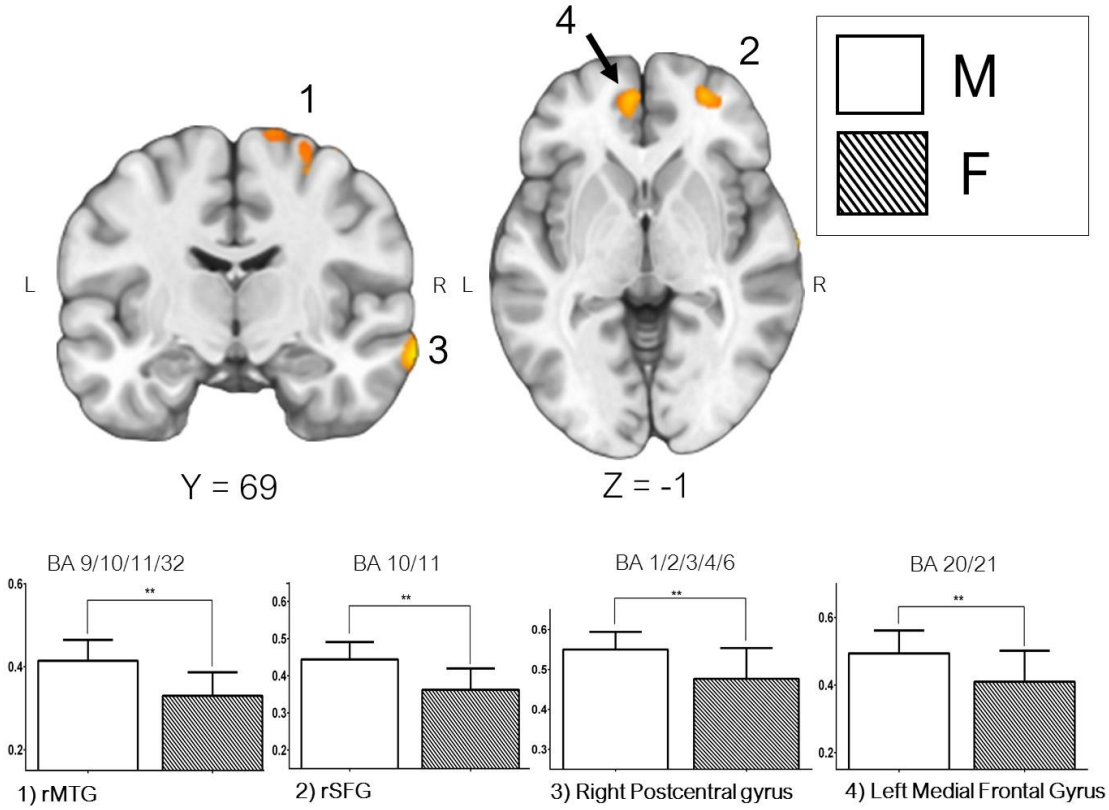

Supplementary Figure1. Sex differences in ReHo in whole sample. Figure shows areas that showed significant main effects of sex. rMTG: right middle temporal gyrus; rSFG: right superior frontal gyrus; M: Males; F: Females. R: right; L: left. * p <0.05; ** p < 0.001.

Supplementary Table 1

ReHo diferences

Brain Region	**Contrast**	**M**		**F**		**CS**	**Peak MNI coordinates**		
		M (SD)		*M (SD)*		(μ*L*)	**x**	**y**	**z**
rMTG	M>F**	0.414 (0.050)		0.3299 (0.0567)		5992	63	1.8	-14.2
Right postcentral gyrus	M>F**	0.550 (0.044)		0.4766 (0.0771)		5007,6	31.5	-33.2	69
rSFG	M>F**	0.419 (0.056)		0.3410 (0.0575)		2996	56	12.2	13.8
LMFG	M>F**	0.493 (0.068)		0.4098 (0.0916)		2910,4	-10.5	43.8	20.8
Post-hoc	**Contrasts**	**CK-M**	**CK-F**	**HC-M**	**HC-F**	**CS**	**x**	**y**	**z**
		M (SD)	*M (SD)*	*M (SD)*	*M (SD)*				
SMA/FPN									
Right postcentral gyrus	CK-F < CK-M**; HC-F *	0.620 (0.057)	0.507 (0.104)	0.605 (0.047)	0.590 (0.041)	4964,8	45.5	-19.2	34
Left precentral gyrus	CK-F < CK-M**; HC-F **	0.640 (0.067)	0.518 (0.116)	0.596 (0.051)	0.606 (0.061)	2439,6	-38.5	-19.2	52

FPN									
rSFG	CK-M > CK-F*	0.588 (0.054)	0.480 (0.115)	0.571 (0.054)	0.550 (0.056)	2311,2	28	-12.2	69.8
lSFG	CK-M > CK-F**; HC-M*	0.456 (0.054)	0.356 (0.090)	0.409 (0.051)	0.379 (0.059)	1926	-14	50.8	-14.2
DAN									
rMTG	CK-M > CK-F**; HC-M*	0.410 (0.072)	0.288 (0.052)	0.366 (0.053)	0.320 (0.056)	4836,4	66.5	-5.2	-14.2
Limbic system and adjacencies									
rPHG	CK-M > CK-F**	0.460 (0.046)	0.366 (0.080)	0.427 (0.042)	0.406 (0.062)	2525,2	35	-26.2	-24.8
Right Claustrum	CK-M > CK-F*	0.567 (0.046)	0.463 (0.110)	0.543 (0.048)	0.541 (0.046)	4108,8	35	-8.8	3.2
Left claustrum	CK-M > CK-F**; HC-M* HC-F > CK-F *	0.514 (0.047)	0.423 (0.088)	0.473 (0.059)	0.492 (0.048)	1968,8	-24.5	15.8	6.8

Note. CS: Cluster size; SMA: sensorymotor network; FPN: frontoparietal network; DAN: Dorsal Attention Network; rMTG: right middle temporal yrus; rSFG: risght superior frontal gyrus; rPHG: right Parahippocampal gyrus; lSFG: left superior frontal gyrus. * $p < 0.05$; ** $p < 0.001$.

Supplementary Table 2

All significant differences in FC

	Areas with altered FC	**CS**	**Peak MNI coordinate**			**Contrast**
Sub-system ROI	**Peak connectivity area and adjacencies**	**(μL)**	**X**	**Y**	**Z**	
Sensory-motor FC						
Right postcentral gyrus						
	Left precentral gyrus and rMFG	6120.4	-31.5	-12.2	55.8	CK-M > CK-F
	lSFG and lMFG	2824.8	-35	36.8	38.2	CK-M > CK-F
	rSFG and rMFG	2225.6	24.5	40.2	24.2	CK-M > CK-F
	rMFG and right precentral gyrus	11684.4	24.5	-8.8	69.8	CK-M > CK-F
	Left cingulate; medial frontal frontal gyrus	28419.2	-3.5	-1.8	45.2	CK-M > CK-F
	Right superior parietal lobule; precuneus; cuneus; and superior parietal lobule	2568	35	36.8	38.2	CK-M > CK-F
	lITG; lMTG; left middle occiptal; and fusiform gyrus	1968.8	-59.5	-54.2	-7.2	CK-M > CK-F
	rIPL	4793.6	42	-43.8	55.8	CK-M > CK-F

	Left insula; postcentral and transverse temporal gyrus	3723.6	-49	-26.2	17.2	CK-M > CK-F
	Left ACC	2996	-7	26.2	20.8	CK-M > HC-M
	Left precuneus lTG	2182.8	-28.0	-47.2	10.2	HC-M > CK-M
	Left precentral and lMFG	9929.6	-31.5	-12.2	62.8	CK-F < HC-F
	rMFG; rSFG; and precentral gyrus	17976	35	-8.8	62.8	CK-F < HC-F
	Bilateral middle frontal and cingulate gyrus	12711.6	0	-8.8	52.2	CK-F < HC-F
	rIFG and rMFG	2182.8	45.5	22.8	20.8	CK-F < HC-F
	lMTG	3210	-49	-71.8	10.2	CK-F < HC-F
	Right caudate	2225.6	35	-36.8	-3.8	CK-F > HC-F
	Right paracentral and medial frontal lobules	6848	3.5	-12.2	48.8	HC-M > HC-F
	Right paracentral lobule and precuneus	4964.8	21	-47.2	59.2	HC-M > HC-F
	Left postcentral and precentral gyrus; precuneus	2996	-28	-40.2	59.2	HC-M > HC-F
	Right insula and rSTG	2140	42	-29.8	17.2	HC-M > HC-F
	Left cuneus and posterior cingulate	4237.2	-17.5	-54.2	20.8	HC-M > HC-F
Left precentral gyrus						
	Right postcentral gyrus	4451.2	38.5	-36.8	66.2	M > F

	Left medial frontal; cingulate and paracentral gyrus	4494	-10.5	1.8	52.2	M > F
	Right postcentral gyrus and rIPL	2439.6	38.5	-26.2	41.8	CK-M > CK-F
	Left postcentral gyrus	4836.4	-38.5	-22.8	48.8	CK-M > CK-F
	lMFG and left cingulate gyrus	3552.4	-7	-8.8	52.2	CK-M > CK-F
	rMTG; rSTG; right angular gyrus	4922	49	-50.8	6.8	CK-M > CK-F
	rSTG and rMTG	2739.2	42	-40.2	3.2	CK-M > HC-M
SFG FC						
lSFG						
	rSFG; rMFG	2354	17.5	40.2	45.2	CK > HC
	lMFG and precentral gyrus	2525.2	-31.5	-5.2	59.2	CK > HC
	Left insula and left claustrum	2354	-52.5	-22.8	3.2	CK > HC
	Left lentiform nucleus and left claustrum	2439.6	-31.5	-5.2	-0.2	CK > HC
	lIPL Left postcentral gyrus	2011.6	-56	-26.2	31.2	CK > HC
	Bilateral paracentral lobule and left precuneus	3295.6	0	-43.8	59.2	CK > HC
	Left cuneus and lingual gyrus	2097.2	-10.5	-78.8	3.2	M > F
	rSFG and rMFG	2782	21	36.8	48.8	CK-M > CK-F

	rSTG and rMTG	3894.8	56	-29.8	6.8	CK-M > CK-F
	rMTG Right supramarginal gyrus	2953.2	45.5	-57.8	20.8	CK-M > CK-F
	Left precuneus and cingulate gyrus	3252.8	-21	-43.8	31.2	CK-M > CK-F
	lIPL Left superior parietal lobules; precuneus; and left angular gyrus	3937.6	-35	-64.8	38.2	CK-M > CK-F
	Right paracentral lobule and precuneus	2354	3.5	-40.2	59.2	CK-M > CK-F
	Right insula and right transverse temporal gyrus	2140	45.5	-29.8	20.8	CK-F > HC-F
	Left postcentral gyrus	4322.8	-56	-22.8	31.2	CK-F > HC-F
rSFG						
	Right postcentral and precentral gyrus; rIPL	15322.4	38.5	-43.8	66.2	M > F
	lIPL Left precentral lobules	11770	-24.5	-43.8	55.8	M > F
	Left medial frontal gyrus and bilateral cingulate gyrus	5136	-3.5	-12.2	52.2	M > F
	Left postcentral and precentral gyrus	220	-45.5	-19.2	31.2	CK-M > CK-F
	Right postcentral gyrus	9416	42	-29.8	45.2	CK-M > CK-F
	Bilateral cingulate and left medial frontal gyrus	2953.2	0	-8.8	48.8	CK-M > CK-F
	Right precuneus and cuneus	1968.8	21	-78.8	34.8	CK-M > CK-F

	Right postcentral gyrus	2867.6	31.5	-47.2	69.8	HC-M > HC-F
RMTG FC						
	Left precuneus and bilateral cuneus	2568	0	-68.2	27.8	M < F
	Right precuneus; middle occiptal and rITG.	2396.8	28	-57.8	52.2	M > F
	rSTG and rITG	4836.4	70	-8.8	-14.2	M > F
	rIFG; rMFG	2225.6	49	50.8	3.2	CK > HC
RPHG FC						
rPHG						
	Right fusiform and rITG	2525.2	52.5	-43.8	-21.2	M > F
	Right precentral and postcentral gyrus; rIPL	5863.6	56	-22.8	38.2	CK-M > CK-F
	rSFG and rMFG	2268.4	23	15	49	CK-M > CK-F
	lMFG; lSFG	3338.4	-24.5	5.2	45.2	CK-M > CK-F
	Right fusiform gyrus and culmen	2482.4	42	-40.2	-24.8	CK-M > CK-F
Claustral						
FC						
Right claustrum						

Bilateral cingulate gyrus	3038.8	14	-29.8	34.8	M > F
rSTG Right and transverse temporal gyrus	8003.6	63	-29.8	6.8	M > F
lSTG Left and postcentral gyrus	4922	-49	29.8	17.2	M > F
Right precentral gyrus	2739.2	42	-15.8	31.2	M > F
Right postcentral gyrus and right precentral gyrus	8388.8	49	-29.8	34.8	CK-M > CK-F
Left precentral gyrus	2568	-1.8	27.8	-45.5	CK-M > CK-F
Right insula; postcentral; rSTG; rMTG	8774	49	-26.2	20.8	CK-M > CK-F
Left insula; postcentral and lSTG	4237.2	-45.5	-26.2	17.2	CK-M > CK-F
Right precuneus; cuneus and posterior cingulate	4237.2	10.5	-71.8	20.8	CK-M > CK-F
Bilateral cingulate gyrus	7104.8	0	12.2	41.8	CK-M > CK-F
rPHG and rMTG; caudate tail	3210	38.5	-40.2	-7.2	CK-F > CK-M
Left striatum (caudate) and ACC	2140	-11	24	12	CK-F > CK-M
rMTG and rSTG	2097.2	49	-43.8	-0.2	CK-M > HC-M
rIPL Right insula; and transverse temporal gyrus	4280	45.5	-36.6	24.2	CK-M > HC-M
Left claustrum					
rIFG; precentral gyrus	3038.8	59.5	15.8	20.8	M > F

rMFG; rIFG	2054.4	42	33.2	-3.8	M > F
Left postcentral and right precentral gyrus; rIPL	7404.4	59.5	-29.8	45.2	M > F
rIPL and right postcentral gyrus	3252.8	63	-29.8	31.2	CK-M > CK-F
Bilateral ACC	6719.6	3.5	29.8	17.2	CK-M > HC-M
Right postcentral gyrus and rIPL	2696.4	-26.2	45.2	63	HC-M > HC-F

Note. CS: cluster size; ACC: Anterior cingulate cortex; rMTG: right middle temporal gyrus; lTG: left middle temporal gyrus; rIFG: right inferior frontal gyrus; rMFG: right middle frontal gyrus; rSTG: right superior temporal gyrus lSTG: left superior temporal gyrus; rMFG: right middle frontal gyrus; lMFG: left middle frontal gyrus; rIPL: right inferior parietal lobule; lIPL: left inferior parietal lobule; rSFG: right superior frontal gyrus; lSFG: left superior frontal gyrus; lITG: left inferior temporal gyrus; rPHG: right parahippocampal gyrus.

CONCLUSIONS

This doctoral thesis states that men and women with crack cocaine use disorder (CUD) have substantial differences in the way the disorder is expressed and their relationship with the biopsychosocial domains. Taking the sections of the work together, it can be seen that sex differences may precede crack cocaine use and probably make a difference later in the course of drug use. This means that there are sex differences across all stages of crack cocaine use, from initial drug use to transition to CUD. After the disease truly starts, sex differences continue to progressively rule out different trajectories for related outcomes. The similarities in general terms are that the magnitudes of detrimental outcomes increase as the disease progresses. Optimal implications of such conclusions include a call for reviewing attitudes toward crack cocaine use prevention, treatment, study, and general understanding.

Depiction of Crack Cocaine Users Considering Sex Differences

Sex differences in the rates of use, prevalence of CUD, sociodemographic profile (including age, education level, income, and employment), crime involvement, and social problems were reviewed. There is published data in this regard, but this thesis included a work investigating the psychosocial profiles of male and female crack users because there were some gaps in the information when taken altogether. Previous works rarely had large samples, not always taken care of statistical corrections, and even more rarely combined psychopathological, sociodemographic, and related variables in the same study. Exceptions are epidemiological studies on use and prevalence, which have used rigorous methods and assessed several participants (UNODOC, 2017; Winstock et al., 2017). Thus, a starting point for constructing a depiction of sex differences in crack cocaine users is to assume that the proportion of males using crack cocaine is at least three times higher than that of females.

Because the data described here came from studies with CUD participants, the conclusions are not specifically applicable to crack cocaine users in general terms. Based on

the results tested in the Empirical Section and reviewed in the Theoretical Section, a depiction of the sociodemographic profile of people with CUD who enroll in detoxification treatment follows. Moreover, a note is important: the thesis presents some models for considering future perspectives, but not all of them could be tested, since in this thesis, works had purposes that were more descriptive.

For the starting point, there are more males than females with CUD seeking treatment, as stated in the literature (this is due to a higher prevalence in males, as well as fewer female-oriented treatments and social pressures and stigma; UNODOC, 2017; Winstock et al., 2017). In addition, some published data have suggested differences in the age of males and females who use crack cocaine (Abdalla et al., 2014), but when large sample was tested here, no difference was found. Considering the number of subjects, it seems that age is not a point of difference, but the conclusion of a single work as the one in Chapter 4 can jeopardize conclusions.

Whether or not there are sex differences in relation to age, the lifespan of drug use and the age of onset may be more relevant for the evolution of aberrancies. Additionally, given that this thesis has shown sex differences in the connectivity of brain networks in crack cocaine users, it would be worthwhile to review the "brain disease" theories about addiction considering known sex differences. Furthermore, the most important theory of sex differences in addictive disorders—the telescoping effect—could also provide evidence, as could its update, the second stepper downward spiral.

To discuss results and present the conclusions, it is necessary to return to a previous point: CUD is not only a brain disorder. This is important to restate because the first suggestive conclusion of this doctoral thesis is that brain triggers may not be the most important starting point of crack cocaine use. Before the start of drug use, psychosocial variables probably play a larger role in making people vulnerable.

Sex Differences Before Drug Use—Dissolving the Protective Factors for Females

Males are more vulnerable to starting to use drugs because they are previously stressed out, whereas females are partially protected by sociocultural factors. In particular, the cultural stigma on males and females using drugs and the violence in drug markets position females as more distant from engagement in drug use (Becker et al., 2016; Courtwright, 2012). Taking a glance at female crack users, it seems that those who begin crack cocaine use had issues in their lives that dissolved those protections before they started to use drugs. These issues were the sociodemographic characteristics that every society has—social, economic, and educational inequalities—in addition to gender inequalities favoring masculine oriented-ones in a cisgender perspective (Stoltman, Woodcock, Lister, Greenwald, & Lundahl, 2015; Williams & Sternthal, 2010).

Additionally, mental disorders and life stress events, well-recognized risk factors for addiction, may also play a role in females' entry into drug addiction (Miller et al., 2011; Yücel, Lubman, Solowij, & Brewer, 2007). Interestingly, stress experiences previous drug use has sex-dependent effects, often impacting females more strongly than males (Potenza et al., 2012; van den Bos, Harteveld, & Stoop, 2009). Thus, a hypothetical conclusion to be drawn is that once females break the "social checkpoint gate" and enter a drug-use spiral, other neurobiological vulnerabilities start to act in interactional ways, pushing females' neuroadaptations more quickly than those of males.

Social inequalities. Data can support the existence of social inequalities in CUD. As aforementioned, possible sex differences in health opportunities are a possible outcome of cultural judgments about the use of drugs by males and females (Courtwright, 2012). However, in the data evaluated, some other points also could reveal social inequalities from a cultural perspective.

