Serotonin transporter gene variation and sensitivity to conditioned cues: cause and cure in cocaine dependence

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The objective of this study is to evaluate whether healthy subjects and cocaine dependent patients carrying the s-variant of the 5-HTTLPR, show functional and structural impairments within the PFC-amygdala circuit and (related) abnormalities in the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON40013

Source
ToetsingOnline

Brief title
CocaSert-study

Condition

- Other condition

Synonym
cocaine addiction

Health condition

verslaving

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZoNMW

Intervention

Keyword: 5-HTTLPR, addiction, cocaine, cue-reactivity

Outcome measures

Primary outcome

- MRI: volume (mL) of all ROIs *

- DTI: FA values within all ROIs *

- BOLD: % change in BOLD signal within all ROIs, during fMRI tasks that assess emotional and rewardprocessing, fear conditioning and drug-cue reactivity*

- BOLD: % change in BOLD signal within all ROIs during a cue-reactivity task *

- 1H-MRS: resting state glutamate concentration in ACC and PFC (per voxel: glutamate/CSF) *

- VAS: % change in VAS-scores for craving elicited by drug-related cues **

In all analysis, the ROIs are the vmPFC, the OFC, the ACC and the amygdala.

* For these outcome measures the main study parameters are the difference between genotypes (s- or l-allele) and group (healthy controls or cocaine dependent patients)

* For these outcome measures, the influence of the 5 other polymorphisms will

be investigated in a exploratory analysis.

Secondary outcome

n.a

Study description

Background summary

Until now, prevention and treatment of cocaine dependence has been only moderately successful, suggesting that the critical mechanisms underlying individual differences in vulnerability to cocaine dependence have not yet been identified. The failure to extinguish (drug-related) conditioned behaviour in response to conditioned stimuli is suggested to be a major factor in the continuation of drug administration and relapse in cocaine dependence. This conditioned behaviour is the target of exposure therapy, in which cocaine dependent patients learn to extinguish drug-related conditioned behaviour. Unfortunately, a substantial part of the patients respond poorly to this type of therapy. A key factor in extinction failure is impaired PFC top-down control over the amygdala, which is suggested to be related to abnormalities within the serotonergic system. Serotonin transporter (SERT) knockout rats show impairments within the PFC-amygdala circuit as well as heightend sensitivity as evidenced by increased cognitive flexibility and a failure to extinghuis drug and fear related behaviour. In humans, the s-variant of the 5-HTTLPR polymorphism is associated with reduced SERT function, functional and structural abnormalities within the PFC-amygdala circuits as well as impaired fear extinction. These studies suggest that the s-allele of the polymorphism may predispose to the development of cocaine addiction and poor responding to exposure thearpy. However, a direct link between this polymorphism and cocaine dependence have not yet been demonstrated. The first objective of this study is to investigate how the 5-HTTLPR polymorphism affects the PFC-amygdala circuitry and (related) cognitive processes in healthy controls and cocaine dependent patients. The hypothesis is that inherited serotonin transporter down regulation predisposes to cocaine dependence due to impaired prefrontal (PFC) top-down control over the amygdala and heightened sensitivity for negative and drug related information. In addition, there are several other genetic polymorphisms that are suggested to affect the sensitivity to conditioned stimuli, including the genes encoding for the serotonin 2C receptor, de GRIN2A subunit in NMDA receptor, the dopamine D2 receptor, catechol-O-methyltransferase and Brain-derived neurotrophic factor.

Study objective

The objective of this study is to evaluate whether healthy subjects and cocaine dependent patients carrying the s-variant of the 5-HTTLPR, show functional and structural impairments within the PFC-amygdala circuit and (related) abnormalities in the neurocorrelates of behavioural conditioning and cognitive processing. More exploratory, the influence of 5 other polymorphisms will be investigated.

Study design

The aim of the study is to investigate how the 5-HTTLPR polymorphism affects the PFC-amygdala circuitry and related cognitive processes in healthy controls and cocaine dependent patients. More exploratory, the influence of 5 other polymorphisms will be investigated..This study follows a cross-sectional design.

Study burden and risks

No adverse events are foreseen. Saliva-derived genotyping and MRI itself are non-invasive. In this study, DCS will be orally administered as a challenge on the first testing day. There is no risk associated with participation. The nature of the burden is classified as minimal to moderate, considering that subjects will have to deliver saliva for genotyping and will have to come to the Spinoza Center for one session. The risks involved are negligible, as all the agents and techniques employed are registered for their use and/or routinely performed at the Spinoza Center. There is no direct potential benefit for the participants, other than indirect benefits as the current pilot study ultimately will hopefully to be able to better predict both cause and cure in cocaine dependence.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Male subjects with cocaine dependence as defined in the Diagnostic and Statistical Manual of Mental Disorders,Fourth Edition (DSM-IV; American Psychiatric Association 1994), and will be determined by a structured interview (Composite International Diagnostic Interview: CIDI) aged 18-40 years. Controls: male healthy volunteers aged 18 - 50 years.

Exclusion criteria

No cocaine dependence Positive DSM-IV/CIDI for any drug other than cocaine, heroin, alcohol or marijuana Major neurological disorders, claustrophobia, peripheral vascular diseases, current use of respiratory, cardiovascular, anticonvulsant or psychoactive medications (SSRIs), or alexithymia A positive urine test result for amphetamines, barbiturates, benzodiazepine metabolites, cocaine (metabolite), opiates, alcohol, and marijuana

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-09-2012
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO

Date:	18-06-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL39596.018.12