Impulsivity, a risk factor in relapse to substance use disorder: investigating neural substrates before and after pharmacological challenges.

Published: 10-10-2008
Last updated: 19-03-2025

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON33825

Source
ToetsingOnline

Brief title
Impulsivity in addiction

Condition

- Other condition

Synonym
alcohol addiction, cocaine addiction

Health condition

middelenafhankelijkheid (alcohol en cocaine)

Research involving

Human

Sponsors and support

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

Intervention

Keyword: alcohol dependence, cocaine addiction, modafinil, N-acetylcysteine

Outcome measures

Primary outcome

Primary outcome variables are: (a) test performance, (b) craving ratings, (c) fMRI activation patterns, (d) relapse. In addition, DNA samples will be taken in order to investigate different polymorphisms in dopamine receptor genes (DRD2 and DRD4) and the Catechol-O-Methyltransferease (COMT) gene, and polymorphisms in the serotonin transporter gene and the gene encoding for the NMDA receptor subunit NR2A.

Secondary outcome

not applicable

Study description

Background summary

During the development of substance dependence, drug-associated stimuli become increasingly relevant to the substance user. Studies on these motivational processes have greatly contributed to our understanding of the neurobiology of addiction, but so far the pharmacological and psychotherapeutic manipulation of these motivationally relevant drug cues have been moderately successful at best, and relapses after treatment are the rule rather than the exception.
In addition to the role of motivational cues, there is growing evidence that deficits in cognitive functioning play a key role in the development, course, and relapse of substance use disorders. In particular, cognitive functions that

involve control over one*s own behaviour, and thus also over behaviour when confronted with motivationally relevant drug cues, appear to be crucial. In human studies, higher impulsivity (disinhibition), diminished planning and decision making abilities are present in both alcohol- and drug dependent persons .
Although impulsivity and the motivational properties of drugs have been studied with various paradigms clinically and preclinically, the relations between these processes and their influence on the course of addiction and treatment success have been largely ignored. In this study, we will therefore study these two processes and their interaction, since it is likely that a diminished control over behaviour (impulsivity) will also influence behaviour that a (former) substance dependent person displays when confronted with motivationally relevant drug cues. For instance, the presence of a glass of beer will have a higher impact on behaviour when (a) a higher response to relevant alcohol cues is present, and (b) higher impulsivity is present, compared to someone who has normal impulsivity, and thus has better control over the response to motivationally relevant drug cues. We will employ neuroimaging techniques to shed more light on the neural substrate of abnormal emotion processing and cognitive deficits in drug addicts and the predictive value of aberrant brain activation patterns in relapse into drug abuse.
The postulated interrelation between poor impulse control, motivational relevance of drug cues, and vulnerability to relapse predicts that improving cognitive performance may represent a promising new approach in the treatment of addictive behaviours. We therefore propose pharmacological challenges with (1) a known cognitive enhancer that has been studied in humans with cocaine dependence (modafinil), and (2) an agent influencing the motivationally relevance of drug cues in animals (N-acetylcysteine). By including these pharmacological challenges, we will be able to determine their effect on impulsivity, motivational relevance of drug cues, and on the prevention of relapse.

Study objective

The goals of the proposed study are: (1) to further elucidate the relations between impulse control, motivational strength of drug cues, and brain activation patterns (using fMRI); (2) to examine the relative strength by which these processes are linked to vulnerability to relapse; and (3) to explore whether pharmacological approaches that improve cognitive functioning may provide new vistas for intervention strategies in the clinical management of alcohol and drug dependence (using pharmacological challenges with modafinil and N-acetylcysteine).

Study design

Alcohol dependent patients, cocaine dependent patients and healthy controls will be tested using relevant neurocognitive tasks on impulsivity and

motivational value of drug cues in a fMRI study both with acute administration with placebo and one of the two mediactions (participants in year 1 will receive modafinil and participants in year 2 will receive N-acetylcysteine) in a randomised double blind cross-over design. In addition, subjects will fill out questionnaires and DNA samples will be taken in order to examine genetic polymorphisms.

Intervention

During the first year of the study, in our randomised double blind cross-over design study, half of each group of participants (healthy controls, cocaine dependent patients and alcohol dependent patients) will receive a single dose of modafinil (200 mg) during the first fMRI session and placebo during the second fMRI session. The other half of the group will receive placebo during the first fMRI session and modafinil during the second fMRI session.

The participants who will be included in the second year of the study will receive N-acetylcysteine (2400 mg) instead of modafinil.

Study burden and risks

The first session will take place in the research facility, requires about 5 hours and will include diagnostic interviews, questionnaires, behavioral tasks inside and outside the scanner and taking DNA samples. During this session, before performing the tasks in the MRI scanner, a single dose of placebo or one of the two medications (year 1 modafinil or year 2 N-acetylcysteine) will be administered. The second session will also take place in the research facility and requires about 4 hours. During this session, questionnaires will be administered and tasks will performed inside and outside the scanner. Again, before scanning, during this second session, a single dose of placebo or one of the two medications will be administered. No adverse health consequences are known using functional MRI scans. The medications can have side-effects, but the chance on having side-effects is expected to be small, because a single dose is administered. Knowledge generated by this study can be of great importance for treatment of addictive disorders.

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

1) 18-60 years old, male
2) Current DSM-IV diagnosis of cocaine dependence or alcohol dependence, but recently detoxified and abstinent
3) Control group does not have any history of addictive behaviors
4) Able to sign informed consent and to comply with all study procedures

Exclusion criteria

1) Currently dependent on cocaine for the alcoholgroup
2) Currently dependent on alcohol for the cocaine group
3) Severe neurological or psychiatric disorders (e.g. major depressive disorder, psychosis, bipolar illness, dementia, or any other diseases that require psychotropic medications)
4) Serious medical illness
5) Known hypersensitivity or allergy to N-acetylcysteine or modafinil, or receiving chronic therapy with medication that could interact adversely with one of the medications under study (antibiotics for example), within 30 days prior to randomization, history of peptic ulceration, asthma.
6) Estimated IQ lower than 85
7) Dutch not as his/her primary language

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2008
Enrollment:	108
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fluimucil
Generic name:	N-acetylcysteine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Modafinil
Generic name:	Modafinil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-10-2008
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2009
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

ID: 25130
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-005538-59-NL
CCMO	NL24576.018.08
OMON	NL-OMON25130