Differences in self-declared ethnicity showed the same trend in males and females. In general, there were more white people, followed by black people and others. However, taking the proportions, there are more white males than females and more black females than males. These results were not major findings, but they are worth noting because they can be used to suggest that social disparities—such as those between males and females—are extended in health care. The average Brazilian crack user is described as nonwhite (Bastos & Bertoni, 2014), but estimates here indicated that more than half of the male sample was white. This needs more investigation, but it is possible that, because there are more male crack cocaine users, known ethnical disparities in access to health care (Nazroo, 2003; Williams & Sternthal, 2010) appear more for male than for female crack cocaine users. This would mean that some non-Caucasian male crack cocaine users lack health care assistance because of social exclusion. In published works, no such sex difference was noticed. As the result is preliminary, it requires replication, but it is an important factor, as ethnicity has a considerable influence in CUD (Evans, Grella, Washington, & Upchurch, 2017).

Economic and educational disparity. Economic status also appeared as a variable of difference between males and females using crack. Overall, users have low education levels, suggesting it is an important contributor to entering into CUD. Moreover, based on the theory of motivated behaviors, the sooner drug use starts, the more it causes brain development to deviate from the typical route (Ernst & Korelitz, 2009; Ernst, Pine, & Hardin, 2006). As the pace of deviation increases, it is particularly expected to cause a lack of cognitive control and motivational systems (Ernst et al., 2006). Additionally, cerebral maturation is also stimulated by other experiences, such as higher education and an enriched environment (Eccles, Barber, Stone, & Hunt, 2003; Hackman & Farah, 2009).The lower education status of female crack cocaine users seems to contribute in a negative way.

Alongside education, there were also sex differences in relation to economic level. As previously stated, lower economic status can have an influence in reducing other protective factors, particularly in countries such as Brazil. Lower income people need to live in peripheries. In countries that are not well developed, peripheries mean places with increased risks for illegal activities, especially drug trafficking. Thus, low income can reduce females' protection from violence in places where drugs are sold, because in fact they may already be living there. In addition, other protective factors for females' crack cocaine use include social prejudice against women who use drugs. However, it is well known that drug users very often have parents who also use drugs (Yur'yev & Akerele, 2016); thus, it is possible that females using crack cocaine had received counterconditioning in this regard at home, particularly taking into account that female crack users tended to declare to have more children.

Mental disorders. Without focusing on particularities, which were outlined in Chapters III and IV, it is remarkable how sex differences exist in relation to mental disorders. More specifically, a lifetime history of psychiatric disorders could be used as background for understanding previous mental disorders as a vulnerability factor for females. Moreover, given the highest rates of differences regarding trauma- and stress-related disorders, there is support for the idea that mental disorders increase vulnerability for drug use (Chambers, Taylor, & Potenza, 2003). In particular, stress-related consequences, especially for those resulting from childhood maltreatment, are impactful in increasing vulnerability for addictive disorders (Andersen & Teicher, 2009). Therefore, although the data are not indisputable because this was not a longitudinal work and did not evaluate data retrospectively, it is possible that premorbid psychiatric disorders contributed to the initiation and escalation of drug use.

Sex-specific theories for drug use initiation. Considering theories of the initiation, habituation, and progression of addiction, it can be concluded that the existence of a mental

disorder could turn females into people with a reward deficiency. In the original model, how the reward system becomes aberrant is not of importance, but the key is inefficacy in processing ordinary rewards as well as possible (Blum, Cull, Braverman, & Comings, 1996). Therefore, mental disorders are more likely to cause a reward deficiency in females than in males, and a possible consequence is that females seek drugs to cope with that emotional pain. This proposal would support self-medication theory (Khantzian, 1987; Khantzian, 1997).

For males, the path is probably different. A possible explanation is that similar forces to those that protect females from initial drug use also help males accept their mental suffering and seek help. In other words, the social stigma toward psychiatric conditions, which are much more acceptable in females than males, make males avoid coping with emotional problems. Even though stigma is an issue in general, it could be protective with regard to drug seeking in males (Corrigan & Watson, 2002; Crocker & Major, 1989). In addition, most mental disorders are more prevalent among females than males (Kessler et al., 2006). However, social context more often puts males in environments that encourage drug use, particularly drinking. As a result, males may start to drink earlier than females and have a more severe history of alcohol use. It is also possible that males may seek other drugs to "self-medicate" from the effects of other substances. This supports the suggestion that males use drugs more often than females to balance effects of other drugs (because alcohol and crack cocaine are a depressive and a stimulant drug, respectively, these substances could counterbalance each other; Kennedy, Epstein, Phillips, & Preston, 2013).

In this model, males would "self-medicate" to cope with physical needs, and females would do so to cope with emotional ones. Therefore, the environment would have an important role in shaping the beginning of drug use, as well as psychiatric status and stress.

Brain Disorders Drive Sex Differences in Habituation and CUD

Unfavorable social conditions would dissolve some of those protective barriers for females. In addition, by combining psychosocial issues with biological vulnerability to neuroadaptations, after the barriers become dissolved, further landmarks in the crack cocaine use pathway become shorter for females than males. Therefore, once they begin drug use, females are particularly vulnerable to advancing faster in a downward spiral through the transition from initial drug use to addiction. This occurs because interactional characteristics make females more responsive to neuroadaptations because of stress, psychiatric disorders, and drug use. Additionally, females are more likely to use drugs to cope with negative affect (Kennedy et al., 2013) and thus to increase doses and push neuroadaptations even more.

Moreover, puberty is the stage of development in which psychiatric disorders usually emerge (Kessler et al., 2005). If females aim to cope with symptoms by using drugs, they may begin in drug use without completing brain development. In addition to the fact that earlier drug use may impact development (Ernst, Romeo, & Andersen, 2009), the maturation of the female brain is slower than that of males (Lenroot & Giedd, 2010). Thus, the development time span of the brain, together with the age of starting drug use, can also explain sex differences in CUD.

Along these lines, if females and males started to use drugs at the same age, females would be at a greater risk. However, for crack cocaine it is even worse for females, who report an earlier onset of drug use. Figure 1 summarizes how psychosocial previous issues may contribute for drug use onset and after that suffer interactions from sex-specific neuroplastic influences. It shows how males have increased vulnerability before drug use, making it easier for them to begin drug use. Nevertheless, although fewer females begin drug use, the spiral evolves faster because of their susceptibility to neuroadaptations after initial use. Changes in brain functioning and structure occur because of the differential influences of

stress, the rhythm of brain development, previous drug use, and the activation effects of the menstrual cycle.

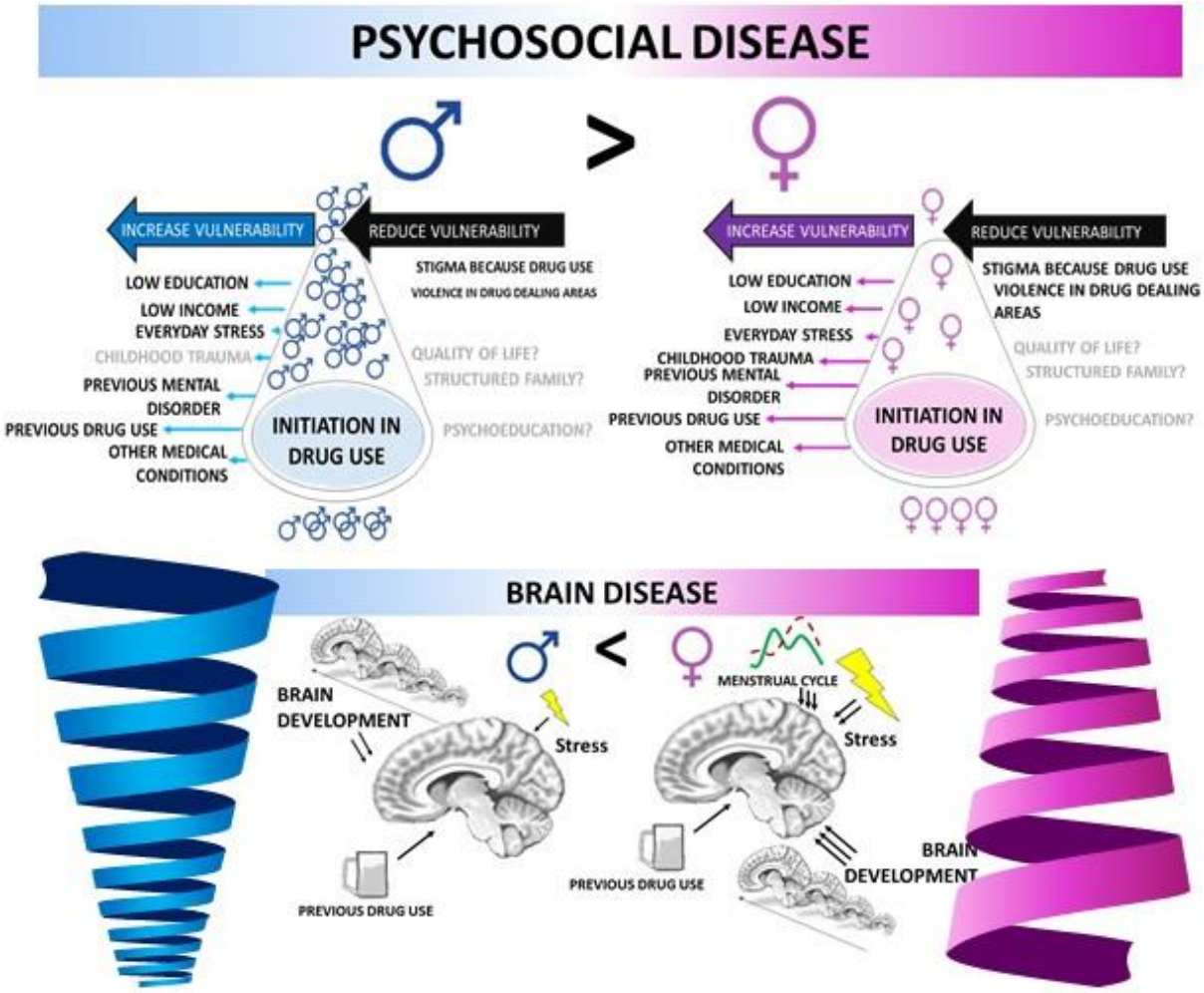

Figure 1. The path from before crack cocaine use to brain disease. The psychosocial environmental forces, together with psychological vulnerabilities play for males to have more vulnerability to use drugs. The sizes of the arrows indicate the strength of each factor. Factors that are not fully supported are shown in gray. As depicted, after the initiation of drug use, the "brain disease" starts to act more intensely. When it starts, neuroadaptations also appear. As shown, at this moment females have more vulnerability, different than when the "psychosocial disease" was in action. The signals between the sex symbols indicate which one has more vulnerability. At the start of drug use, the downward spiral starts. In the figure, the spiral for males is larger at the top and then gets thinner because it

is easier to get into the spiral for males, but there are more steps along the way. For females, as neuroadaptations happen faster, the top of the spiral is thin, because they are not as quick to start down that path. However, after they land on that path, their spiral is faster, has fewer steps, and seems more difficult to stop. When on the path to CUD, the brain is particularly vulnerable to some variables, represented in the figure. The number of arrows indicates how strong each variable is for males and females. It is worth noting that previous drug use has the same impact for both groups. The real difference is that males are likely to have more previous drug use, but not necessarily dimorphic vulnerability for CUD development as a result.

As can be seen, the menstrual cycle seems to have an important role in the dimorphic crack cocaine use trajectories. In particular, activation effects occur because of the presence of sex hormones. In this regard, the fluctuations during a cycle, especially from estrogen and progesterone, increase rewarding effects and promote plasticity, respectively (Collins, Evans, Foltin, & Haney, 2007; Evans & Foltin, 2006; Lukas et al., 1996). In this thesis, the menstrual cycle was unfortunately not considered as a controlling variable. However, it is important to note that data on periods was taken during the research, but the determination of the phase was extremely limited due the use of hormonal contraceptives and even amenorrhea caused by crack cocaine use (Cooper, Foltin, & Evans, 2013).

However, this thesis indicates directions for future research by suggesting that the menstrual cycle has a role in the initiation and transition to CUD. A theoretical hypothesis about the influence of the menstrual cycle in the female transition is depicted in Figure 2. As shown, when estrogen is higher, rewarding sensations are higher (Lukas et al., 1996; Sofuoglu et al., 1999). Nevertheless, as estrogen falls and progesterone increases, cocaine-induced effects decrease. As a behavioral response, those who develop pathological

conditions will escalate doses in attempts to achieve previous rewards. The strategy will lead to unsuccessful results and, because of progesterone-induced facilitation to neuroadaptations (Rilling & Young, 2014), tolerance and abstinence will escalate together. At a certain point, the continuation of this path will make the previously desired reward become a need to avoid dysphoria. At this point, habituation will start, and the second stage of the spiral will commence. Alternative models when there are medical conditions, acute stressors, or a combination of such factors can become implicated in the interaction, causing even faster advances. Moreover, the original suggestion of the downward spiral assumes that more women will start drug use while trying to cope with dysphoria (Becker, Perry, & Westenbroek, 2012).

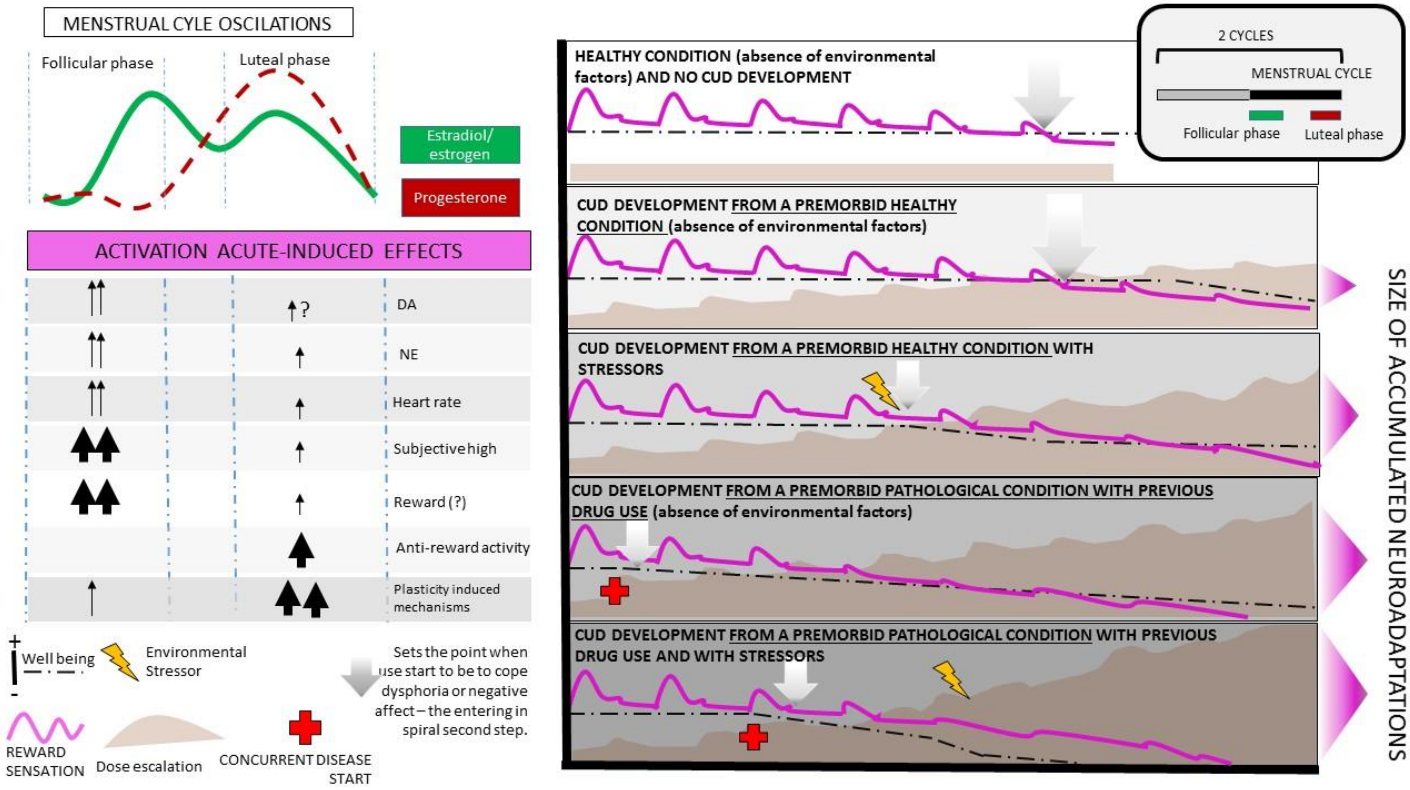

Figure 2. A model of the influence of menstrual cycle on the transition from initial crack cocaine use and pathological consequences. Taking into account the major phases of the menstrual cycle and fluctuations of the main hormones during the follicular and luteal phases, together with data on effects of acute use of cocaine, a model of interaction and differential effects of such an activation was suggested. The follicular

phase increases the hedonic pursuit, in addition to giving females a memory about the rewarding effects. The luteal phase causes activation effects similar to those of reward deficiency. In addition, the luteal phase accompanies an increase in plasticity. Therefore, as females escalate doses to seek the rewarding effects they previously achieved because of interactional estrogen effects, neuroadaptations accumulate. Thus, there is no meaningful return from the previous dosage, which progresses. The model additionally highlights how other intervenient factors can have a place. As aforementioned, dysphoria may lead to drug use as a coping strategy, particularly in females. As a consequence, the presence of a mental disorder could make the escalation more pronounced. Likewise, stress may also acutely cause a huge increase in dose consumption and reduction in well-being. The model is initial, but it is known that the accumulation of stress events will lead to chronic changes that may persist, increase the risk of stress response, and increase susceptibility to the reward system even more. The accumulation of neuroadaptations is shown by the sizes of the triangles in the right margin. In the model, the size of neuroadaptations was a measure of how much a reward deficiency syndrome appeared with increased tolerance for drug use.

The Brain Disease Evolves—Habituation and Progression

The accumulation of neuroadaptations and earlier transition to CUD in females support the existence of telescoping effects, taking into account the clinical profile of females as worse than that of males. Likewise, data on the higher severity of drug use in females in comparison to males, as discussed in Chapter IV, support this finding. However, at the level of the brain, this seems inaccurate to report, as the effects appear to evolve in opposite directions, although apparently neither of them is good. Therefore, there is support for telescoping effects, but caution should be taken when discussing the progressive detrimental consequences. This is necessary because one can imagine that similar biological changes may occur, but they may happen faster in females. One suggestion is that after neuroadaptations start, males and females may follow some different pathways.

The involvement of reward-related areas is probably a shared characteristic, which means it is a similarity. Moreover, differences in the salience network (SN) FC also seem present. The SN is an attentional network that interacts with reward processing by selecting emotionally relevant stimuli in the environment (Hester & Luijten, 2014; Killgore et al., 2003; Volkow et al., 2011). In this sense, the results indicate that SN is the only network that has higher FC strength in female crack cocaine users. As the data were collected in resting conditions, female crack cocaine users intrinsic brain functioning appears most focused in internalized and emotion-related processes. Male crack cocaine users, on the other hand, showed much higher inter- and intra-network FC, which may represent highly connected, implicitly driven mechanisms, since the core of controlling networks was not found with stronger FC. Figure 3 depicts a summary on results of the Chapter 5 by grouping differences related to intra- and inter-network FC related to those brain networks that are often are associated to have changes in mental disorders (i.e., SN,

DMN, Control Network, FPN, and DAN). The objective of this figure is to show how male crack cocaine users have higher coherence in intrinsic brain connectivity across different networks that seem interconnected by some of those ReHos, particularly those related to sensory-motor processing. Female crack cocaine users, however, had only one increased FC signal, which linked a multimodal integrative structure that plays a role in awareness (Crick & Koch, 2005; Schulz, 2016) with the salience network.

