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Stress and social cognition in cocaine users

Submission date	Recruitment status	[ ] Prospectively registered
11/06/2019	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
28/06/2019	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
19/07/2023	Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims
Cocaine users show deficits in cognitive skills, e.g., empathy, mental perspective-taking, and decision-making, which are accompanied by impaired social functioning in daily life. There is evidence that stress (more specifically a lack in stress tolerance) may be one of the main reasons why people lose control over their substance use. Moreover, cocaine chronically influences the hormone release in the main stress-response system of the body, the hypothalamic-pituitary-adrenal axis (HPA axis). Thus, it is assumed that cocaine use leads to lasting changes in the stress-response system. Consequently, it was supposed that the dysfunctions in the stress-response system and cognition play an important role in the development and maintenance in cocaine addiction. However, it is not yet known how stress influences cognition in cocaine users. Specifically, it is unclear (a) whether alterations in stress responses due to cocaine use impact cognition, and (b) whether changes in cocaine use lead to adaptations of the stress response and cognitive functions under stress. This study investigates how cocaine use influences stress and cognition over time.

Who can participate?
Cocaine users without polysubstance use pattern and healthy adults between 18 and 50 years of age

What does the study involve?
Participants are first invited to a screening session to check inclusion and exclusion criteria based on demographic, clinical and drug use related variables. They further perform a number of cognitive tasks. For the primary outcome, they perform: the Multifaceted Empathy Test (MET), a measure of empathy, and a social and non-social decision-making test battery containing the Social Discounting, Delay Discounting and Columbia Card Task (CCT) to measure empathy and decision-making without the influence of stress. After the screening, participants are invited to two further sessions: a baseline and a 4-months follow-up. The procedure as well as the tasks are the same for baseline and follow-up. Participants do two stress challenges, the Trier Social Stress Test (TSST) and the Cocaine Cue Video Test. The TSST is a test to provoke psychosocial stress by an unprepared speech and math task performed in front of a jury. The Cocaine Cue Video Test is a video depicting cocaine preparation and consummation to induce craving. The order of the stress challenges varies. Participants are either first experiencing the TSST and later the Cocaine Cue Video Test or vice versa. The same is true for the test batteries that are done after each stress challenge. Participants either first do a social cognition test battery and later a

social and non-social decision-making test battery or vice versa. The social cognition test battery contains the MET and the Movie for the Assessment of Social Cognition (MASC), a measure of mental perspective-taking, and the social and non-social decision-making test battery entails the Social Discounting, Delay Discounting, CCT and the Distribution and Dictator Game. The stress response is measured by hormonal, genetic and electrophysiological data. Hormonal and genetic data is measured by 15 blood samples and 13 saliva samples. Electrophysiological data (heart rate and skin conductance) is measured during the entire session. Pupil size is measured with an Eye Tracker during the Cocaine Cue Video Test. Participants are asked to restrain from illegal drug use 72 hours, from alcohol use 24 hours and from caffeine use two hours before each measurement. Moreover, participants give hair and urine samples for objective analysis of substance use at screening, baseline and follow-up.

What are the possible benefits and risks of participating?
Subjects are compensated for their participation in the study. Upon request, participants receive feedback on their cognitive performances. Additionally, participants who are interested in reducing their substance use will have access to a list of specialized clinics and hospitals. Moreover, participation will make an essential contribution to basic research and prevention in cocaine use. The risk for venous blood taking is small and it is performed by trained specialists. The two stress challenges may induce short lasting mood changes that do not differ from light mood changes in daily life. A specialized team of psychologists and technical medical assistance will monitor participants' psychological and physiological well-being at all times and data collection will be interrupted in early evidence of harm of the stress measurements.

Where is the study run from?
Psychiatric Hospital of the University of Zurich (Switzerland)

When is the study starting and how long is it expected to run for?
June 2016 to July 2020

Who is funding the study?
Swiss National Science Foundation (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
131

Study information

Scientific Title
The effect of psychosocial and craving-induced stress on social cognition and decision-making in cocaine users: a longitudinal approach

Acronym
SSCP

Study objectives
Regarding the effect of stress on behavioral measures the researchers hypothesize the following:
1. Both psychosocial and craving-related stress enhances drug craving in cocaine users but not in controls
2. Psychosocial stress evokes an HPA response and changes in the peripheral expression of stress-related genes in cocaine users and controls (e.g., down-regulation of the glucocorticoid receptor gene)
3. Craving induced by the drug cue paradigm elicits only an HPA response in cocaine users but not in controls
4. Psychosocial stress differently influences social and non-social decision-making, empathy and mental perspective-taking in cocaine users and controls
5. Craving-induced stress does not affect any measure in controls but alters social cognition as well as social and non-social decision-making in cocaine users

With regard to the interaction of both stressors the researchers expect the following:
6. Psychosocial stress interacts with stress load elicited by drug craving and vice versa. Specifically, we hypothesize that previous psychosocial stress might influence the craving response to a subsequent confrontation with drug cues in cocaine users. In contrast, if craving stress is induced first, subsequent psychosocial stress is augmented

