Mapping dopaminergic function using phMRI in healthy volunteers and amphetamine users

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- to assess whether signal loss on phMRI (BOLD or ASL) in d-AMPH users is related to DA release and/or D2 receptor density -to assess which MRI technique (BOLD or ASL) is best in assessing cerebral DA neurotoxicity when compared to SPECT.

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

Summary

ID

NL-OMON37495

Source
ToetsingOnline

Brief title
Dopamine phMRI in amphetamine users

Condition

- Other condition

Synonym
addiction, Substance dependence

Health condition

kinder en jeugd psychatrie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: European Research Area

Intervention

Keyword: amphetamine, dopamine, phMRI, SPECT

Outcome measures

Primary outcome

BOLD: % change in BOLD signal intensity from baseline (ROI)

ASL: % change in CBF from baseline (ROI CBF/100 mg tissue)

SPECT: difference in binding ratio between baseline and after d-AMPH

administration (striatal ROI binding/binding in occipital cortex)

Secondary outcome

Visual analogue rating scale (VAS)

Outcome measures of neuropsychological tests: Stroop Word Colour Test (STROOP),

Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT), Iowa

Gambling Task (IGT), Digit Span test, Tower of London Test, Emotional Go-NoGo

Task, Attention Network Task

Study description

Background summary

Amphetamine (AMPH) is a drug that is used to treat disorders such as narcolepsy and attention-deficit hyperactivity disorder (ADHD), but it is also regularly used for recreational purposes. However, animal studies have revealed that repeatedly administration of high doses of AMPH may be neurotoxic to the dopaminergic (DA) neurotransmitter system. For example, repeated amphetamine treatment in nonhuman primates damages dopaminergic nerve terminals as is evident from decreases in DA concentration, density of the dopamine transporter

(DAT) and the vesicular monoamine transporter (VMAT-2) (Ricaurte, 2005). Furthermore, amphetamine administration resulted in reductions in striatal [18F]DOPA uptake in the striatum (Melega, 1996). In humans, there is evidence that recreational and repeated use of combined d-AMPH and ecstasy use might be neurotoxic to DA neurons (Reneman, 2002).
There is an apparent lack in studies on d-AMPH neurotoxicity in humans, which might be related to the fact that most in vivo imaging modalities (such as PET and SPECT) involve radioactive exposure and also are relatively expensive. Recent work suggests that DA function can also be evaluated non-invasively using magnetic resonance imaging (MRI) by measuring hemodynamic changes following a d-AMPH challenge, called pharmacological MRI (phMRI). Pharmacological-induced changes in hemodynamic responses can be assessed using BOLD (blood oxygenation-level dependent) contrast and arterial spin labelling (ASL). Jenkins et al. (2004) showed that MPTP-lesioned primates show a blunted hemodynamic response to a d-AMPH challenge compared to controls. In a recent explorative study we applied ASL-phMRI and SPECT to investigate dopaminergic abnormalities in AMPH users. The results indicated a blunted hemodynamic response in DAergic regions and a decrease in striatal DAT in AMPH users compared to controls (Schouw, submitted 2012). However, no correlation was found between the changes in the hemodynamic response and changes in DAT. Both studies demonstrate that phMRI is a highly promising technique to assess DAergic function, but in order to maximize its potential it is important to investigate the underlying correlates of the changes we observe. However, it is unclear what the neural underpinnings of this hemodynamic response are. One possibility is that it reflects DA release from the synaptic terminal. To investigate this possibility phMRI could be compared to other well-validated techniques such as PET or SPECT measuring DA release.
To this end, in this study we want to assess whether phMRI and (123I-IBZM) SPECT are both able to detect an increase in DA release as induced by AMPH administration in 20 healthy male volunteers and 20 amphetamine users. Ultimately, it is expected that DA phMRI will open a new horizon in the diagnosis and treatment of individuals exposed to this drug of abuse as well as patients suffering from neuropsychiatric disorders, such as ADHD.

Study objective

- to assess whether signal loss on phMRI (BOLD or ASL) in d-AMPH users is related to DA release and/or D2 receptor density
-to assess which MRI technique (BOLD or ASL) is best in assessing cerebral DA neurotoxicity when compared to SPECT.

Study design

BOLD- and ASL DA-phMRI studies will be conducted and compared to a [123I]IBZM SPECT scan as reference (gold standard). One 123I-IBZM SPECT scan session with a d-AMPH challenge will be conducted. In addition, the BOLD and ASL DA-phMRI

studies can be studied in one scan session following an i.v. challenge with the dopamine releaser d-AMPH. These sessions will take place with an interval of 3 weeks. The order of the SPECT and phMRI scan will be randomized to control for order effects.

Study burden and risks

No serious side effects are foreseen. MRI itself is a non-invasive imaging modality. In this study, a low dose amphetamine challenge (0.3 mg/kg i.v.) will be administered during the MRI study. Furthermore, low dose amphetamine (0.3 mg/kg) is nowadays frequently
administered in PET and SPECT studies, to study amphetamine induced dopamine release. The pharmacy of
the AMC will provuide the d-amphetamine, conform GMP annex 13 criteria. No serious side effects of the low
dose d-ampehtamine are foreseen. It has been shown that while some subjects experience large increases in
happiness, restlessness and energy, other subjects experience almost no subjective effects following 0.3
mg/kg, and that the quality and intensity of the subjective responses to low dose amphetamine were similar
during a second exposure (Abi-Dargham 2003). The radiation exposure of the SPECT scan is classified as
category II, and routinely conducted at the AMC also in healthy human volunteers. Moreover, [123I]IBZM is
a registated radioligand, which is produced routinely using GMP-criteria.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
, Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
, Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healty male volunteers, aged between 18 and 30 years. Use of amphetamine on at least 40 occasions in the past year in group of amphetamine users.

Exclusion criteria

Contraindications for MRI (e.g. osteosynthetic material, pacemaker, artificial cardiac valves); claustrophobia. Symptomatic cardiovascular disease, moderate-to-severe hypertension, hyperthyroidism, glaucoma, hypersensitivity or idiosyncrasy to sympathomimetic amines, agitation, and history of drug abuse, or use of psychotropic drugs that affect DA function, such as methylphenidate and cocaine (anamnestic). Finally, cardial conduction disorder (abnormal ECG) en renal disease.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-01-2013
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	26-07-2012
Application type:	First submission
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	NL39823.018.12