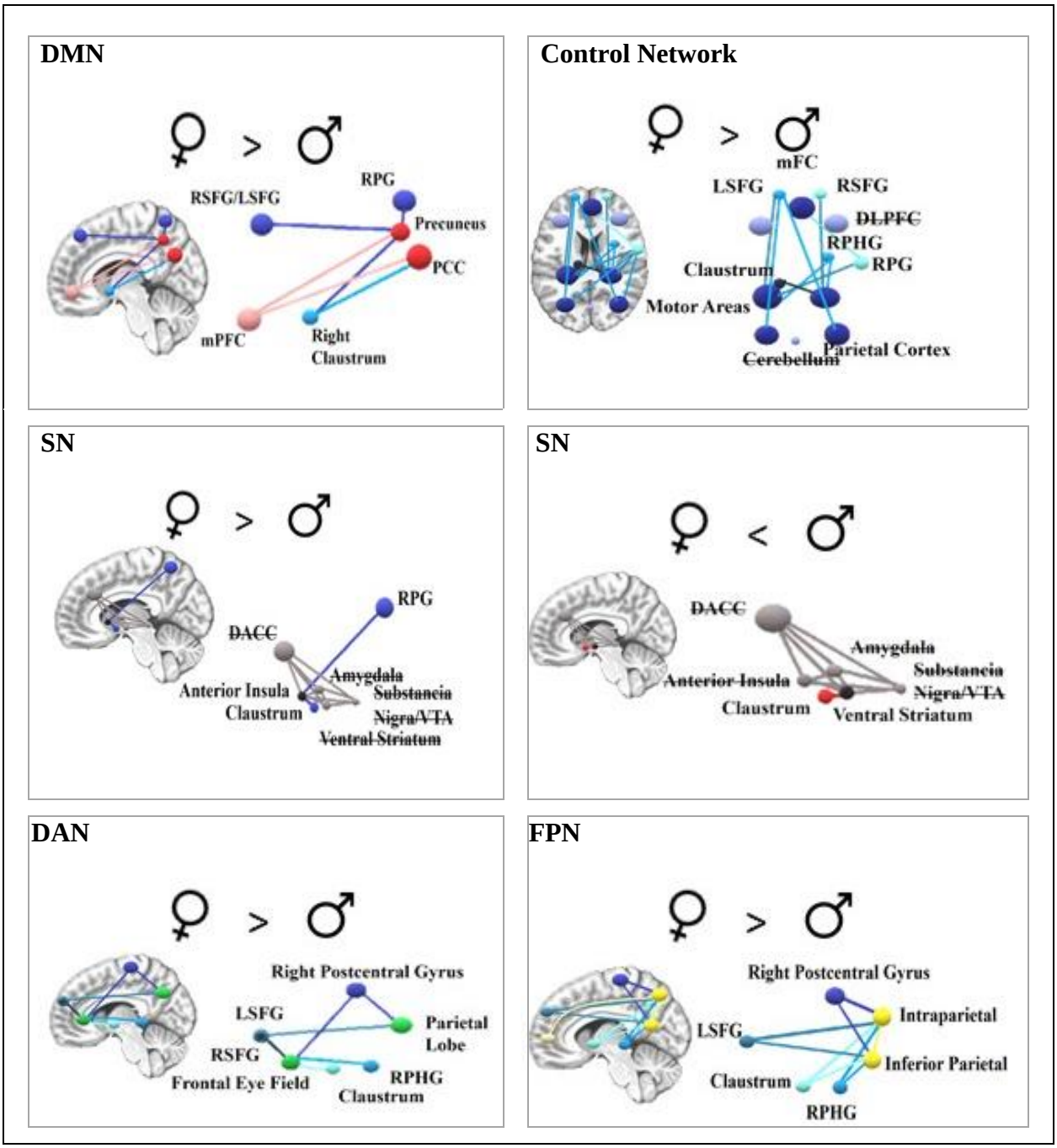

Figure 3. Sex differences linking ROIS and different networks into differentiated networks/systems. The figure shows a summary of the findings of FC between nodes with high ReHo connecting brain networks. The signs above the pictures indicate whether each FC was higher for CK-M or CK-F. When a node or edge is in a weaker color, it means there is no difference between groups at that point of the network. DMN: default mode network; SN:

salience network; DAN: dorsal attention network; FPN: frontoparietal network. RSFG: right superior frontal gyrus; LSFG: left superior frontal gyrus; RPG: right postcentral gyrus; PCC: posterior cingulate gyrus; mPFC: medial prefrontal gyrus; mFC: medial frontal gyrus; RPHG: right parahippocampal gyrus; DLPFC: dorsolateral prefrontal cortex; VTA: ventral tegmental area; DACC: dorsal part of anterior cingulate cortex.

The results are incorporated into a final propositional model for integrating brain functional results into sex-specific models. For males, a hyper-responsive state probably occurs because of the higher FC between networks. In females, the accumulation of psychosocial events, such as ones regarding stress, probably leads to a reduction in overall functioning by an allostatic mechanism that works by helping the reward system to maintain its integrity (Koob & Le Moal, 2001, 2008). However, because of the psychosocial learning that female have and the increased likelihood of using drugs to cope with negative affect, female crack cocaine users learn that stress is a cue. This manifestation can be noticed in higher levels of stress-induced craving in females (Kennedy et al., 2013; Potenza et al., 2012; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). Thus, the neuroadaptations that would work to protect them may further increase their risk of drug use. Figure 4 shows a summary of this final model of how male and female crack cocaine users brain FC results in different types of malfunctioning, contributing to disease progression.

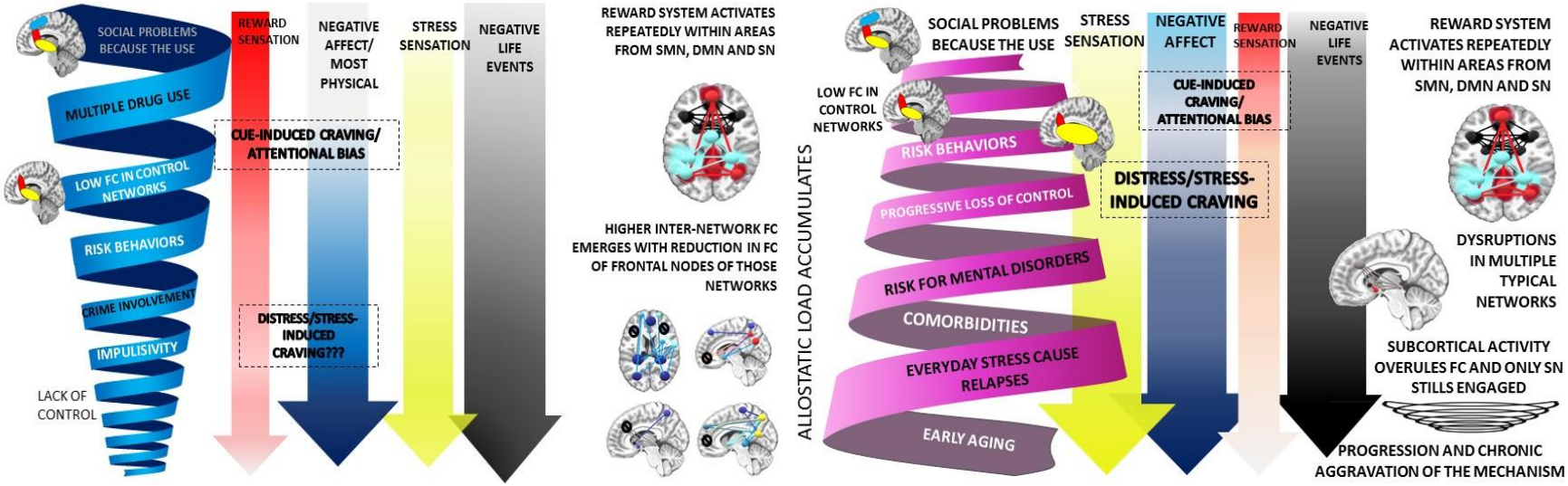

Figure 4. Propositional models for the CUD progression. In the figure, a combination of the results and background data support different models for male and female crack cocaine users, suggesting pathways may have similarities, but also sex differences. Sizes of signs and darker colors meant more intense occurrences.

A propositional model for male crack cocaine users brain disease networks. Males showed increased FC across different networks. In particular, the results for DMN, control network, FPN, and DAN indicate that there is increased overall FC in a large-scale network. The nodes that seem to bridge different networks in one single large network are mostly those within the limbic and motor areas. In conclusion, neuroadaptations in males probably involve dopaminergic projections, linking reward-related areas with motor ones by mesocorticolimbic (MCL) functional networks (Nieoullon & Coquerel, 2003). It seems that male crack cocaine users integrate multiple sensory, internal, and cognitive networks. However, these increases do not appear to encompass some critical controlling areas, including the dlPFC, mPFC, and ACC. Given the considerable controlling roles of these structures in their respective networks, the brain functioning of male crack cocaine users seems to be oriented to salience and behavioral initiation. Such results give support for suggesting that males with CUD are more driven by salience-incentive theory, as supported by hypofrontalization networks.

Before concluding the male crack cocaine brain model, something interesting must be noted. Previously, the self-medication hypothesis was presented as a strategy for males to cope with acute physical discomfort. However, it is possible that male crack cocaine users actually try to reestablish PFC activity by taking stimulants. That would deactivate the coupling between motor and limbic areas, which also matches the findings of works based on rs-fMRI following acute cocaine use (Konova et al., 2015; McHugh et al., 2014). Thus, this use would not be "self-medication to cope with a condition" but rather to cope with an internal brain state that arises in the sensory-motor neurons.

A propositional model for female crack cocaine users brain disease networks. Females did not show higher FC across any network besides the SN. In this context, female

crack cocaine users had higher claustrum-SN FC. The claustrum is a structure that plays an integrative function. The higher SN FC with it suggests that females probably include emotional-relevant information in the integration of multimodal processing most of the time. This would cause different reactions than in male crack cocaine users, even though males also has claustrum-SN FC. This would be the case for two main reasons: This is the single FC higher in females, whereas males have several controlling networks involved that can play a role in controlling emotionally driven answers (although the core controlling areas are not strong in those networks). Moreover, in males the structure linking SN with the claustrum is the insula, which has characteristics of interoceptive emotional regulation, which is partially like those functions from the claustrum. In males that FC would mean an interoceptive system. However, in females the striatum is a reward-related area and may participate in triggering responses.

Additionally, female crack cocaine users are particularly susceptible to stress effects. FC changes are linked with higher integration of internalized memories, which is often noticed in traumatic conditions. Given the higher susceptibility to stress in females, in addition to reduced overall FC, it would be a natural conclusion that allostatic effects have occurred. However, in contrast to the theory, the reward system did not appear to be unaffected. In reality, allostatic load probably accumulated, trying to keep the reward system working on. This failed as it was initially supposed to be because of the accumulation of effects, but for a supervisory system of rewarding system it seems to had worked. Thus, although reward system may not still working as if there was no negative issues, the SN does increase its functioning.

Thus, psychosocial distress may cause disruptions in the functional connectome of female crack cocaine users because a biologic mechanism is attempting to keep the reward system working, which is the allostatic load model for addictive behavior (Koob & Le Moal, 2001). As a

consequence, maintenance of the supervisory system of reward processing is still strong (or increases in strength). The final consequence is that females have a lack of control caused by many mechanisms and reduced FC with controlling networks. This would also explain the increased relapse and involvement in risky situations because of reduced cognitive control. Moreover, in addition to reduced cognitive control, allostatic load keeps an attentional system focused on cues and everything that could be interpreted as they are—the SN. Thus, when emotionally relevant stimuli are noticed, sensitization of MCL pathways appears, and responses may be higher than in males (Li et al., 2005; Li & Sinha, 2008; Potenza et al., 2012). An important note here is that CK-F probably interpret negative affects like cues. This probably occurs because of conditioning, as females more often use drugs to cope with negative feelings (Kennedy et al., 2013). When feeling bad they have a memory of drug, which is triggered by the links between the SN and the claustrum and limbic areas.

Future Directions

The conclusion of this doctoral thesis could be summarized to indicate a need for attention to sex differences in crack cocaine use. The parts of this thesis had descriptive characteristics, so there was no testing of hypothesis on the mechanisms that drive CUD in dimorphic ways. In this line, the thesis has described the existence of sex differences and the need to address them. In conclusion, some hypothetical models combining the results were suggested. Moreover, prospective directions for research and clinical practice in this regard are presented.

Directions for prevention considering sex differences. As stated, although no part of this thesis was longitudinal, the sex differences noticed may not be due solely to the consequences of drug use. Therefore, some points may show differences even before the onset of

the disease. Premorbid sex differences may include a combination of sociodemographic and mental health issues. An initial depiction of female vulnerability was presented, but in fact, studies need to focus on being more predictive about the weights of different variables in drug use initiation. Moreover, ways to address social stigma need to be included in such models. The best model, despite the well-known difficulties of carrying out such studies, would be cohorts of children from peripheric zones. Studies with the sons and daughters of drug users could also be useful in depicting possible vulnerability factors in a more complete and sex-specific way.

Research on the topic must evolve to give better support to prevention. However, there were differences between male and female crack cocaine users in age of drug use onset for many drugs. Marketing campaigns more focused in children and adolescent male alcohol use, for example, would be worth testing, since early alcohol use and progression in males seems to occur at same time that crack cocaine use and may interact with it for initiation.

Directions for studying sex differences in drug use initiation. Probably one of the most necessary goals of future research in making clear the sex differences in the pathways leading to CUD is the menstrual cycle. After drug initiation, multiple interactional variables may play a role in facilitating neuroadaptations in females, and the menstrual cycle may have a remarkable impact. Although there is a background integrative studies still not testing it more detailed. Most studies have focused on understanding the acute effects of the menstrual cycle in relation to the effects of crack cocaine. A suggestion would be animal studies to focus on the effects of the menstrual cycle on crack cocaine use progression. Additionally, as proposed previously, it would be interesting to test how the phases of the menstrual cycle interact with other relevant variables in drug use, such as stress and mental disorders. Moreover, the

investigation of the maintenance of such effects on already addicted females would also be interesting.

In this thesis, negative affect and motivations for drug use were used as a core background for supporting differences in the CUD course. However, more detailed studies along these lines may be required. Although difficult, qualitative research could help on promoting advances in this regard. Furthermore, maybe an appearance of this phenomenon could be addressed by using retrospective questionnaires.

Directions for understanding and addressing sex differences in CUD progression. According to the results, CUD runs a different course in males and females. As suggested, the culmination of many interactions between activation of the different phases of the menstrual cycle, behavior response, previous experiences, and environment make females have a faster transition to CUD and advance more quickly in the disease in comparison to males, leading to a more severe outcome. Indeed, the results supported that the brains of male and females who use crack show lower FC between networks, which may be related to a worse outcome.

The suggested mechanisms that support the evolution of sex differences after CUD development is one of the classical theories of addiction—the allostatic load. Since stress and reward systems overlap with each other, it is suggested that the stress system changes its functioning in order to keep rewarding system integrity. Here there is a lack of knowledge that future experimental studies could address. First, the existence of this allostatic mechanism needs to be better understood. In fact, an alternative that our results could suggest is that rather than the reward system still working well, the SN does. The SN is a network that supports the emotional systems. By this token, studies testing the SN relationship with different types of emotional response are of interest.

Furthermore, the progression of the uncoupling of different networks is probably a sign of early aging which, in line with the telescoping theory, probably comes earlier for females than males, as it is a hypothesized negative outcome. New techniques on testing the advances of aging could be used in this regard for further studies on sex differences. In addition, the suggested faster aging may have different signs in males and females, as it is more noticeable in the rs-fMRI of females than males. Thus, although suggestive that the differences in rs-fMRI could also be a sign of early aging, it is unclear if indeed there is earlier aging in females than in males who use crack cocaine.

The conclusions of this doctoral thesis must also be taken into consideration as directions for future CUD treatments. In female treatment, additional attention to comorbidities and trauma should be prioritized. Although it needs investigation, the restoration of inter-network FC could be interesting to test. For males, drugs and the adequate addressment to treat drug addiction still be a focus. Previous works on the increasing functioning of PFC areas in other addictive disorders have indicated that there is a match for the hypofrontality in males who use drugs, as such interventions have reduced craving. However, these interventions worked by increasing activity, not necessarily reestablishing FC between frontal areas and other controlling networks. As a result, such interventions may affect brain hyperactivity in such individuals, which according to impulsivity theory would not be good (Jentsch & Taylor, 1999; Moeller et al., 2001). However, such hyperactivity may have core controlling areas such as central nodes that balance hyperactivity.

From a clinical perspective, it has already been stated that there is a need for sex-specific treatments. Considering the number of sex differences, this conclusion is not baseless. However, empirical data supporting that female- or male-only treatments have higher retention rates or

result in a longer period of abstinence than mixed-sex treatments could validate this idea even more.

Final Statements

As a final conclusion, this doctoral thesis indicates that there are sex differences in CUD. The results reinforce a background for sex differences in CUD and fulfill the call for more research on the field. Moreover, if possible meta-analyses are carried out in the future, the adequate reporting of values for males and females in studies may become necessary. Additionally, the results suggest that the development of CUD has dimorphic characteristics. Because of as a result, further studies on biopsychosocial mechanisms must consider the existence of sex differences, and maybe even test for different pathways. Finally, strategies for addressing the prevention and the treatment of CUD may also require sex-specific interventions, although by now there is little support for such sex-based interventions.

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COMPLEMENTARY SECTION

COMPLEMENTARY SECTION 1: Crack-Cocaine Dependence and Aging Effect on Working Memory

Breno Sanvicente-Vieira, Júlia Kommers-Molina, Tatiana De Nardi, Ingrid Francke, Rodrigo Grassi-Oliveira.

COMPLEMENTARY SECTION 2: Resting-State Functional Magnetic Resonance Imaging as a Tool for Psychological Sciences: Fundaments, Methods, Definitions and Possible Applications

Breno Sanvicente-Vieira, Leonardo Rothmann, Nathalia Bianchini Esper, Rodrigo Grassi-Oliveira, Alexandre Rosa Franco

COMPLEMENTARY SECTION 1

Crack-Cocaine Dependence and Aging Effect on Working Memory

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ABSTRACT

Objective: To compare the working memory (WM) performance of young adult crack-cocaine dependent users, healthy older adults and a control group of healthy young adults.

Methods: A total of 77 female participants took part in this study, 26 young adult crack-cocaine dependent users (CRK), 19 healthy older adults (HO), and 32 healthy younger adults (HC). All participants completed the N-back verbal task.

Results: A multivariate analysis of covariance (MANCOVA) was performed. The model included education, income, and medication use as covariates. A group effect [$F(6,140) = 7.192$, $p < 0.001$] was found. Post-hoc analyses showed that the performance of the CRK and HO groups was reduced compared to the HC group in two N-back conditions. No differences between HO and CRK group on WM performance were found.

Conclusions: CRK participants perform similar to HO participants on WM, despite well-known age effects on WM and the young age of CRK. The data points to a possible parallel between cognitive declines associated with crack use and developmental aging.

Keywords: working memory; crack cocaine; aging; substance use-related disorders, cognition

Introduction

Crack-cocaine use has been shown to cause toxic effects on the brain, particularly in the prefrontal cortex (PFC). Subsequently, such abnormalities associate to neuropsychological impairments, including deficits in the working memory (WM) [1, 2]. Interestingly, PFC alterations [3] and decline in WM performance are recognised as normal consequences of natural aging [4]. Imaging data supports that gray matter volume loss over time is twice as fast among cocaine users as in healthy individuals. Given that gray matter volume in PFC has been related to WM performance, it is presumed that cocaine use impacts WM as well, this has been corroborated by behavioural results [5]. In addition, preliminary data suggests that cocaine use and aging have interactive effects on neuropsychological integrity, increasing impairments and everyday problems [6].

WM is a high-demand cognitive process that involves maintaining and manipulating information in the absence of external cues. WM has been described as critical to several other cognitive processes, such as executive functioning and social cognition, and to everyday functioning [7]. Deficits in WM performance are also associated with clinical symptoms found among cocaine users, for example, higher impulsivity traits [1] and higher dosages of drug consumed [8].

Given the suggested importance of WM to the neuropsychological functioning of cocaine users and the hypothesis that cocaine use could cause a decline in WM performance, this study sought to compare the WM of young adult crack-cocaine users to healthy older adults and healthy young adults. The hypothesis is that adult crack-users would show a WM performance equivalent to the older group instead of their same age group.