Regarding the longitudinal analyses the researchers expect the following:
7. The HPA axis (at the endocrine and molecular level) is plastic and partially recovers during successful abstinence, while baseline differences between cocaine users and controls are

aggravated in users with increased cocaine use at follow-up
8. Susceptibility to stress and plasticity of the HPA axis will predict change in cocaine consumption

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/04/2016, Kantonale Ethikkommission Zürich (Stampfenbachstrasse 121, 8090 Zurich, Switzerland; Tel: +41 (0)43 259 79 70; Email: Info.KEK@kek.zh.ch), ref: BASEC ID 2016-00278

Study design
Four-year single-center longitudinal case-control study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet

Health condition(s) or problem(s) studied
Cocaine use disorder

Interventions
Eighty regular cocaine users and 50 healthy stimulant-naïve controls will be assessed at screening, baseline and at a 4-month follow-up. Participants are first invited to a screening session for the approval of in- and exclusion criteria and for the assessment of demographic and clinical variables as well as drug consumption patterns. They further perform the Multifaceted Empathy Test (MET; Dziobek et al., 2008), a measure of empathy, and a social and non-social decision-making test battery containing the Social Discounting (Strombach et al., 2015), Delay Discounting (Kirby et al., 1999) and Columbia Card Task (CCT; Figner et al., 2009) to measure empathy and decision-making without the influence of stress. After the screening, participants are invited to two further sessions: a baseline and a 4-months follow-up. The procedure, as well as the test instruments, are identical for baseline and follow-up. Participants undergo two stress challenges, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) and the Cocaine Cue Video Test. The TSST is a well-established test in order to provoke psychosocial stress primarily by an unprepared speech and mental arithmetic performed in front of an audience. The Cocaine Cue Video Test is a video-based task depicting a cocaine preparation and consummation scene to induce craving and subsequently craving-induced stress. The order of the stress challenges varies. Participants either first experience the TSST and in the second half of the assessment the Cocaine Cue Video Test or vice versa. The same is true for the test batteries that are implemented after each stress challenge. Participants either first undergo a social cognition test

battery and in the second half of the assessment a social and non-social decision-making test battery or vice versa. The social cognition test battery comprises the MET and the Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006), a measure of mental perspective-taking, and the social and non-social decision-making test battery entails the Social Discounting, Delay Discounting, CCT and the Distribution and Dictator Game (Charness & Rabin, 2002; Engelmann & Strobel, 2004). Ten blood samples using an intravenous catheter and 13 saliva samples are taken from the participants at pre-defined intervals to assess endocrinological and gene expressive stress parameters during the assessment. Furthermore, stress is also measured on an electrophysiological level (heart rate, heart rate variability, electrodermal activity) while performing the TSST and Cocaine Cue Video Test. Participants are asked to restrain from illegal drug consumption 72 hours, from alcohol consumption 24 hours and from caffeine consumption two hours prior to each measurement. Hair and urine samples are taken for objective and quantitative analysis of substance use during all three sessions.

Intervention Type
Other

Primary outcome measure
1. Social decision-making is measured by the Social Discounting Task at screening, baseline, and follow-up; and by the Distribution Game and Dictator Game at baseline and follow-up
2. Decision-making as a function of information use is measured by the Columbia Card Task at screening, baseline, and follow-up
3. Tolerance of delayed gratification is measured by the Delay Discounting task at screening, baseline, and follow-up
4. Empathy is measured by the Multifaceted Empathy Test (MET) at screening, baseline, and follow-up
5. Mental and emotional perspective-taking is measured by the Movie for the Assessment of Social Cognition (MASC) at baseline and follow-up.
6. Cortisol, ACTH, and noradrenaline (i.e., endocrinological stress markers) are measured by 10 blood samples, while cortisol and alpha-amylase are determined in 13 saliva samples at baseline and follow-up
7. Gene expression for 16 stress-related genes of interest (NR3C1, FKBP5, ADRA2A, SLC6A2, CRH, CRHR1, CRHR2, SLC6A3, SLC6A4, FOS, EGR2, EGR1, NFKB1, NFKB2, SP1, IL1B) are measured by 5 blood samples in PAXgene Blood RNA Tubes (PreAnalytiX Cat. No. 762165, BD) at baseline and follow-up
8. Electrophysiological stress markers: heart rate, heart rate variability, and electrodermal activity (EDA) are recorded using a BIOPAC System (Goleta, CA, USA) during the TSST and during the Cocaine Cue Video Test at baseline and follow-up
9. Pupil size in response to the Cocaine Cue Video Test recorded using the Eyelink 1000 remote system (SR Research Ltd, Canada) at baseline and follow-up