Method

Participants

Since crack-cocaine use [9] and cognitive aging [10] show gender effects, only women were included in this study. Seventy-seven women were recruited and selected by convenience. The sample was separated into three groups, healthy control adult participants (HC, n = 32), healthy older participants (HO, n = 19), and crack-cocaine dependent users (CRK, n = 26). The age cut-offs used to determine the participants as adults or older adults were based on the criteria established by the World Health Organization (WHO), adults between 19 and 59 years old and aged adults are more than 60 years old [11]. The two groups of young adult participants (HC and CRK) were age-controlled to avoid age-related biases. The exclusion criteria were as follows: a history of neurological illness, head injury, actual pregnancy, dementia symptoms as assessed by the Brazilian version of the Mini-Mental State Examination (MMSE) [12], current treatment for any substance or alcohol dependence (in the controls only), and any psychoactive drug use within 24 h prior to testing (except caffeine and prescribed drugs). The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (SCID-I) [13] was used for determining the exclusion/inclusion of healthy participants.

All healthy participants (HC and HO) were recruited through institutional advertisements and assessed by a clinical interview. All participants from the CRK group fulfilled the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for cocaine substance dependence, confirmed by the SCID-I. The CRK group came from a public inpatient detoxification program. Patients had abstained from drugs or alcohol for at least 14 days at the time of the cognitive evaluation (M = 17.30 days, SD = 0.55 days). Among the CRK group, the mean age of alcohol use onset was 14.97 (SD = 5.35); the mean age of cocaine/crack use onset was 18.32 (SD = 8.4) and the lifetime cocaine/crack use time

was around 7.67 years (SD = 9.87). Among the CRK group, some participants fulfilled criteria for depression (n = 7), post-traumatic stress disorder (n = 3), alcohol use dependence (n = 8), and cannabis use disorder (n = 4). All CRK participants referred to use smoked cocaine (i.e., crack).

Instruments and procedures

To assess WM performance, the Brazilian version [4] of one verbal N-back task described by Dobbs & Rule [14] was used. In the task, one number is presented at each second. Unlike in the digit-span task, rather than remembering a list of numbers, the subject must identify when the current stimulus matches a stimulus *n* steps back in the sequence. The N-back task was selected because it is a popular WM test. As its loading increases, more and more cognitive effort is demanded, making it sensitive enough to detect subtle WM differences between groups. In this study, three different target conditions, "n = 1," "n = 2," and "n = 3" were used. Before each procedure, a study phase was conducted to make sure each participant understood the rules. The participant should remember the number at *n* steps back in the list following the presentation of each further item. There was a total of ten items to be remembered in each condition and it is assumed that the more the participant can remember, the better their WM performance.

Data Analyses

The data were screened for violations on normality and log transformations were performed when necessary. The demographic variables were compared using one-way ANOVA. Additionally, N-backs 1, 2, and 3 were used in a multivariate analysis of covariance (MANCOVA) as dependent variables. The group was included as a fixed factor and all individual variables that had shown significant group differences were considered as covariates in the MANCOVA model except age, since it took part in our group variable.

Post-hoc tests based on Tukey's test were performed to examine pairwise comparisons. The significance level was set at $\alpha < 0.05$ (two-tailed).

Results

The groups differed in years of formal education, individual income antipsychotics and use of antidepressants, and these were included as covariates in the MANCOVA model. The group was set as the fixed factor and the measures of the N-back 1, 2, and 3 were the dependent variables. A significant group effect was found [$F(6,140) = 7.192$, $p < 0.001$]. The Tukey post-hoc analysis showed that CRK and HO groups exhibited similar WM performances in all N-back levels and also that both CRK and HO groups performed more poorly than the HC group in N-back 2 and 3. Table 1 shows the comparative results.

Table 1 Demographic, clinic and WM comparisons between groups

	HC (n = 32)	HO (n = 19)	CRK (n = 26)			
	Mean (SD)	Mean (SD)	Mean (SD)	df	Statistics	Post-hoc
Age (years)*	27.75 (9.69)	69.79 (4.69)	27.88 (7.10)	2, 74	F = 373.41	HC, CRK < HO
Years of education*	15.47 (4.69)	11.05 (3.70)	7.58 (2.95)	2, 74	F = 50.303	CRK < HO < HC
Income (US$/month)**	1972.79 (1869.68)	2946.84 (2593.16)	678.91 (1988.78)	2, 74	F = 3.391	CRK < HC < HO
Medications						
Antipsychotics*	-	0	11	1	$x^2 = 26.308$	-
Anticonvulsants**	-	6	10	1	$x^2 = 5.908$	-
Antidepressants	-	5	6	1	$x^2 = 2.899$	-
Mood stabilizers	-	4	6	1	$x^2 = 1.696$	-
Working memory						
N-back 1	8.84 (1.08)	7.89 (1.15)	7.54 (2.14)	2, 72	F = 1.69	-
N-back 2*	6.69 (1.90)	3.68 (2.26)	2.50 (2.79)	2, 72	F = 7.04	CRK, HO < HC
N-back 3*	5.34 (2.42)	2.42 (1.15)	1.15 (1.31)	2, 72	F = 18.42	CRK, HO < HC

$p < 0.001$

** $p < 0.05$

Note. Post-hoc analyses were based on Tukey's test. For working memory variables, results were controlled for years of education, individual income and medication use.

Discussion

Behavioural WM data indicated similar performances among crack-cocaine users and healthy older adults, which is poorer than that of healthy younger adults. Such results are in agreement with previous studies of differences in WM performance of both cocaine dependents [2, 8] and healthy old participants [3, 4] with typical healthy young adult participants.

Our results add suggestive data on the hypothesis of previous studies that cocaine use may cause a "fast-track" aging processes [5, 6]. A previous study found evidence that both cocaine users and healthy older adults show white matter reductions in the hippocampus and pre-frontal cortex compared to healthy younger adults [5]. Since the integrity of gray matter in these brain regions has been related to WM integrity [10], our results further support these findings. Notwithstanding, further detailed investigations, for example, looking for neurobiological evidence of the origins of cognitive problems within healthy, elderly adults and crack-cocaine users would be interesting. Heroin has been shown to cause cellular changes similar to those found in aging and it is possible that these accelerated aging processes would contribute to earlier behavioural problems in drug users [15].

The main limitations of this study include the use of a single measure for the evaluation of WM, lack of a wider neuropsychological investigation; the early time of abstinence of crack-cocaine users and the presence of other psychiatry disorders, and the incompatibility between groups regarding individual characteristics. General intelligence is an important issue that could account for WM performance and other individual differences among groups. The similar results on N-back for cocaine dependents and healthy old participants may have different aetiologies, meaning that differences could be as a consequence of different neuropsychological functions, for instance processing speed [6] and inhibition, [10] and not necessarily WM impairments. Early abstinence among crack-cocaine

users could affect WM performance differently than in other phases of the substance use. Finally, the sample was heterogeneous with regard to income, years of formal education, and medication use. Statistical methods were used to control for such differences since a comprehensive evaluation of individual characteristics was not possible.

It is not possible to state that crack-cocaine dependence ages WM, nor identify the origins of the WM impairments within each condition. However, the data is relevant, particularly for crack-cocaine dependent patients. To date, treatments for drug use are planned mainly for young adults, even though there are increasing numbers of older adults with drug use problems. According to these results, the WM performance of crack-cocaine users does not match with the expected WM performance. It is possible that actual interventions do not fit the capacities of crack users. Studies focusing on WM training showed that combined to motivational interview it can help to improve executive functions performance in cocaine dependents [16]. In addition, WM training was found to help on reducing delay discounting on stimulant addicts [17]. In summary, participants with crack-cocaine dependence, despite their younger age, exhibited almost the same performance of participants over 60 years old, while healthy, young adults performed significantly better.

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COMPLEMENTARY SECTION 2

Resting-State Functional Magnetic Resonance Imaging as a Tool for Psychological Sciences: Fundaments, Methods, Definitions and Possible Applications

Breno Sanvicente-Vieira, Leonardo Rothmann, Nathalia Bianchini Esper, Rodrigo Grassi-Oliveira, Alexandre Rosa Franco

Abstract

Psychological sciences focus on the study of behavior, emotions and individual thinking. To do so, it has an interdisciplinary characteristic, which makes advances in other fields important to psychology. Neuroscientific studies provided useful information in recent decades in this regard. For example, they revealed that previous dichotomist assumptions were mostly wrong. A remarkable advance was the use of functional magnetic resonance imaging (fMRI), which measures fluctuations in the blood oxygenation-level dependent (BOLD) signal during cognitive tasks, or more recently, even when the participant is not performing an explicit task – a method called resting-state fMRI (rs-fMRI). In rs-fMRI, researchers can find distinct areas showing functional connectivity (FC). Studies use different mathematical approaches to consistently describe groups of brain areas that show FC at rest: brain networks. Hence forward, the interpretation of the role of those networks became necessary, particularly because alterations in the typical functioning could be a trait, consequence or a risk for mental disorders. This narrative review aimed to give some support for those whom are interested to understand how rs-fMRI can help psychology, by reviewing some rs-fMRI principles and concepts.

Keywords: rs-fMRI; connectome, psychology, neuropsychology, neuroscience.

Resting-State Magnetic Resonance Imaging as a Tool for Psychological Sciences: Fundaments, Methods, Definitions and Possible Applications

Resting-state functional magnetic resonance imaging (rs-fMRI) is a well-established method within the neuroimaging research community; however, it is scarcely used in psychology (Biswal, 2012; Cole, Smith, & Beckmann, 2010; Fox & Greicius, 2010). It refers to the *in vivo* study of the co-activation of different brain areas in the absence of a cognitive demand. It has revealing discoveries about the working of brain networks without limitations of previous methods, which became a great achievement in the last decade, since the *connectome* emerged as an obsession (Biswal, Van Kylen, & Hyde, 1997; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009; van den Heuvel & Hulshoff Pol, 2010). However, some epistemological questions hinder the development of the promising knowledge that multidisciplinary interplays could bring in a faster way. Rs-fMRI emerged most from medical and physician research (Biswal, Yetkin, Haughton, & Hyde, 1995; Cole et al., 2010; Lee, Smyser, & Shimony, 2013) and unfortunately, psychological and behavioral sciences have gaps in those technical areas, and those from technical areas may have gaps in psychological knowledge as well (Cranney et al., 2011). Therefore, both the neuroscientific knowledge in psychological formation (Goldberg & Garno, 2005) and psychological knowledge in other scientific areas could help in promoting better and more conclusive findings if combined (Berninger & Richards, 2002; Cole et al., 2010). In particular, the application of such results in the clinical practice is one limitation, requiring psychological and behavioral sciences to help with interpretations (Lee et al., 2013; Yahata, Kasai, & Kawato, 2017).

Given this brief picture of rs-fMRI as a tool, this narrative review focuses on informing students and researchers that want a brief and easy-to-understand reading about the technical aspects of rs-fMRI. To accomplish this objective, we planned to cover some objectives: (a) to point out exactly how neuroimaging can help psychology as science (b); to

give principles of magnetic resonance techniques (c); to describe rs-fMRI and the "products" it can provide (including networks it revealed) (d); and to discuss some promising use of rs-fMRI for psychology.

Can Neuroimaging Inform Psychology?

Yes, neuroimaging indeed can inform psychology. However, the psychology must inform neuroimaging. For a quick reaffirming of that: imaging methods made lesion studies mostly unnecessary. Moreover, only because neuroimaging non-invasive characteristic and its great spatial and temporal precise information, *Functional Psychology theory* could be hold as more valid than other theories.

In the following section, magnetic resonance imaging (MRI) and functional MRI (fMRI) are explained, particularly some methods used in studies with rs-fMRI. Until now, there is a support for the understanding that to know about how the brain works is an undisputable way to inform psychology. It can reveal by consistent and palpable evidence how the connections and activity of specific systems can influence each specific cognitive function. Moreover, it has applications that are not yet widespread, but nevertheless, are promising. For example, there are results from neuroimaging using a resting-state exam in positron emission tomography (PET) before treatment that could predict what will be the better intervention for response in patients with major depressive disorder (medication or cognitive behavioral therapy). It means that in the future, psychologists and psychiatrists shall be able to decide about what intervention to use, because a rs-fMRI exam (McGrath, Kelley, Holtzheimer, Iii, & et al., 2013). Using rs-fMRI, diagnostic predictions can become more and more consistent (Craddock, Holtzheimer, Hu, & Mayberg, 2009; Heinsfeld, Franco, Craddock, Buchweitz, & Meneguzzi, 2018). Moreover, nowadays there is a call for hypothesis-driven strategies for interventions, and fMRI is useful in this regard. For example, given that craving involves a set of brain regions, including the dorsolateral PFC (dlPFC) (Li

et al., 2012), studies attempted to test methods that regulate dlPFC function to reduce craving (Fregni et al., 2008). In addition, based in the knowledge of craving processing in the brain, machine-learning methods also attempt to build up feedback techniques for controlling craving (Karch et al., 2015).

Moreover, studies with fMRI give perspectives. For example, taking into account addictive disorders, one could find out the brain areas/systems disrupted in processing flexibility, for example. Alternatively, other could find routes for the transition from initial drug use to addiction, which could help in promoting preventive strategies. Finally, neuroimaging can be used to assist in diagnosing mental disorders. In fact, there is already recognition from neuroimaging data, since the substance that can cause addiction is described as: "…a substance/behavior that causes activation of the reward system, despite its pharmacological proprieties…" (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force., 2013). It means that there are psychological changes, and neuroimaging is a valuable resource in trying to understand pathways leading to the disease and to try to revert that (George & Koob, 2010; Sutherland, McHugh, Pariyadath, & Stein, 2012). Because of this, details of the methods are reviewed.

Magnetic Resonance Imaging

Given the background for a need for data about neurobiological functioning with no invasive methods, the Magnetic Resonance Imaging (MRI) scan meant a technology with no comparison for behavioral sciences (Cabeza, 2001; Huettel et al., 2014). In simple words, with MRI it is possible to measure with good spatial resolution (it means the correct identification of small areas) without requiring operations, lesions, dangerous interventions and other invasive methods, which mostly non-ethical and therefore not available for research purposes. More than that, the technology enabled the measuring of the brain at work by quantifying fluctuations in brain signals with good temporal resolution as well. The temporal

resolution depends on the blood oxygenation-level dependent (BOLD) signal (see below) as well as physical limitations from the MRI.

The method has foundations in the magnetic signal that protons produce in the moment of the acquisition, for a more detailed review, see Mazzola (2009). For this, the MRI needs a strong magnetic field. Just remember, everything is made of atoms (including our body!). Thus, the MRI sends electro-magnetic pulses that shake atoms and cause a distortion in the magnetic field. Following that, the magnetic field starts to return to the previous format, which occurs with protons returning to their previous orientation before the pulse. As brain tissues have a different density of protons, the receiving coils (a part of the MRI scanner) register a signal according to the relaxing times (T1, T2 or T2* - time-constants that define to time it takes a proton to reorient to the main magnetic field). To register the data, the machine operator sets a field of view (FOV) that is the area from which the machine will extract images. In neuroscience, most studies focus their FOVs in the brain or specific brain or Central Nervous System (CNS) areas. Acquisitions of signals from the FOV occur in slices, which means that FOV is sliced. Each slice has *voxels*: small cubes, in general 3mm for each side in brain exams. Different types of images can be acquired, some structural, other functional; the pulse sequence determines what kind of image is registered (Huettel et al., 2014).

For neuroscience, functional images measure the brain at work. For this, it is necessary to measure a temporal signal. A temporal signal of each voxel is collected. After that, combining all the slices, a timeline indicates the fluctuation signal in each voxel (Matthews, Honey, & Bullmore, 2006). FMRI is just possible due the BOLD signal – the measure taken for each voxel. The simplest explanation for the BOLD signal is that it refers to the variation in the oxygen blood flux. More precisely, it measures the variation in blood-oxygen in regions of the brain due to neuronal activity. It is only a relative, not an absolute,

measurement of brain activity. This indirect measure is the BOLD signal (Ogawa, Lee, Kay, & Tank, 1990).

BOLD signal

As stated, the BOLD signal is an fMRI measure. However, providing a better background for it is necessary. The starting point for understanding is as follows: every stimulus generates an excitatory activity, which demands energy (look, it is psychobiology knowledge integrating physics!). Thus, restoration and maintenance of neuronal membrane potentials, necessary for integration and signaling, require energy. Even when there are no direct demands, such as when people are sleeping, there is implicit functioning and energy demanded – do not forget that we dream and that there are implicit functions that are still active all the time. The energy demanded produces fluctuations in neuronal signal activity. Brain cells utilize Adenosine Triphosphate (ATP) by using glucose and oxygen as primary energy sources. The oxygen attached to hemoglobin molecules transports the essential nutrients to specific areas to generate ATP and promote synapse. The background for brain activity in fMRI consists in the logical assumption that when a brain area is working, it requires ATP and therefore, it consumes energy – in other words, it requires oxygen (Huettel et al., 2014).

In 1936, Linus Pauling and his student discovered that the hemoglobin molecule has a different magnetic response depending on whether it is oxygenated. While oxygenated hemoglobin (Hb) has paramagnetic characteristics, deoxygenated hemoglobin (dHb) has diamagnetic characteristics. The signal computed from these variations in Hb/dHb is called the BOLD signal. Importantly, it does not return units of total consumption; it measures fluctuations, meaning that certain brain areas can consume more oxygen than others. However, if during a given task there is an increase in the BOLD signal in a specific area, the signal will show that area as having a higher participation in that task. Remember that BOLD

signal fluctuations are a relative measure, meaning that one can find an area "more activated" even though this given area is consuming less oxygen in total amounts. Essentially, we are measuring the percentage of the signal increase when we are performing a specific task. Similarly, the fluctuations can also reveal patterns of deactivation (Huettel et al., 2014).

For knowledge, it is also important to highlight that the BOLD response to a given task/stimuli refers to the hemodynamic responses. It is of interest since hemodynamic response is not immediate. It takes 3-5 seconds to happen between the stimuli presentation and the variation in signal response. After the increase, it is common to have a brief deactivation and, after that, the return to the baseline signal, which occurs around 10 seconds after the stimulation has finished. Figure 1 illustrates an example (Norris, 2006). Moreover, it is also important to note that sometimes, measures can reveal deactivations, which is a reduction in BOLD signal in contrast to a previous moment. For example, in a later section we will discuss the Default Mode Network (DMN), more pronounced in those moments when people are "doing nothing." Interestingly, when people start to do a particular thing, for example, to calculate something, the DMN areas deactivate for the increase in activation of other brain areas, as those we will discuss later that encompass control networks (Sridharan, Levitin, & Menon, 2008).

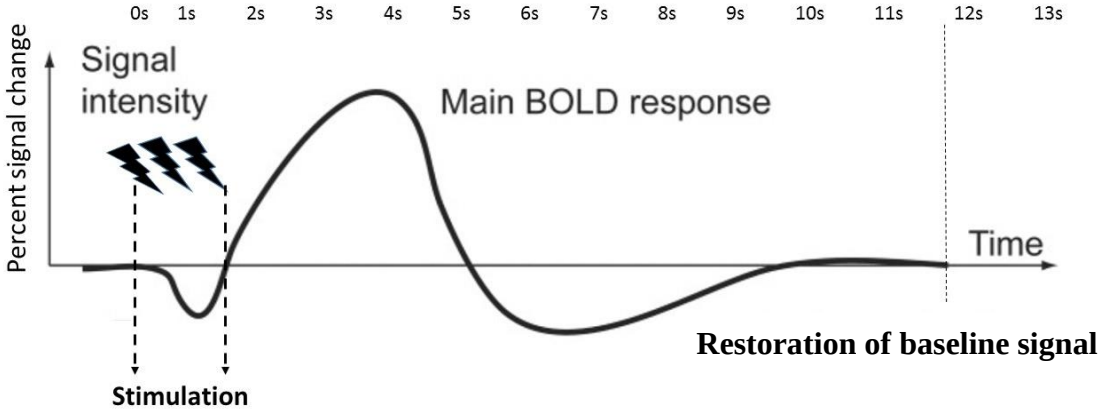

Figure 1. Hemodynamic fluctuation and BOLD response. Adapted from Norris, 2006 [8]. The figure shows a typical hemodynamic response. Imagine that in time 0, a person has a stimuli presentation (e.g., to put his hand in a hot water). In a brief first moment, sensory neurons in the brain will consume more oxygen. In response, an increase in oxygen consumption by those areas will happen. The compensatory mechanism leads to a reduction and after that a restoration in the signal to as before the stimuli presentation (the hand in hot water).

Before going on, an observation must be made. MRI measures something extremely subtle. And by measuring it, there are issues that can bias the signal registration. Most of time, the interference in the signal is referred as "noise." The noise distorts the signal and can mask the real neuronal activity. Noises can occur for different reasons, from normal distortions in the MRI magnetic field, to movements in the head and even the breath and the heartbeat. Thus, after the exam, a series of pre-processing steps are needed in order to "clean" the signal and "validate" it (Huettel et al., 2014).

[8] Adapted by permission from **John Wiley and Sons** and **Copyright Clearance Center: John Wiley and Sons. Journal of Magnetic Resonance Imaging.** Principles of magnetic resonance assessment of brain function, David G. Norris (2006).

Tasks in fMRI

Since fMRI knowledge and measure are supported in the assumption of BOLD signal fluctuations, the use of such a method initially was assumed to require tasks evoking neuronal activity. Otherwise, researchers initially thought there would be no fluctuations and nothing to measure. Note that later, with rs-fMRI this premise proved to be wrong, but as rs-fMRI has very low fluctuations, initially the correcting procedures for noise indeed could not remove signal fluctuations as they can now.

Here it is important to make a pause for note something: Without psychologists or people with psychological knowledge, there would be no consistent way to develop an fMRI study, in the beginning. It would happen since studies would not know exactly what to measure, or what they were measuring (Cabeza, 2001; Cole et al., 2010). Moreover, the definition of specific tasks requires caution for evaluating the exact moment of interest, since the same task can involve multiple different functions or processing. For example, think of a task in which participants should read something on a screen and then answer, moving their right or left hand according to what they read. Different moments in the exam would acquire neuronal activity for reading, interpreting, planning the action and moving the hand (Huettel et al., 2014; Norris, 2006).

Interestingly, it took a long time since the MRI machine was introduced to neuroscience research for scientists to discover that even without a particular task or demand, the brain has low frequency signals (<0.1Hz) (Biswal et al., 1995) that can be used to study brain functional connectivity. Obviously, when researchers conceived of it, they logically concluded what they already knew since functionalism became the most accepted theory for cognitive processing: brain function emerges from the collective interactions of distributed brain areas (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The surprise was that integrated function happens even when someone is (apparently) doing nothing. This method

of investigation of the brain in the absence of specific challenges became a new and promising method for neuroscience and its name is rs-fMRI. It is promising because it has an easy reproducibility and has no problem with task instructions.

Rs-fMRI

Rs-fMRI can be seen as a task, but a task that has as its cognitive demand the intrinsic brain activity. In rs-fMRI studies, the instruction that participants have restricts them to remain "still without moving and trying to not engage in any particular thinking." There are small differences in each study, sometimes requiring participants to stay looking at a cross in the center of a screen, or to stay with eyes closed. In general, a rs-fMRI run takes a duration of between 4-10 minutes long (Biswal et al., 2010; Cole et al., 2010; Lee et al., 2013; Lowe, 2012; Margulies et al., 2010; Van den Heuvel & Hulshoff Pol, 2010). Given that the brain stays working in a spontaneous way, researchers started to investigate the patterns of intrinsic brain function. One point that sometimes causes confusion is how to analyze those fluctuations extracted from the resting-state brain. Thus, the data extracted is always the same (i.e., fluctuations of the BOLD signal in the whole brain registered by slices divided into voxels), but the method used to analyze it changes sometimes; nevertheless, approaches converge to similar directions/results.

Despite the evolution of the method and different statistical approaches to manipulate data, the key assumption is that there are systems and networks working together for information processing (Fox & Greicius, 2010; Greicius, Supekar, Menon, & Dougherty, 2009). Then, since 1995, when Biswal and colleagues reported the existence of correlations between pre-motor and post-motor bilateral brain areas even in the absence of motor activity, other studies investigated other areas as correlated without any demand. Given that, rs-fMRI enabled the association of brain areas regarding functional activity, even areas that were not spatially close to each other. Then, functional networks emerged in neuroscientific literature

(Bressler & Menon, 2010; Bullmore & Sporns, 2009; Cole et al., 2010; Damoiseaux et al., 2006; Fuster, 2000; Greicius et al., 2009).

Functional connectivity (FC)

Most of those conclusions taken from rs-fMRI studies indicate the existence of patterns of coherence in the functioning of multiple brain areas, drawing networks. By this, the integration of functioning denotes a connection. Thus, an important concept is *functional connectivity* (FC). Literally, "FC is defined as the temporal correlation between spatially remote neurophysiological events" (Fingelkurts & Kähkönen, 2005). Since the BOLD signal is the value that the MRI uses to draw the mapping of neuronal activation, one can get rs-fMRI acquisitions and look for temporal associations in the BOLD signal fluctuation across different brain areas to depict FC. To do so, we use a set of computations. For example, analysis can follow a model-driven method – that is, taking some *a priori* knowledge about the investigation. Alternatively, the analysis can follow a data-driven method, which is to select the way to investigate by the conclusions without an *a priori* knowledge about the system and brain regions (Cole et al., 2010; Tomasi & Volkow, 2011). There are some specific methods, such as seed-based correlation, regional homogeneity (ReHo), independent components analysis (ICA) and Graph Theory to investigate patterns of functional connectivity (Margulies et al., 2010). Although each of the methods are useful and used in rs-fMRI research, all of them have limitations. To assuage these limitations, multiple procedures are necessary. The most common analyses for rs-fMRI follow here.

Seed-based correlation. The seed-based correlation is the most frequently used approach in rs-fMRI (Cole et al., 2010; Dosenbach et al., 2007). This approach assumes that if the BOLD signal time-series of different regions correlate, these regions are functionally connected. To compute a seed-based correlation analysis, it is necessary to give an *a priori* definition, which is the setting of a *seed*, or Region of Interest (ROI). Thus, this is a model-

driven method, in which before the analysis, researchers define a brain region to test its FC. The model calculates a map of FC for the time series of the seed (a seed cannot encompass a single voxel, thus, a seed encompasses a group of voxels with different BOLD signal fluctuations). After that, by using a script, it calculates all other time-series in the brain and test it for correlations with the mean time-series of the seed, generating a FC map. The map reveals what brain areas showed higher correlation coefficients with the ROI, which means that these areas are "connected" (Cole et al., 2010; Margulies et al., 2010; Tomasi & Volkow, 2011; Uddin et al., 2009). Figure 2 illustrates a didactic flow of steps in a seed-based correlation method for rs-fMRI investigation.

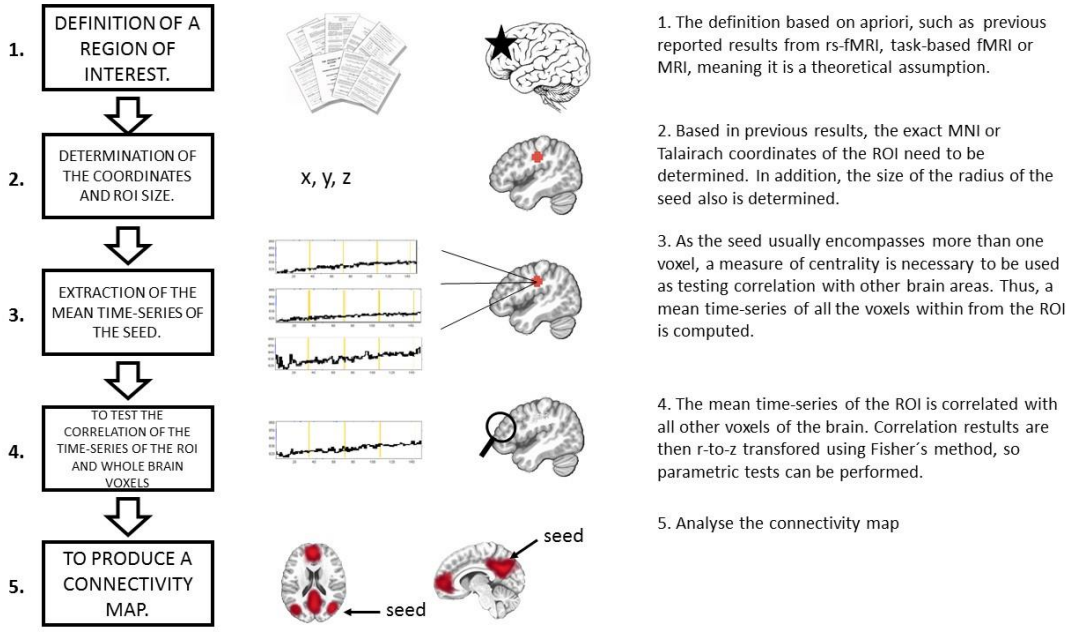

Figure 2. A brief flowchart on the theoretical and technical steps for analyzing rs-fMRI with a seed-based method.

ReHo. ReHo is a data-driven method for rs-fMRI analysis (Margulies et al., 2010). It assumes the need for temporal associations in the activity in voxels that are spatially close to each other and show coherence in BOLD signal fluctuations. Thus, this method evaluates whole brain and looks for groups of close voxels that correlate to each other in BOLD

signaling. The calculation used comes from Kendall's coefficient concordance (KCC) (Kendall & Smith, 1939). By using the KCC, those coefficients of correlations of each voxel are ranked and build up groups of voxels that have similar coefficients, determining a cluster that is termed a "neighborhood." Researchers can set the minimum neighborhood size, the most used being those of 7, 19 and 27 voxels (Zang, Jiang, Lu, He, & Tian, 2004). The assumption for ReHo is that each cluster may have a core of activity, which interacts with neighborhoods. Thus, this whole-brain analysis tests all fluctuations in the BOLD signal and retrieves areas that concentrate more neuronal activation or dysfunctional connectivity. Thus, this type of analysis maps basic connectivity in neighborhoods by getting the interconnectivity from a voxel-by-voxel correlation. The steps for ReHo analysis are in Figure 3.

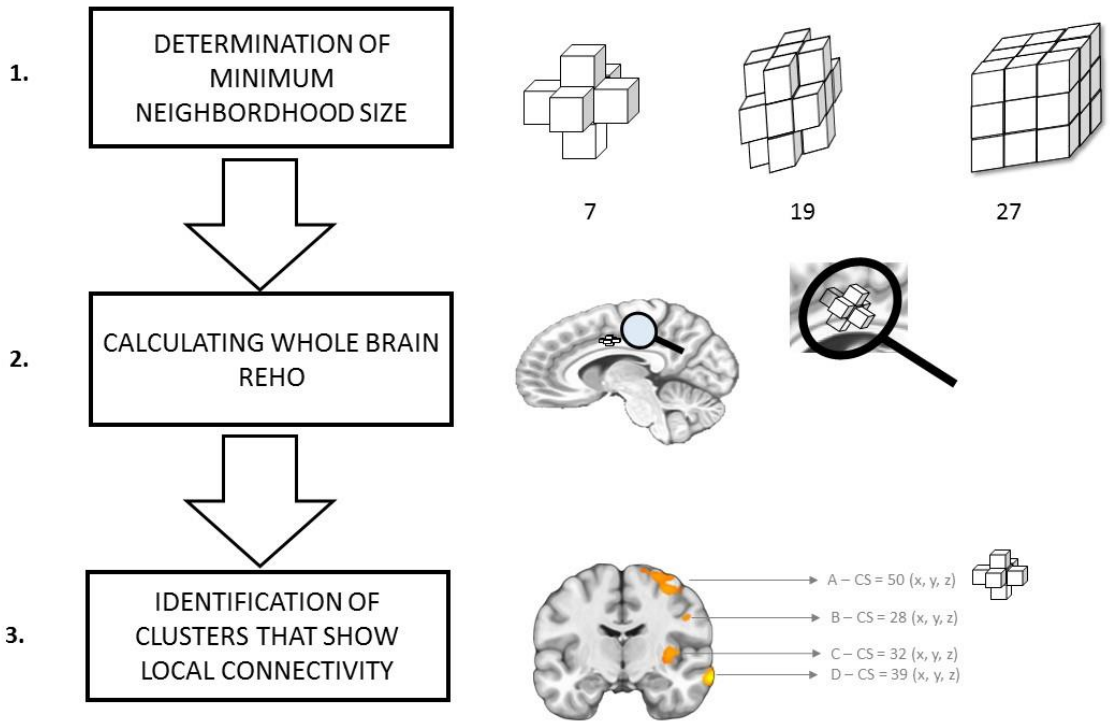

Figure 3. A brief flowchart on the theoretical and technical steps for analyzing rs-fMRI with ReHo.

ICA. ICA is a data-driven method for rs-fMRI investigation. It computes single and separated signals from multiple and mixed data, transforming multiple and varied information in components of a whole (Bell & Sejnowski, 1995). This method produces groups of brain areas that relate to each other and returns to investigator sets of areas that showed independent activity. It means that it gives two outcomes: (a) a given relation between groups of areas; and (b) the production of different groups of areas usually working together. To calculate independent components, information within these data must be independent from others. The main limitation of the method is that some areas can be shared between two networks, and ICA can take this area out of a network because it is not independent. Unfortunately, that would make those most important nodes (that participate in more than one network) to be out of the results. For the other side, data on ICA can reveal networks, having no need of *a priori* definition.

Graph theory. Graph theory focuses on FC; but more than that, it enables us to investigate the architecture of networks. Because of it, graph theory enables us to measure different patterns of FC. For example, it enables to measure small-world networks (sub networks inside a bigger one that show a little higher FC between nodes or is spatially closer). In addition to the efficiency of an edge (which is a link between nodes that interplay to each other, not only being connected, but interfering in functioning); and the centrality of a node – which is a node that is a center of others building up a network (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010).

Functional organization – brain networks and systems

Given remaining assumptions from *Functional Psychology* that cognitive and emotional processes involve the participation of different brain structures in a functional way, descriptions of networks, systems and circuits became of interest (Power et al., 2011). In the truth, there is a center foundation assuming the whole CNS as a dynamic, integrated and

organized network. Nevertheless, inside the CNS dynamics, different networks, systems and circuits have specific functions (Liu, Slotine, & Barabási, 2011). Such integration has hierarchical levels, going from complex and more simple networks, to systems, circuits, brain areas, neurons and more (Bullmore & Sporns, 2009; Milo et al., 2002). That named *human connectome* is the whole network involving the CNS (Bullmore & Sporns, 2009).

Thus, since neuroscientific conclusions pointed out that the gold-standard method for understanding functions is to understand how the psychological machinery works, different methods on neuroscience help on elucidating that. Therefore, by using similar methods as those described for measure FC in rs-fMRI, some researchers use similar statistical approaches in fMRI tasks. For example, by determining an ROI and testing its FC during a working memory (WM) task, one can reveal second level-structures that play a role together with the so-called dlPFC. In this line, by finding areas that show FC with the dlPFC during WM tasks, researchers could reveal a WM system (Glahn et al., 2005). Importantly, evaluating FC during a task reveals a mechanism, not a trait (Dosenbach et al., 2007). Although literature is not consistent in differentiating networks, systems and circuits by strict means, if we take in hand important data on those most-used terms, and some superficial definitions, we can draw conceptualizations for each one (Corbetta & Shulman, 2002), which is valuable for interpreting studies. However, for all readers it is important to keep in mind that, sometimes, papers use those terms as synonyms. Here, for a better understanding, we differentiate networks and systems and describe some examples of them, but we encourage readers always to double-check what authors are referring to in their studies.

System. A good definition for system would be groups of items that have pairwise relationships during a giving demand/task (Bullmore & Sporns, 2009). Empirical and theoretical works on this topic already emerged and assumed that certain brain areas probably work together to produce a given outcome. Examples of systems are the “reward system,”

"spatial working memory system" or "selective attention system." Therefore, we can assume systems are groups of brain areas that are consistently interdependent for the reaching of an equilibrium. The items in a system are *nodes*, and they are interconnected by *ties* (Liu et al., 2011). The best way to figure such systems is empirical research using imaging methods, such as fMRI and PET scans with tasks. However, this concept emerged before the technology was available. Because of it, there are systems mostly based in theoretical assumptions and just partially supported by evidence, as you will see it is the case of limbic system (Rajmohan & Mohandas, 2007).

Circuits/pathways. Circuits are connected neuronal areas – which means, networks – that are composed of specific cell types. Often these cells are specialized in one type of function or synapse. For example, the so-called dopamine pathways regard specific circuits involving brain areas that work with dopamine (DA). Commonly, circuits compose networks or systems (Bullmore & Sporns, 2009).

Networks. Different from systems, a network refers to a group of nodes that are connected, independently of a current demand. Note that when referring connected it does not necessarily means *interconnected* or that does exist *interdependency* between nodes (Liu et al., 2011). That is, nodes have relationships, but are not dependent on each other as a rule. Combining data on FC, conclusions of brain areas that consistently show BOLD signal correlations at rest and under demand indicated networks do exist, representing functional associations between structures in a stable way (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Biswal et al., 1997). Different studies identified groups of brain areas with stable FC, independent of the method used. There are seminal works that revealed main networks (Biswal et al., 1995; Biswal et al., 1997; Damoiseaux et al., 2006; Greicius et al., 2009; Jiang, He, Zang, & Weng, 2004; Uddin et al., 2009).

Interestingly, systems often are parts of one or two networks. A system can be a product of two coupling parts of one network, or it can be a product of separated networks, and it works by interconnecting them. In the following, you will see that different networks compose the control network, for example. Specific executive functions may require networks to work in an integrated way, which means networks may need to have integrative systems to produce certain demands (Menon & Uddin, 2010).

Default Mode Network (DMN). The DMN is one of the most studied and discussed networks into rs-fMRI. It is the core of the intrinsic neuronal connectivity as it is positively activated when people are at rest (Damoiseaux et al., 2006; Greicius et al., 2009; Lee et al., 2016; Mars et al., 2012; Spreng, Mar, & Kim, 2009; Weis, Hodgetts, & Hausmann, 2017). Taking into account the areas involved in DMN and neuropsychological knowledge, nowadays we can conclude it encompasses brain areas related to autobiographical memory, social cognition, consciousness and awareness (Greicius et al., 2009; Spreng et al., 2009). Thus, because of psychological knowledge, we learned that when people are not engaging in a specific demand, we think in ourselves, probably remembering or wondering about the future, involving other people and their emotional states. Anatomically, DMN involves regions within the medial PFC (mPFC), posterior cingulate cortex (PCC), precuneus and posterior lateral cortices (Gusnard & Raichle, 2001). Figure 4 illustrated areas encompassing the DMN in illustrations 4.A and 4.B.