Secondary outcome measures
1. Social network is measured by the Social Network Questionnaire at screening
2. Motivation, tiredness, happiness, craving, stress, angriness, disgust, anxiety are all measured by a Visual Analogue Scale at screening, baseline and follow-up
3. Substance consumption patterns are measured by the Interview for Psychotropic Drug Consumption (IPDC) at screening, baseline and follow-up
4. Recent drug use is measured by substance concentrations in hair (~50 substances and major metabolites) at screening, baseline and follow-up
5. Spatial working memory and visual processing are measured by the Spatial Working Memory, Rapid Visual Information Processing and Matching to Sample Visual Search tasks from the

Cambridge Neuropsychological Test Automated Battery (CANTAB) at screening
6. Childhood trauma is measured by the Childhood Trauma Questionnaire at screening
7. Empathy and optimism bias are assessed with an experimental task (“Optimism Bias and Empathy Task”) at screening
8. Psychiatric Symptoms are measured by the Brief Symptoms Inventory (BSI) at screening, baseline, and follow-up
9. Potentially stressful life events are measured by the Holmes-Rahe Stress Inventory at screening, baseline, and follow-up
10. Goal attainment is measured by the Goal Attainment Scale at screening
11. Self-control is measured by the Self-control scale at screening
12. Consumption habit is measured by the Self-Report Habit Index at screening
13. General smartphone activity is assessed by an application that is installed with the participant's consent on their smartphones at screening and uninstalled at follow-up
14. Craving is measured by the Cocaine Craving Questionnaire at baseline and follow-up
15. Quality of life is measured by the Global Health Questionnaire at baseline and follow-up
16. Post-Traumatic Stress Disorder is measured by the Post Traumatic Stress Disorder questionnaire (PTSD-10) at baseline and follow-up
17. Anxiety is measured by the Beck Anxiety Inventory (BAI) at baseline and follow-up
18. Depression is measured by the Beck Depression Inventory (BDI-II) at baseline and follow-up
19. Severity of substance consumption is measured by the Drug Use Disorders Identification Test (DUDIT) at baseline and follow-up
20. Personality traits are measured by the Structured Clinical Interview for DSM-IV II (SCID-II) at screening
21. Psychiatric disorders are measured by the Structured Clinical Interview for DSM-IV I (SCID-I) at screening
22. Attention-Deficit/Hyperactive Disorder is measured by the ADHD self-rating scale at screening
23. Impulsivity traits are measured by the Barratt Impulsiveness Scale at screening
24. Estimated verbal IQ is measured by the German Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) at screening

Overall study start date
01/06/2016

Completion date
31/07/2020

Eligibility

Key inclusion criteria
General inclusion criteria:
1. To be able to read, understand and provide written informed consent
2. To be fluent in German
3. Women and men between the ages of 18 to 52 years
4. For women at baseline and follow up: not during menstruation phase

Specific inclusion criteria for cocaine users:
1. Estimated lifetime cocaine consumption >100 g
2. The abstinence duration from cocaine is <6 months
3. No regular use of opioids
4. No current polytoxic drug use pattern

5. No DSM-IV/5 Axis I adult psychiatric disorders — except for other substance use disorders (with exception of opioids), attention deficit hyperactivity disorder (ADHD), and a past depressive episode

Specific inclusion criteria for controls:
1. No DSM-IV/5 Axis I adult psychiatric disorders (except for tobacco use disorder)
2. No illegal drug use: less than 15 occasions and not during the last month (with the exception of cannabis)

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
130 participants with 80 cocaine users and 50 healthy stimulant-naïve controls

Total final enrolment
123

Key exclusion criteria
1. Family history of genetic mediated (h2 > 0.5) psychiatric disorders according to DSM-IV/5
2. Presence of severe neurological disorder or brain injury
3. Current diagnoses of infectious diseases or severe somatic disorder
4. History of autoimmune, endocrine or rheumatoid arthritis
5. Intake of medication with potential action at central nervous system during the last three days
6. Participation in the Zurich Cocaine Cognition Study (KEK-Nr. E-14/2009)
7. For women: pregnancy or breastfeeding
8. Subjects can be excluded for matching reasons (age, sex, nicotine status)

Date of first enrolment
01/10/2016

Date of final enrolment
31/07/2019

Locations

Countries of recruitment
Switzerland

Study participating centre

Psychiatric Hospital of the University of Zurich
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Sponsor information

Organisation
Psychiatric Hospital of the University of Zurich

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/01462r250

Funder(s)

Funder type
Government

Funder Name
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung

Alternative Name(s)
Schweizerischer Nationalfonds, Swiss National Science Foundation, Fonds National Suisse de la Recherche Scientifique, Fondo Nazionale Svizzero per la Ricerca Scientifica, Fonds National Suisse, Fondo Nazionale Svizzero, Schweizerische Nationalfonds, SNF, SNSF, FNS

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Results and Publications

Publication and dissemination plan
Publications are planned in high-impact peer-reviewed journals around the next four years after the overall trial end date.

Intention to publish date
31/07/2024

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		11/10/2022	19/07/2023	Yes	No