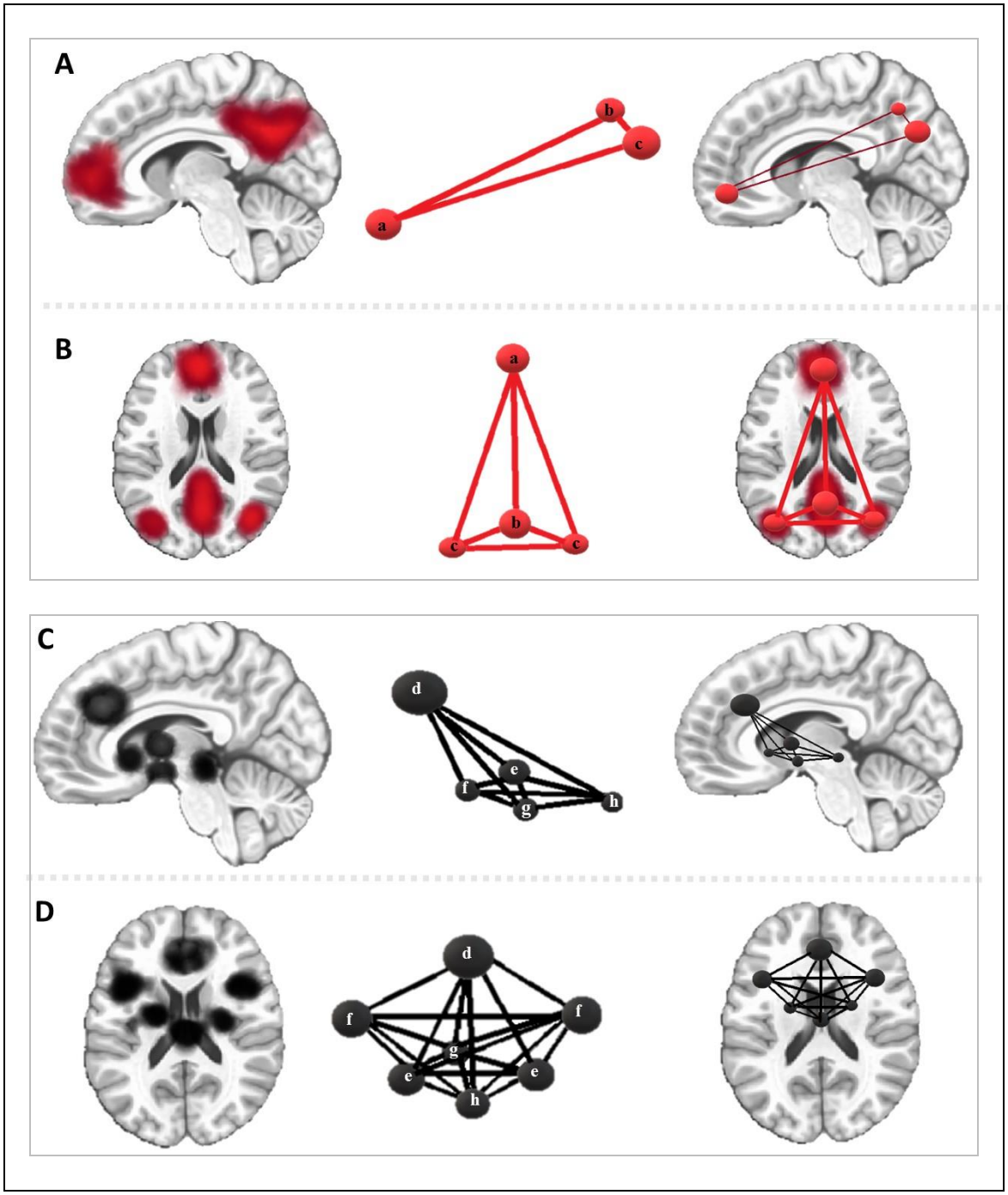

Figure 4. Intrinsic brain networks: DMN and Salience Network (SN). Illustrations 4.A and 4.B show DMN areas, in red; Illustrations 4.C and 4.D, in black, show SN. Each network is depicted on sagittal and axial views of the brain in this order. In each line, figures show illustrations based on activation, the network scheme and a combined picture with the schema on the brain. Note that illustrations do not show active areas, but areas connected. Moreover, in pictures we could not include 3D perspective, which do, in fact,

exist. Thus, consider that it is a representation, and smaller or bigger nodes mean the node is more distant or closer. In addition, remember that areas are the core of the activation, but an active brain area can extend from a central point. Finally, the representation of the schema without the brain is not matching with the size.

a: mPFC (medial prefrontal cortex); b; precuneus; c: PCC (posterior cingulate cortex); d: dorsal part of anterior cingulate cortex (dorsal ACC); e: amygdala; f: anterior insula; g: ventral striatum; e: substantia nigra/ventral tegmental área (VTA).

Moreover, DMN has anti-correlations with other brain networks involved in task-demanding experiments. For example, DMN shows this pattern with the Dorsal Attention Network (DAN, Fox et al., 2005). In addition, systems can couple or partially link areas of DMN to other networks, meaning inter-network FC (Uddin et al., 2009). It means that certain hubs of DMN can participate in other networks, even though there is not entire network correlation. For example, social cognitive brain systems overlap mPFC (Gilbert et al., 2006), while the precuneus participates in episodic memory systems (Rocca et al., 2014). However, mPFC does not participate so actively in episodic memory, nor the precuneus in social cognition, although these areas have some connectivity with the system because they form part of a network, they are not parts of the system *per se.*

Salience Network (SN). SN is a cognitive network that has system functions, but in general, has implicit functions (which means those functions people are not necessarily aware they are doing). It acts particularly in identification of relevant stimuli and events (Childress et al., 1999; Li, Kosten, & Sinha, 2005; McHugh et al., 2014; Potenza et al., 2012; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011). The SN has as main regions the anterior insula and the dorsal portion of the ACC, but also encompass the amygdala, ventral striatum and the *substantia nigra*/VTA mostly due neurotransmitter circuits (Menon, 2015). Figure 4 depicts

SN anatomy in illustrations 4.C and 4.D. Considering the areas involved in SN, one can conclude that it encompasses brain areas related to cognitive and affective processing. Indeed, because of its role in processing emotional and affective information, SN contributes to social behavior and communication. Interestingly, SN participates in the implicit "selection" of stimuli from all kind of inputs, including those internal and external. Due to this multimodal processing (images, thoughts, emotions, sounds) SN has an important functioning in self-awareness due to the integration of information and linking it to conscious. Similarly, neuroplastic adaptations, as those in drug use can make SN to has such a strong functioning, not enabling conscious to manipulate information. Moreover, it has connections with other networks, including the Auditive Network and the large Visual Network (Craig & Craig, 2009; Gogolla, Takesian, Feng, Fagiolini, & Hensch, 2014).

Control Networks or DLPFC network. As cognitive sciences stresses, executive functions encompass a set of processes that guide thought and behavior, allowing purposeful actions and decision-making toward an objective, being determinant tools for social and cognitive human abilities (Barkley, 2012; Kluwe-Schiavon, Viola, & Grassi-Oliveira, 2012; Kluwe-Schiavon, Viola, Sanvicente-Vieira, Malloy-Diniz, & Grassi-Oliveira, 2016; Miller, 2000). Executive functions are not exclusively located into the PFC, despite its great involvement (Andrés, 2003). The main cognitive network involves the dlPFC, medial frontal cortex (including the ACC, note that are overlapping with SN), parietal cortex, motor areas, and cerebellum (Barch, 2002; Bellebaum & Daum, 2007; D'Esposito, 2007). Cognitive networks encompass a set of areas that can be subdivided into two smaller networks. Commonly definitions of cognitive networks are separated; otherwise, a very large cognitive network would hinder the investigation. Some authors divided it in three networks, considering dlPFC network exclusively from control network, but in fact dlPFC would be too big. In addition, it encompasses areas that in the true are part from the control network, thus,

here it was neglected. These different areas participate in controlling WM, complex cognitive executions, planning and execution of actions toward goals (Miyake & Shah, 1999).

Therefore, initiation, inhibition, WM, flexibility, planning and vigilance are executive functions that are "products" of a superordinate network – the cognitive network. Thus, the cognitive network has a range of domains considered distinct subnetworks (Niendam et al., 2012) that are responsible for different mechanisms. The control network includes as most important subnetworks DAN and the Fronto-Parietal Network (FPN). Figure 5 illustrates those control networks. Note that control network, or dlPFC network is the larger one and has nodes very close to all points from those other networks. Because the nodes are not entirely encompassing other networks, there is some discussion about whether these networks are or are not parts of the control network. Regardless of these discussions, it is the consensus that all three work in control (Niendam et al., 2012).

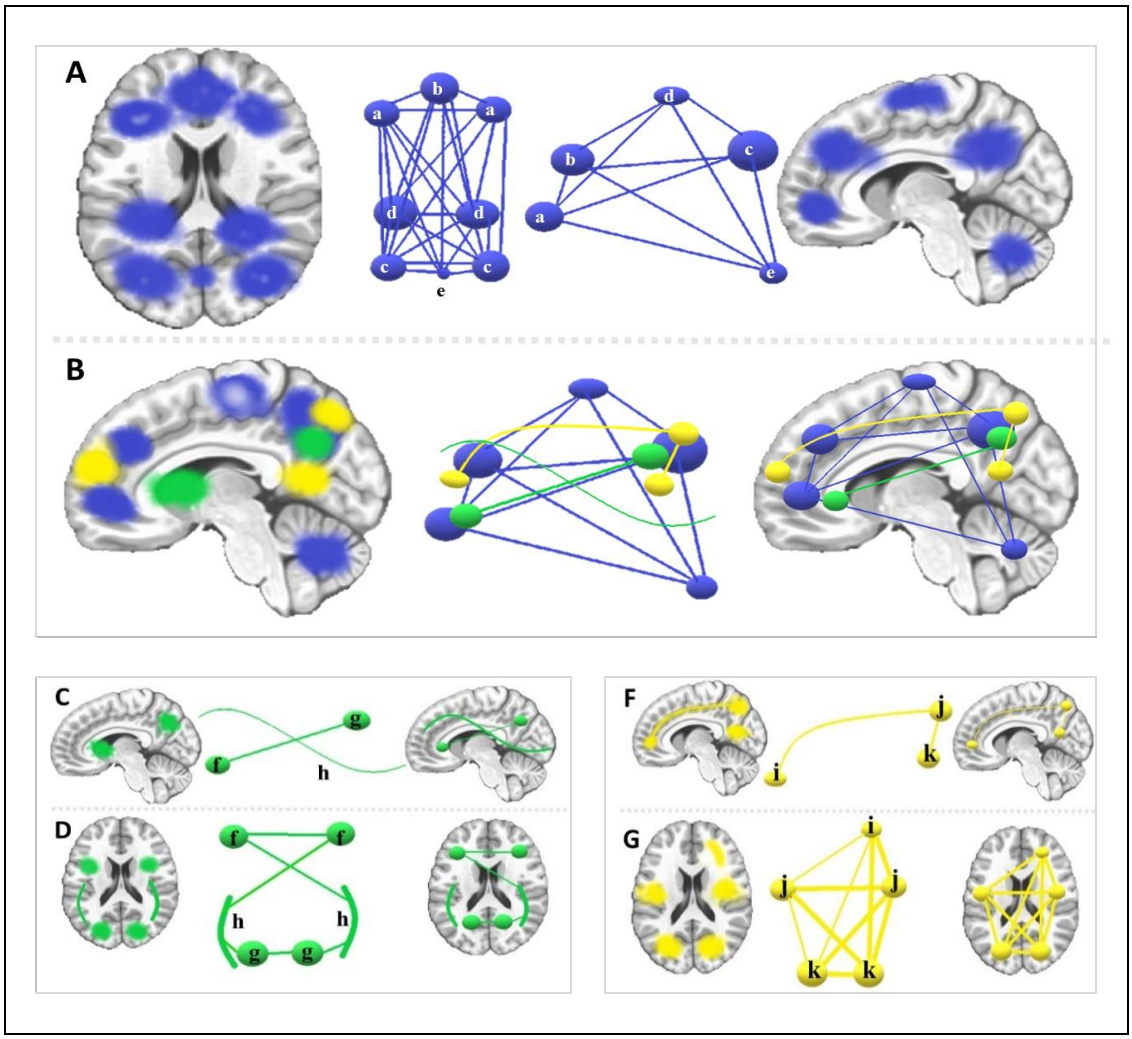

Figure 5. Control networks, the larger control network, FPN and DAN. Illustration 5.A shows the larger cognitive network (a.k.a. dlPFC Network). From left to right, axial view, schema of the network in axial view, schema of the network in sagittal view and sagittal view. As control network is too large, its two secondary control networks are described. Illustrations in 5.B are displayed the main control network areas, in blue. Note that blue areas encompass other areas from subnetworks, in yellow the FPN and green DAN. Illustrations in 5.B show the sagittal view, the schematic over position of schemas and axial view. Although the control network is close and has parts that are shared with the others, note that the centers of the areas are not exactly the same, resembling questions whereas FPN and DAN are

subnetworks or not. Illustrations 5.C and 5.D show DAN, C in sagittal and D in axial views. From left to right, it shows activation areas, the schema of the network and the schema over the brain. Note that DAN has one area that is not a node, but an edge salient (h). That is not a cortical area, but a white fiber tract. Illustrations 5.F and 5.G show the FPN. In 5.F is the sagittal view and in 5.G the axial view. From left to right, it shows activation areas, the schema of the network and the schema over the brain.

a: DLPFC; b: medial frontal cortex; c: parietal cortex; d: motor areas; e: cerebellum; f: frontal eye fields; g: posterior parietal cortex; h: superior longitudinal fasciculus; i: superior frontal sulcus cortex; j: intraparietal junction; inferior parietal cortex.

DAN. As mentioned, DAN involves cognitive control, particularly explicit inhibition. Because it exerts control over instinctive behaviors, some call it the executive control network (ECN), but there is some confusion between DAN, ECN and dlPFC networks, thus we preferred to use DAN for this smaller network within a larger control network (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Fox et al., 2006). The DAN involves the frontal eye fields and the posterior parietal cortex. It is connected by the superior longitudinal fasciculus (a white fiber tract that links posterior and anterior parts of both hemispheres to each other) (Ptak & Schnider, 2010), supporting visual spatial planning. Its anatomic illustration is in Figure 5. In addition, DAN activity associates with the PFC in sustained attention or activities (Dosenbach et al., 2006; Yarkoni et al., 2005). The DAN can modulate the capture of attention through a mechanism that temporarily increases the saliency of behaviorally relevant events and decreases the saliency of irrelevant events. DAN has systems that, in healthy conditions, may control SN where it is possible (Ptak & Schnider, 2010).

Fronto-Parietal Network (FPN). Brain activity in the intraparietal, inferior parietal and the superior frontal sulcus cortex has previously been correlated with WM (Olesen, Nagy, Westerberg, & Klingberg, 2003). The FPN is particularly active and noticed during task performances, which for some could show that it is in fact a system. However, correlated deactivations at rs-fMRI supported it as a network (Olesen et al., 2003). There is a functional overlay between spatial WM and spatial selective attention, which means DAN, in this network (Awh & Jonides, 2001). In addition, other cognitive functions, including cognitive control, response selection, episodic memory and problem solving have similar regions of the frontal lobes (Duncan & Owen, 2000). The FPN participates in different cognitive functions because its nodes encompass systems. Some call such systems as FPN systems. Among regions that interact with FPN, some of the most commons are the lateral frontopolar cortex, anterior prefrontal cortex, dlPFC, ACC and medial frontal cortex, lateral cerebellum, anterior insula, caudate, and the anterior inferior parietal lobule (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008).

Sensory-motor network (SMN). The SMN was the first network described in rs-fMRI studies. Then, Biswal and colleagues (1995) were investigating the sensorimotor cortex signals. A romantic but not very true summary of the story is that he was planning to discover how brain signals in motor cortex change from different hand movements. His paradigm consisted in one moment of movement, other than rest and a second movement in a different way. He failed that point in proving what he wanted because the signals were too similar. Then, he tried to reduce other signals (which we call noise) that could be biasing those that he was interested in. He applied his signal processing skills to reduce noises caused by the respiration and by the heartbeat. In fact, he discovered that those noises were not so important. Frustrated, looking for those lots of time-series that were not conclusive, he noticed that fluctuations in sensorimotor cortex had similar temporal shapes in all conditions.

Henceforward, he decided to test those fluctuations in groups of voxels from the sensorimotor cortex to all other brain voxels. Please note that in fact he put a seed in the sensorimotor cortex and invented the seed-based correlation method. His findings revealed a strong correlation in those low-signals from one side of the sensorimotor cortex with those from the other hemisphere. Thus, he concluded that the bilateral sensorimotor cortexes in fact encompass the same network (Biswal et al., 1995).

After that, the method became more popular and revealed other networks. For sensorimotor areas, it revealed that in fact there was FC between brain areas mostly involved in sensory and motor functions, including the postcentral gyrus, precentral gyrus and supplementary motor areas. This set of connected nodes received the name of SMN. After that, repeated works documented the SMN using different methods (Biswal et al., 1995; Biswal et al., 1997; Damoiseaux et al., 2006; Filippi et al., 2013; Greicius et al., 2009). Interestingly, SMN has inputs and outputs connecting it with different networks and studies very often report SMN inter-network FC with other relevant brain networks and systems.

Limbic system. The limbic system has an historical background that is relevant. The word "limbic" comes from Latin *limbus*, which means a *nowhere place*. Early neuroscientists as James Papez and Paul Broca used this term to describe brain areas that were not either exactly in the diencephalon, nor in the telencephalon (Catani, Dell'Acqua, & De Schotten, 2013; Swenson, 2006). The most common brain areas described as part of the limbic system are cingulate gyrus, the parahippocampal gyrus (PHG) and the subcallosal area (Rajmohan & Mohandas, 2007). The subcortical limbic structures include the amygdala, mammillary bodies, hypothalamus, some thalamic nuclei and the ventral striatum (Catani et al., 2013). These areas contributes to linking visceral states and emotion to cognition and behavior (Mesulam, 2000).

Then, researchers attributed emotional processing to the limbic system. In this line, the Limbic System as it has been conceived, a center for emotions, was discarded by fMRI data that revealed other brain areas, including some cortical ones, as the ventromedial PFC (vmPFC) have strong participation in it (Mesulam, 2000). In fact, it has important participation in emotional processing, but today we know that emotions are processed differently due its valence. Thus, the limbic system has few system properties recognized and it was more a theoretical system than an empirical one. Today, there are works that in fact mention it more because of its anatomy than its functionality.

For years, some psychiatric conditions had been attributed to dysfunctions in the limbic structures. In fact, limbic structures are well-wired and participate in different systems, including emotion regulation, social interaction and motor response (Catani et al., 2013). This system can also primarily affect the memory of older people with some neurodegenerative disorders. Those theories needed reformulations and nowadays it is common to find works mentioning the *corticolimbic network* in psychiatric disorders, but in fact it is more probably a circuit than a system (Contreras-Rodríguez et al., 2016).

Other relevant networks and circuits/pathways. For psychological sciences, some networks are not so important. It does not mean we are counseling a young psychologist to neglect them. However, given the presumed role of these networks in psychological functioning nowadays, we will not address in detail such networks, circuits and systems as we could do in this paper. Given available space, plus the clinical relevance, we focused on those most important for psychological and behavioral sciences. For your information, there are other relevant networks often described in rs-fMRI studies: the visual processing, the auditory processing and memory networks (Damoiseaux et al., 2006).

Moreover, it is important to highlight that among circuits and pathways, those related to neurotransmitters are the most recognized. By this token, be aware of dopaminergic

circuits, likewise of serotoninergic circuits and of GABAergic circuits. Probably the plural (i.e., circuits rather than circuit) grabs your attention. Different circuits are described to each neurotransmitter often because of a variety of receptors. For example, there are brain areas that are rich in a specific kind of receptor, which makes it receive a distinction circuit from another one that has more density of a different receptor (Tekin & Cummings, 2002).

How does rs-fMRI contribute to Psychology and Behavioral Sciences?

This method is still novel for psychology sciences, but there are results supporting informative data for promoting new interventions for some psychological conditions. Moreover, there are perspectives that advances in rs-fMRI will be useful for predicting the progression of disorders, treatment adherence or even as a diagnostic resource (Lee et al., 2013; Rosazza & Minati, 2011).

One good example for understanding how rs-fMRI could inform psychological sciences regards its contributions for understanding the development of neurocognitive disorders. For a long time, studies have tested if neurocognitive disorders would appear following mild cognitive impairments, but studies are not conclusive. In this line, rs-fMRI studies are building up more and more evidence that subjects with initial neurocognitive symptoms show alterations in FC that later are more pronounced in participants diagnosed. In this regard, studies indicate that normal aging shows a reduction in DMN FC. Particularly, the subsystem into DMN that integrates the hippocampus and the precuneus reduces (Sheline & Raichle, 2013). According studies, the progression and in neurocognitive disorders more accelerated disengagement of the hippocampus and the precuneus also is noticed with other DMN areas, contributing to dysfunctional hippocampus-related systems (Andrews-Hanna et al., 2007).

In the case of how rs-fMRI could contribute for developing new strategies for treating psychological conditions, one example for one disorder with no efficient treatment

regards cocaine use disorder (CUD). In diagnosed patients, there is an increased FC in mesocorticolimbic (MCL) brain areas, causing DMN, SN, SMN and some limbic areas to be coupled into a large network (Contreras-Rodríguez et al., 2016; Konova, Moeller, Tomasi, Volkow, & Goldstein, 2013). According to psychological conclusions, it would mean cocaine users have attentional bias: rapid reward system triggering in a default fashion. In other words, it is possible that their DMN becomes a different shape, enhancing behavioral problems. Moreover, it would disengage and deactivate control networks, making hard them to cope with craving, for example (Sutherland et al., 2012). Given that, other studies found that stronger DAN FC predicts longer abstinent times, motivating evidence-based trials to test stimulation of DAN as a way to disengage that large MCL network (McHugh, Gu, Yang, Adinoff, & Stein, 2017).

Finally, the use of rs-fMRI as a tool for diagnostics is also promising (Fox & Greicius, 2010). Differences in rs-fMRI are common in mental disorders (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Konova et al., 2013; Lei et al., 2017; Liao et al., 2010; Shen, Wang, Liu, & Hu, 2010). Some authors suggest that there is already sufficient data for using rs-fMRI in clinical diagnostic of mental disorders, particularly for major depressive disorder and schizophrenia. For gauging how promising it is, a study tested one mathematic algorithm in a *machine learning* study. This method uses computational algorithm to predict outcomes. In the study, authors tried to use that to predict schizophrenia diagnoses. The model had 93% accuracy in predicting schizophrenia in patients that in fact have the diagnosis and 75% of accuracy for heathy controls (Shen et al., 2010). However, results indicate that in the true, rs-fMRI can inform the predominance of specific functions, but not clearly define diagnoses. Thus, more consistently, rs-fMRI data do support differences in the pathophysiology of some symptoms. For example, by using it is possible to determine

presence of internalization or externalization symptoms, which may be useful for further treatment planning (Craddock et al., 2009; Wang, Hermens, Hickie, & Lagopoulos, 2012).

Perspectives

In this narrative review, we highlighter that rs-fMRI is a striking method for psychological sciences. The method measures associations in the fluctuations of the BOLD signal in the brain at rest. The use of this tool can inform psychologists on multiple levels..

For one side, the psychology interdisciplinary characteristic is a beacon in the scientific development and advance, since it has several sources and more and more resources. Indeed, in recent decades, since the explosion of neuroscience, psychology evolved in a fast proportion in regards to neurological and psychopathological evidences. However, some question whether psychology "still exists" or if it is disappearing into the medical approaches that have emerged (Goldenberg & Krystal, 2017; Schwartz et al., 2016; Seybold, 2016). By this token, novel neuroscientific approaches cause at same time a euphoria and a resistance from psychologists (Collins, 2017). Moreover, novel methods and the fast progression of neuroscientific knowledge also brought problems due to the lack of knowledge with resources and even data interpretation, since graduation courses and general academic formation require continuous updates that unfortunately are not always possible to be accomplished. As a result, imbalances and limitations in the progression of both fields occur. Thus, some conclusions could draw a picture in which there is a lack in psychological knowledge from non-psychological professionals, but also that the expert psychological knowledge is failing in doing what is one of its bests contributions – integrating multiple disciplines toward an effective progression in the science. As a final statement, one could say that psychological and non-psychological sciences related to neuroscientific are not enough *functionally connected* in terms of scientific progression. The solidification of such a psychology-technical neuroscience bridge would be profitable for everyone.

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APENDIX A

Paper from the thesis already published.

Revista Brasileira de Psiquiatria. 2016;38:58–60
Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2015-1708

BRIEF COMMUNICATION

Crack-cocaine dependence and aging: effects on working memory

Breno Sanvicente-Vieira, Júlia Kommers-Molina, Tatiana De Nardi, Ingrid Francke, Rodrigo Grassi-Oliveira

Developmental Cognitive Neuroscience Research Group (GNCD), Centre of Studies and Research in Traumatic Stress (NEPTE), Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil.

Objective: To compare the working memory (WM) performance of young adult crack-cocaine dependent users, healthy older adults, and a control group of healthy young adults.
Methods: A total of 77 female participants took part in this study: 26 young adult crack-cocaine dependent users (CRK), 19 healthy older adults (HO), and 32 healthy younger adults (HC). All participants completed the N-back verbal task.
Results: A multivariate analysis of covariance was performed. The model included education, income, and medication use as covariates. A group effect ($F_{6,140} = 7.192$, $p < 0.001$) was found. Post-hoc analyses showed that the performance of the CRK and HO groups was reduced compared to the HC group in two N-back conditions. No differences between the HO and CRK groups on WM performance were found.
Conclusions: CRK participants perform similar to HO participants on a WM task, despite the well-known effects of age on WM and the young age of CRK. These data point to a possible parallel between cognitive declines associated with crack use and developmental aging.

Keywords: Working memory; crack cocaine; aging; substance use-related disorders; cognition

Introduction

Crack-cocaine use has been shown to cause toxic effects on the brain, particularly in the prefrontal cortex (PFC). Such abnormalities are associated with neuropsychological impairments, including deficits in working memory (WM).[1,2] Interestingly, PFC alterations[3] and decline in WM performance are recognized as normal consequences of natural aging.[4] Imaging data supports the hypothesis that gray matter volume loss over time is twice as fast among cocaine users as in healthy individuals. Given that gray matter volume in PFC has been related to WM performance, it is presumed that cocaine use impacts WM as well, which has been corroborated by behavioral results.[5] In addition, preliminary data suggest that cocaine use and aging have interactive effects on neuropsychological integrity, increasing impairments and everyday problems.[6]

WM is a high-demand cognitive process that involves maintaining and manipulating information in the absence of external cues. WM has been described as critical to several other cognitive processes, such as executive functioning and social cognition, as well as to everyday functioning.[7] Deficits in WM performance are also associated with clinical symptoms found among cocaine users, such as higher impulsivity traits[1] and higher dosages of drug consumed.[8]

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Submitted Mar 16 2015, accepted Jun 18 2015.

Given the suggested importance of WM to the neuropsychological functioning of cocaine users and the hypothesis that cocaine use could cause a decline in WM performance, this study sought to compare the WM of young adult crack-cocaine users to that of healthy older adults and healthy young adults. The hypothesis is that adult crack users would exhibit WM performance equivalent to that of the older group instead of their age-controlled healthy peers.

Method

Participants

Since crack-cocaine use[9] and cognitive aging[10] show gender effects, only women were included in this study. Seventy-seven women were recruited and selected by convenience. The sample was separated into three groups: healthy adult controls (HC, n=32); healthy older participants (HO, n=19); and crack-cocaine dependent users (CRK, n=26). The age cutoffs used to determine the participants as adults or older adults were based on the criteria established by the World Health Organization (adults, 19-59 years; older adults, > 60 years).[11] The two groups of young adult participants (HC and CRK) were age-controlled to avoid age-related biases. The exclusion criteria were as follows: history of neurological illness, head injury, current pregnancy, dementia symptoms as assessed by the Brazilian version of the Mini-Mental State Examination (MMSE),[12] current treatment for any substance or alcohol dependence (controls only), and any psychoactive drug use

APENDIX B. PARECER CONSUBSTANCIADO DO PROJETO DE PESQUISA

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK.
Pesquisador: Rodrigo Grassi de Oliveira
Área Temática:
Versão: 3
CAAE: 39868314.0.0000.5336
Instituição Proponente: UNIAO BRASILEIRA DE EDUCACAO E ASSISTENCIA
Patrocinador Principal: MINISTERIO DA CIENCIA, TECNOLOGIA E INOVACAO
FUNDO NACIONAL ANTIDROGAS - FUNAD

DADOS DO PARECER

Número do Parecer: 2.166.639

Apresentação do Projeto:
O pesquisador principal do estudo:" ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK" encaminhou ao CEP-PUCRS, emenda contendo os seguintes documentos:
Carta Emenda - Contendo a justificativa para a adição de um novo objetivo ao projeto
Emenda Alvo - referencial teórico referente a adição no novo objetivo ao trabalho
TCLE

Objetivo da Pesquisa:
O pesquisador principal do estudo:" ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK" encaminhou ao CEP-PUCRS, emenda contendo os seguintes documentos:
Carta Emenda - Contendo a justificativa para a adição de um novo objetivo ao projeto
Emenda Alvo - referencial teórico referente a adição no novo objetivo ao trabalho
TCLE

Avaliação dos Riscos e Benefícios:
O pesquisador principal do estudo:" ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK" encaminhou ao CEP-PUCRS, emenda contendo os seguintes documentos:
Carta Emenda - Contendo a justificativa para a adição de um novo objetivo ao projeto

Endereço: Av.Ipiranga, 6681, prédio 50, sala 703
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3320-3345 **Fax:** (51)3320-3345 **E-mail:** cep@pucrs.br

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Emenda Alvo - referencial teórico referente a adição no novo objetivo ao trabalho
TCLE

Comentários e Considerações sobre a Pesquisa:

O pesquisador principal do estudo:" ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK" encaminhou ao CEP-PUCRS, emenda contendo os seguintes documentos:
Carta Emenda - Contendo a justificativa para a adição de um novo objetivo ao projeto
Emenda Alvo - referencial teórico referente a adição no novo objetivo ao trabalho
TCLE

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos foram apresentados

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

O CEP-PUCRS, de acordo com suas atribuições definidas nas Resoluções n° 466 de 2012 (e suas complementares) e da Norma Operacional n° 001 de 2013 do Conselho Nacional de Saúde, manifesta-se pela aprovação da emenda.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BASICAS_906192 E1.pdf	25/04/2017 14:39:54		Aceito
Outros	CartaEmenda.pdf	25/04/2017 14:37:27	Rodrigo Grassi de Oliveira	Aceito
Outros	EMENTAALVOSA.pdf	25/04/2017 14:33:17	Rodrigo Grassi de Oliveira	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_BIO_word.doc	25/04/2017 14:32:33	Rodrigo Grassi de Oliveira	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_BIO_word.pdf	25/04/2017 14:32:05	Rodrigo Grassi de Oliveira	Aceito
Outros	CARTA RESPOSTA CEP_ProMUC.pdf	15/01/2015 17:14:31		Aceito
TCLE / Termos de	TCLE__4_etapa_B_versão_word	15/01/2015		Aceito

Endereço: Av.Ipiranga, 6681, prédio 50, sala 703
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
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TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE-4-etapa A - com rubrica_ATUALIZADO 1401_(pdf).pdf	15/01/2015 17:06:23		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE-3-com rubrica_ATUALIZADO 1401_(pdf).pdf	15/01/2015 17:05:19		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE-2-com rubrica_ATUALIZADO 1401_(pdf).pdf	15/01/2015 17:04:57		Aceito
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Projeto Detalhado	PROJETO DETALHADO.pdf	05/12/2014		Aceito

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Continuação do Parecer: 2.166.639

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Outros	LATTES_Clarice Madruga(colaboradora).pdf	04/12/2014 20:32:00		Aceito
Outros	LATTES_Lucas Araújo de Azeredo(colaborador).pdf	04/12/2014 20:31:31		Aceito
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Outros	LATTES_Elisa Brietzke(colaboradora).pdf	04/12/2014 20:30:39		Aceito
Outros	LATTES_Alexandre Franco(colaborador).pdf	04/12/2014 20:30:10		Aceito
Outros	LATTES_Augusto B(colaborador).pdf	04/12/2014 20:29:50		Aceito
Outros	LATTES_Frederico Garcia(colaborador).pdf	04/12/2014 20:29:30		Aceito
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TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE__4_etapa_A_versão word(sem rubrica).docx	04/12/2014 19:42:42		Aceito
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Continuação do Parecer: 2.166.639

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TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE2_rubricado.pdf	04/12/2014 19:36:30		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE1_rubricado.pdf	04/12/2014 19:35:36		Aceito
Outros	carta aprovacao CC SIPESQ.pdf	04/12/2014 14:04:18		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

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PORTO ALEGRE, 10 de Julho de 2017

Assinado por:
Denise Cantarelli Machado
(Coordenador)

Endereço: Av.Ipiranga, 6681, prédio 50, sala 703
Bairro: Partenon **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (51)3320-3345 **Fax:** (51)3320-3345 **E-mail:** cep@pucrs.br

APENDIX C. TERMOS DE CONSENTIMENTO LIVRE E ESCLARECIDO DOS ESTUDOS

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
COMITÊ DE ÉTICA EM PESQUISA - CEP - PUCRS

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – ESTUDO 1

(PARTICIPANTE)

Participante nº____

INFORMAÇÕES SOBRE A PESQUISA:

Título da pesquisa: **ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK: VITIMIZAÇÃO PRECOCE, SINALIZAÇÃO DE OCITOCINA E COGNIÇÃO.**

Pesquisador responsável: Prof. Dr. Rodrigo Grassi de Oliveira.

Você está sendo convidada(o) a participar de uma pesquisa que será realizada pela Faculdade de Psicologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), coordenada pelo Prof. Dr. Rodrigo Grassi de Oliveira. O objetivo desta pesquisa é investigar características biológicas e psicológicas entre pessoas que usam e que não usam crack e criar novas formas de atenção à mulher usuária de crack. Em especial, você está sendo convidada (o) a participar de um dos estudos deste projeto de pesquisa, que investiga o funcionamento de um hormônio, conhecido como ocitocina, que pode influenciar a maneira como as pessoas pensam.

Este estudo investigará a existência de diferenças hormonais (a ação da ocitocina) e diferenças cognitivas (algumas funções como atenção, memória e a forma como você percebe os pensamentos e as emoções das outras pessoas). Sua participação pode, indiretamente, ajudar na identificação de um alvo para futuros tratamentos e estratégias de prevenção ao uso do crack.

MÉTODOS QUE SERÃO UTILIZADOS:

Caso você concorde em participar dessa pesquisa, é importante você ter conhecimento dos procedimentos que estão previstos a serem realizados em três sessões de avaliação de aproximadamente uma hora cada:

a) Na primeira sessão, que deve durar cerca de uma hora, profissionais treinados realizarão com você avaliações psiquiátricas e cognitivas.

b) Na mesma semana, uma segunda sessão de avaliação (de duração estimada em 60 minutos) será realizada. Nesta segunda sessão você:

- responderá a testes neuropsicológicos, que serão aplicados por um dos membros da equipe usando papel e caneta ou um computador;
- responderá a algumas perguntas a respeito de experiências estressantes que você pode ter vivido ao longo de sua vida, incluindo a infância;
- realizará uma coleta de sangue (20 ml, a mesma quantidade que uma colher de sopa) para a análise do funcionamento da ocitocina.

c) Na terceira sessão (estimada em 45 minutos de duração), você responderá algumas perguntas a respeito de sintomas de ansiedade, depressão e relacionados à abstinência de drogas que você pode ter sentido nas últimas semanas.

OUTROS ESCLARECIMENTOS:

1. Os dados da pesquisa serão publicados em revistas científicas nacionais ou internacionais, mas sua identidade será mantida no mais rigoroso sigilo. Ou seja, serão omitidas todas as informações que permitam a sua identificação, ou a de qualquer outro participante.
2. Os dados coletados, incluindo o seu sangue, serão anonimamente armazenados por um período de cinco (5) anos pelo Grupo de Pesquisa em Neurociência Cognitiva do Desenvolvimento (GNCD), e poderão ser utilizados em futuros projetos, desde que estes sejam aprovados pelos Comitês de Ética de Instituições envolvidas.
3. O sangue que será coletado será armazenado temporariamente em laboratório da PUCRS e posteriormente será utilizado para análises do seu perfil hormonal e de alterações no funcionamento de um gene específico (o do receptor de ocitocina). Estas alterações na função do gene são chamadas também de epigenéticas. Após as análises o material biológico será descartado de forma segura.
4. Você tem o direito de ser mantido atualizado sobre os resultados desta pesquisa, portanto, se essa for sua vontade, pedimos que forneça seu e-mail ou outro contato.

   E-mail/contato: _____

5. Você não terá nenhum tipo de custo financeiro ao participar deste estudo, e, caso você tenha algum gasto inesperado ao participar da pesquisa, o valor será compensados pela equipe de pesquisa.
6. A equipe de pesquisa reconhece que cobrirá quaisquer danos causados pela pesquisa ao participante com a devida indenização em qualquer caso de eventualidade.
7. Durante sua participação nesta pesquisa, nenhum tipo de risco é previsto, mas mesmo assim, caso necessário, você receberá todo tipo de assistência de forma imediata e gratuita. Além disso, caso ocorram complicações decorrentes de sua participação, seja de forma direta ou indireta, você também receberá assistência imediata e integral sem nenhum tipo de custo.
8. Embora a sua participação nesta pesquisa não preveja nenhum tipo de risco, algumas pessoas podem se sentir incomodadas ao responder certas perguntas, ou com a duração de alguns procedimentos. Você pode abrir mão de participar quando quiser, mas em caso de qualquer incômodo, a equipe de pesquisa tentará minimizar o seu mal-estar. Outro procedimento que por vezes pode causar algum desconforto é a coleta de sangue. A agulha pode causar uma pequena dor, semelhante a uma picada de um inseto. Um profissional treinado realizará a coleta de sangue e todo o cuidado será tomado para que o procedimento seja o mais rápido e indolor possível.
9. A sua participação nesse estudo é voluntária e gratuita, se você decidir não participar, ou se quiser desistir em qualquer momento, tem absoluta liberdade de fazê-lo. Sua decisão em não participar desta pesquisa não implicará em quaisquer tipos de prejuízo.
10. Salientamos que, a qualquer momento, você pode decidir se retirar da pesquisa. Não haverá qualquer tipo de implicação para você no caso de sua descontinuação como participante.

11. Estes termos seguem as regulamentações do Conselho Nacional de Saúde na Resolução Nºs 466/12 e da Comissão Nacional de Ética em Pesquisa.
12. Caso você tenha alguma dúvida sobre essa pesquisa, você pode buscar esclarecimentos com o pesquisador antes mesmo de assinar este documento, seja pessoalmente ou através do telefone (51) 3320-3500, ramal 7740, ou celular (51) 9376-7286.
13. Se você tiver interesse em questões éticas desta pesquisa, ou quiser saber mais sobre seus direitos como participante, você pode entrar em contato com o Comitê de Ética em Pesquisa da PUCRS.
    Endereço: Av. Ipiranga 6681 – Prédio 40 – Sala 505, Porto Alegre/RS – Brasil – CEP: 90619-900. Fone: (51) 3320.3345; e-mail: cep@pucrs.br. Horário de atendimento: segunda a sexta-feira, das 08:00 às 12:00 horas e das 13:30 às 17:00 horas.

CONSENTIMENTO LIVRE E ESCLARECIDO:

Após a leitura desse termo, afirmo:

1. **Acreditar ter sido suficientemente informada(o) sobre a justificativa e os objetivos dessa pesquisa, bem como a respeito dos procedimentos que serão realizados e dos eventuais riscos associados.**
2. **Todas as minhas dúvidas foram respondidas, mas ainda assim, sei que posso buscar novos esclarecimentos a qualquer momento.**
3. **Saber que todas as informações sobre a minha pessoa serão confidenciais, e que só serão divulgadas de forma que a minha identidade seja totalmente preservada, garantindo meu anonimato, portanto.**
4. **Declaro ter recebido uma cópia deste documento.**
5. **Concordo voluntariamente em participar deste estudo.**

Muito obrigado,

Prof. Dr. Rodrigo Grassi de Oliveira - 082819

Local e data

Nome do Participante

Assinatura do Participante

Documento do Participante (RG/CPF)

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
COMITÊ DE ÉTICA EM PESQUISA - CEP - PUCRS

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – ESTUDO 3

(PARTICIPANTE)

Participante nº____

INFORMAÇÕES SOBRE A PESQUISA:

Título da pesquisa: **ALVOS DE PROTEÇÃO À MULHER USUÁRIA DE CRACK: VITIMIZAÇÃO PRECOCE, SINALIZAÇÃO DE OCITOCINA E COGNIÇÃO.**

Pesquisador responsável: Prof. Dr. Rodrigo Grassi de Oliveira.

Você está sendo convidada a participar de uma pesquisa que está sendo realizada pela Faculdade de Psicologia da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), coordenada pelo Prof. Dr. Rodrigo Grassi de Oliveira. O objetivo desta pesquisa é investigar o impacto de algumas diferenças psicobiológicas entre homens e mulheres usuários de crack e desenvolver novas alternativas de proteção à mulher usuária de crack. Em especial, você está sendo convidada a participar de um dos estudos desta pesquisa, que pretende comparar os efeitos na atividade cerebral causados por uma substância que tem como princípio ativo a ocitocina (um hormônio que existe no corpo humano naturalmente) em comparação a uma solução que possui apenas substâncias que não tem princípio ativo, como o soro fisiológico. Esta solução sem princípio ativo é conhecida como placebo. Tanto a ocitocina como o placebo serão ingeridos por você através de uma forma de spray intranasal.

O uso continuado de cocaína, e de crack, pode causar alterações biológicas e psicológicas, incluindo modificações no padrão de atividade cerebral em resposta a estímulos relacionados a drogas. Como há estudos indicando que a ocitocina intranasal, um composto sintético semelhante à ocitocina – um hormônio natural produzido pelo organismo – pode auxiliar na diminuição de sintomas de abstinência de drogas, este estudo investigará se a ocitocina intranasal interfere na atividade cerebral em resposta a estímulos relacionados a drogas. Mais especificamente, o objetivo desta pesquisa é comparar os efeitos agudos da ocitocina intranasal com os efeitos agudos de uma solução placebo (spray com solução salina sem a ocitocina) na resposta a estímulos relacionados a drogas. Os resultados dessa pesquisa podem auxiliar a identificar um alvo para intervenções farmacológicas para usuários de crack. Portanto, a sua participação pode auxiliar a alcançar evidências de um alvo terapêutico para redução de sintomas de fissura, ou *craving*, pelo crack.

Como para sua participação um exame de ressonância magnética será realizada, garantimos que o retorno deste exame lhe será proporcionado através de documento médico oficial fornecido por um radiologista. Logo, a sua participação acarretará em um benefício direto para você que é a realização de um exame médico tecnológico e pouco acessível à população em geral. Além disso, participando deste estudo você pode contribuir para a descoberta de um importante alvo terapêutico para o tratamento de transtornos por uso de cocaína e crack. Logo, um benefício indireto de sua participação é a possibilidade de contribuir para descobertas com potencial para estimular novas propostas de tratamentos, uma vez que medicamentos podem ser desenvolvidos utilizando propriedades que ativem as mesmas áreas cerebrais que a ocitocina, caso nossos resultados sejam positivos neste sentido.

O spray intranasal composto de ocitocina que será utilizado nessa pesquisa é devidamente regulamentado pela ANVISA, sob registro nº: 1006800340021.

MÉTODOS QUE SERÃO UTILIZADOS:

Caso você concorde em participar dessa pesquisa, é importante você ter conhecimento dos procedimentos que estão previstos a serem realizados em três sessões de avaliação distintas:

a) Em uma primeira sessão, você passará por diferentes procedimentos:

- Você responderá a uma entrevista de avaliação psiquiátrica de aproximadamente 40 minutos. Nesta mesma sessão, uma avaliação médica será realizada para certificar que você não possui nenhuma contraindicação para participar neste estudo (ex: gravidez e lesões na mucosa nasal). Por fim, nesta sessão você também responderá a alguns testes de inteligência, cuja duração aproximada é de 30 minutos. Após a realização desta primeira sessão, sua participação no estudo pode ser desconsiderada caso você preencha algum critérios de contraindicação para a participação nesta pesquisa, como gravidez, ou possua prótese metálica. Nessa mesma sessão será realizada uma coleta de sangue (20 ml, a mesma quantidade que uma colher de sopa) que não lhe causará nenhum risco. Entretanto, no momento da coleta de sangue você pode sentir um desconforto, a agulha pode causar uma pequena dor, semelhante a uma picada de inseto. A coleta de sangue será realizada por um profissional treinado e todos os cuidados e esforços serão feitos para o procedimento ser o mais rápido e indolor possível.

b) A segunda e a terceira sessões de avaliação serão realizadas no Instituto do Cérebro, que fica no Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, em Porto Alegre, Rio Grande do Sul, Brasil. Caso você não possa se deslocar sozinha, transportaremos você em veículo apropriado, fornecendo cuidados necessários gratuitamente. Nestas sessões serão realizados os seguintes procedimentos, exatamente na ordem listada a seguir:

- Você inalará um spray contendo um composto com a ocitocina intranasal, ou com solução placebo. Você não será informado em qual das sessões você estará recebendo a ocitocina ou a solução sem o composto sintético. Em cada uma das sessões você inalará um dos dois compostos. O pesquisador que acompanhará você também desconhecerá qual solução você está recebendo. Outros estudos já utilizaram sprays iguais e nenhuma ocorrência foi relatada.

- Você será acompanhada até a máquina de ressonância magnética funcional, que realiza um exame que avalia áreas de funcionamento cerebral. O aparelho possui uma mesa, na qual você será acomodada, ficando deitada. O aparelho é cilíndrico e dispõe de uma espécie de bobina para a captação de imagens. Você permanecerá durante todo o exame na mesa. O técnico sairá da sala, mas ficará em constante contato com você através de um aparelho de

comunicação interna, através do qual vocês poderão conversar. Relaxe e permaneça imóvel, o máximo que puder durante o exame. Em caso de qualquer desconforto haverá uma campainha para você fazer contato com a equipe. Algumas pessoas podem se sentir incomodadas com o barulho durante o exame. Durante o exame você ouvirá um barulho parecido com o de batidas regulares, isso significa que as imagens (as "fotos" da atividade do seu cérebro) estarão sendo adquiridas. O exame tem duração aproximada de 40 minutos.

- Após o término do exame de ressonância magnética funcional, você será liberada. No caso de não poder retornar por dificuldade de transporte, ou quaisquer outros motivos, a equipe disponibilizará, de forma gratuita e com a cobertura de todos os requisitos necessários o seu transporte de retorno.

c) As aplicações dos sprays, a avaliação médica, a avaliação psicológica, a coleta de sangue e o exame de ressonância magnética funcional serão realizados por profissionais capacitados com recursos técnicos para evitar desconfortos e garantir sua assistência em caso de necessidade. A equipe de pesquisa possui capacitação pessoal e todos os materiais necessários para realizar todos os procedimentos da melhor forma possível, assegurando seu bem-estar e segurança.

OCORRÊNCIA DE DANOS OU EFEITOS INDESEJÁVEIS:

- Embora pouco relatados, o uso da ocitocina pode acarretar em eventuais desconfortos e riscos: contrações uterinas, reações alérgicas, náuseas e dor de cabeça. Quaisquer reações adversas ou inesperadas que possam surgir implicarão na imediata interrupção de sua participação na pesquisa, e garantiremos todas as medidas para o seu bem-estar e evitar qualquer tipo de prejuízo a sua saúde. Além disso, você passará por uma avaliação médica que avaliará se existe algum risco em sua participação, como gravidez ou doenças respiratórias.
- Para algumas pessoas, o preenchimento de escalas e a realização de testes/tarefas pode ser uma atividade exaustiva e incômoda. Nesses casos, a equipe de pesquisa fará o possível para diminuir eventuais desconfortos e abreviar ao máximo o protocolo de pesquisa.
- O exame de ressonância magnética funcional não implica em riscos à saúde, pois é um procedimento não invasivo, no qual não é necessária a aplicação de material radioativo, por exemplo. Entretanto, algumas pessoas podem sentir alguns desconfortos durante a realização do exame em função de, no período de 40 minutos de realização do exame ser exigido o máximo de imobilidade. Além disso, o espaço é pequeno, algumas pessoas sentem-se ansiosas, principalmente pessoas com claustrofobia. Outro ponto que pode causar desconforto durante o exame é o barulho da máquina. Embora existam tais desconfortos eventuais, nenhum efeito à saúde ocorrerá. Caso você relate desconforto durante o exame e não deseje continuar o realizando, imediatamente o exame será interrompido sem que isto lhe cause qualquer tipo de prejuízo.

OUTROS ESCLARECIMENTOS:

1. Os dados da pesquisa serão publicados em revistas científicas nacionais ou internacionais, mas sua identidade será mantida no mais rigoroso sigilo. Ou seja, serão omitidas todas as informações que permitam a identificação de qualquer participante.
2. Os dados coletados serão anonimamente armazenados por um período de cinco (5) anos pelo Grupo de Pesquisa em Neurociência Cognitiva do Desenvolvimento (GNCD), e poderão ser utilizados em futuros projetos, desde que estes sejam aprovados pelos Comitês de Ética de Instituições envolvidas.
3. O sangue que será coletado será armazenado em laboratório da PUCRS e posteriormente será utilizado para análises do seu perfil hormonal e de alterações na função do gene do receptor de ocitocina (também conhecidas como epigenéticas) que podem ter ocorrido em um gene que participa da sinalização de ocitocina. Após as análises, o seu material biológico será seguramente descartado.
4. Você tem o direito de ser mantido atualizado sobre os resultados desta pesquisa, portanto, se essa for sua vontade, pedimos que forneça seu e-mail ou outro contato.

   E-mail: _____

5. Você não terá nenhum tipo de custo financeiro ao participar deste estudo, quaisquer gastos implicados em sua participação serão compensados pela equipe de pesquisa.
6. A equipe de pesquisa reconhece que cobrirá quaisquer danos causados pela pesquisa com a devida indenização.
7. Durante sua participação nesta pesquisa, caso necessário, você receberá todo tipo de assistência necessária de forma imediata e sem custos. Além disso, caso complicações ocorram decorrentes de sua participação, seja de forma direta ou indireta, você receberá assistência integral também sem nenhum tipo de custo.
8. A sua participação nesse estudo é voluntária e gratuita, se você decidir não participar, ou se quiser desistir em qualquer momento, tem absoluta liberdade de fazê-lo. Sua decisão em não participar desta pesquisa não implicará em quaisquer tipos de prejuízo.
9. Salientamos que, a qualquer momento, você pode decidir se retirar da pesquisa. Não haverá qualquer tipo de implicação para você a sua descontinuação como participante.
10. Estes termos seguem as regulamentações do Conselho Nacional de Saúde na Resolução Nos 466/12 e da Comissão Nacional de Ética em Pesquisa.
11. Caso você tenha alguma dúvida sobre essa pesquisa, você pode imediatamente questionar o pesquisador pessoalmente, ou se quiser, pode buscar esclarecimentos com os pesquisadores através do telefone (51) 3320-3500, ramal 7740, ou celular (51) 9376-7286.
12. Se você tiver interesse ainda em saber mais sobre aspectos éticos desta pesquisa, ou quiser saber mais sobre seus direitos como participante, você pode entrar em contato com o Comitê de Ética em Pesquisa da PUCRS. Endereço: Av. Ipiranga 6690, Prédio 60 (sala 313), Porto Alegre/RS – Brasil – CEP: 90610-900. Fone/Fax: (51) 3320.3345; email: cep@pucrs.br. Horário de atendimento: segunda a sexta-feira, das 08:00 às 12:00 horas e das 13:30 às 17:00.

CONSENTIMENTO LIVRE E ESCLARECIDO:

Após a leitura desse termo, afirmo:

Rubrica Responsável Rubrica Participante Rubrica Pesquisador

1. **Acreditar ter sido suficientemente informada sobre a justificativa e os objetivos dessa pesquisa, bem como a respeito dos procedimentos que serão realizados e eventuais riscos associados.**
2. **Todas as minhas dúvidas foram respondidas, mas ainda assim, sei que posso buscar novos esclarecimentos a qualquer momento.**
3. **Saber que todas as informações sobre a minha pessoa serão confidenciais, e que só serão divulgadas de forma que a minha identidade seja totalmente preservada, garantindo meu anonimato, portanto.**
4. **Declaro ter recebido uma cópia deste documento.**
5. **Concordo voluntariamente em participar deste estudo.**

Muito obrigado,

Prof. Dr. Rodrigo Grassi de Oliveira - 082819

Local e data

Nome do Participante

Assinatura do Participante

Documento do Participante (RG/CPF)

APENDIX D

Published paper related to the theme of the thesis published within the PhD.

ARTIGO ORIGINAL

Propriedades psicométricas da *Cocaine Selective Severity Assessment* (CSSA) em mulheres usuárias de *crack*

Psychometric properties of Cocaine Selective Severity Assessment (CSSA) in crack users

Bruno Kluwe-Schiavon[1], Saulo Gantes Tractenberg[1], Breno Sanvicente-Vieira[1], Caroline Silva de Oliveira Rosa[1], Adriane Xavier Arteche[2], Júlio Carlos Pezzi[3], Rodrigo Grassi-Oliveira[1,4]

RESUMO

Objetivo: Este estudo teve como objetivo adaptar a *Cocaine Selective Severity Assessment* (CSSA) para o português do Brasil e verificar as propriedades psicométricas do instrumento em uma amostra de usuárias de *crack*. **Métodos:** Após as etapas de tradução e adaptação, 125 mulheres usuárias de *crack*, internadas em uma unidade pública de desintoxicação, foram avaliadas. Para caracterização da amostra e análise das validades concorrente, de construto e preditiva, foram utilizados os seguintes instrumentos: SCID-I, ASI-6, BDI-II e CCQ-B. **Resultados:** A análise fatorial exploratória identificou cinco fatores, com níveis adequados de consistência interna tanto para os fatores quanto para o escore geral da CSSA. Quanto à validade concorrente, a CSSA vai ao encontro de instrumentos já utilizados na clínica e em pesquisas. Em relação à validade de construto e preditiva, a CSSA pode ser sensível ao declínio dos sintomas de abstinência durante o processo de desintoxicação do *crack*. **Conclusões:** Nossos achados foram além da tradução e adaptação da CSSA, proporcionando testes de validade e sugerindo que a CSSA é um instrumento confiável na avaliação dos sintomas de abstinência do *crack*.

Palavras-chave
Transtornos por uso de substâncias, fissura, comportamento aditivo, medidas psicométricas, cocaína.

ABSTRACT

Objective: This study aimed to describe the translation and adaptation of Cocaine Selective Severity Assessment (CSSA) into Brazilian Portuguese and verify the psychometric properties in a sample of crack cocaine users. **Methods:** After the translation and adaptation steps, 125 female crack cocaine-dependent inpatients who were enrolled in an inpatient detoxification unit were evaluated. To characterize the sample and realize the analysis of concurrent validity, construct validity and predictive validity the following instruments were used: SCID-I, ASI-6, BDI-II e CCQ-B. **Results:** The exploratory factorial analysis identified five factors and revealed appropriate levels of internal consistency, as well as the total score of the CSSA. The concur-

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APENDIX E

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Effects of crack cocaine addiction and stress-related genes on peripheral BDNF levels

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ABSTRACT

This study examined the effects of glucocorticoid receptor (*NR3C1*), corticotropin-releasing hormone receptor 1 (*CRHR1*), and brain-derived neurotrophic factor (*BDNF*) genes on susceptibility to crack cocaine addiction and BDNF levels. Crack addicted patients who sought treatment (n = 280) and non-addicted individuals (n = 241) were assessed. Three SNPs in *NR3C1* (rs6198, rs41423247, and rs10052957), three in *CRHR1* (rs12944712, rs110402, and rs878886), and one in *BDNF* (rs6265) were genotyped. No significant effect was seen in the case-control analyses. Crack cocaine addicted patients showed significantly lower serum BDNF levels. Significant effects were observed for *NR3C1* rs41423247 and rs10052957. These effects were restricted to non-addicted individuals and they were supported by significant gene-by-disease status interactions. For *CRHR1*, all SNPs were associated with BDNF levels. Although there were significant effects only in the analysis restricted to non-addicted individuals, the lack of significant results in the gene-by-disease status interaction analyses suggest a general effect on BDNF levels. The haplotype analyses presented the same effect seen in the single marker analyses. This study suggests that SNPs in the *NR3C1* and *CRHR1* genes may influence BDNF levels, but this effect is blunted in the context of crack cocaine addiction. Therefore, our data may be interpreted in light of several studies showing pronounced effects of crack cocaine on BDNF levels. Since peripheral BDNF is a biomarker for several psychiatric phenotypes, our results may be useful in interpreting previous associations between stress-related SNPs, drug addiction, and depression.

1. Introduction

Brain-derived neurotrophic factor (BDNF) levels have been associated with several aspects of crack cocaine addiction, including drug severity, craving, memory impairment, and relapse (Corominas-Roso et al., 2013a, 2013b; D'Sa et al., 2011; Narvaez et al., 2013; Pedraz et al., 2015; Sordi et al., 2014; Viola et al., 2015, 2014; von Diemen et al., 2014). Therefore, BDNF levels have been suggested as a biomarker for outcomes related to crack cocaine use (von Diemen et al., 2016). Such outcomes and even vulnerability to drug addiction are similarly predicted by hypothalamic-pituitary-adrenal (HPA) axis functioning (Sinha, 2013). Interestingly, the existing literature links the HPA axis activation to altered BDNF expression in the brain (Suri and Vaidya, 2013), suggesting that variants in stress-related genes may potentially modulate peripheral BDNF, as well as the risk of drug addiction.

BDNF expression is controlled in a complex manner and several aspects of its synthesis and signaling are modulated by the HPA axis

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APENDIX F

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Similarities between adult female crack cocaine users and adolescents in risky decision-making scenarios

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ABSTRACT

Background: Although previous studies have shown that both adolescence and drug addiction can influence risk-taking and decision-making processes, the underlying mechanisms remain unclear. Specifically, there is a lack of evidence as to whether these conditions could affect deliberative and affective processes involved in risk taking, such as feedback learning and valuation of profits and risk. *Objectives*: The objectives were to compare the role of feedback and the use of information in risk-taking behavior between female crack cocaine users and adolescents. Additionally, we aimed to investigate whether sensation seeking, impulsivity, depressive and anxiety symptoms, executive functioning, and working memory performance could explain differences in risk-taking behavior. *Method*: This is a quasi-experimental study comparing 27 low-income adult female crack cocaine users (CU) to 18 female adolescents (AD) within two conditions (no-feedback or delayed-feedback) of the Columbia Card Task (CCT). In order to investigate CCT reference values for adult females, we also included 20 female non-drug-users with regular education and income as a reference group (RG). *Results*: A similar pattern of risk-taking behavior was found between CU and AD within the CCT no-feedback condition. When delayed feedback was provided, AD exhibited a similar pattern of risk-taking behavior in the no-feedback condition, while CU showed a reduction of risk-taking behavior. Both groups exhibited higher risk taking than the RG within the CCT no-feedback condition, but only the AD group showed higher risk-taking behavior within the CCT feedback condition. Depressive symptom severity and working memory deficits were associated with higher risk-taking behaviors in CU. Executive functioning deficits were associated with higher risk-taking behavior in AD. *Conclusions*: Adult female crack cocaine users and female adolescents took similar risks during risky decision-making scenarios where feedback about their own performance was absent. However, when participants were provided with such feedback, it modulated risk-taking behaviors in crack cocaine users but not in adolescents.

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Drug addiction; Development; Decision making; Cocaine; Choice behavior; Judgement; Adolescents; Risk taking

Drug addiction is conceptualized as an impulsivity–compulsivity disorder (Koob & Kreek, 2007) in which not only the beginning but also the maintenance of drug-seeking risky behaviors are related to maladaptive choices (Lucantonio, Stalnaker, Shaham, Niv, & Schoenbaum, 2012; Volkow & Baler, 2014). Therefore, drug dependence has been associated with poor decision making, specifically in contexts that trigger affective responses, such as real-life stressful situations or neuropsychological tasks (e.g., Reversal Learning; Iowa Gambling Task, IGT; and Delay-Discounting Task) in an experimental setting that investigate decision making in terms of uncertainty about choices (Johnson, Bruner, & Johnson, 2015; Torres et al., 2013). Some authors argue that drug users have reduced capacity to evaluate reward and punishment (Hulka et al., 2014), failing to incorporate ongoing feedback to guide future behaviors in "affective" gambling tasks (Cunha, Bechara, de Andrade, & Nicastri, 2011; Verdejo-Garcia & Bechara, 2009). These

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