A double-blind functional MR study to investigate the stability of the signal at baseline and following the administration of cognitive tests in placebo condition and after oral administration of a benzodiazepine in young healthy male subjects

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

Summary

ID

NL-OMON33167

Source
ToetsingOnline

Brief title
Reproducibility of cognitive fMRI tests after placebo and benzodiazepine

Condition

- Other condition

Synonym
n.v.t.

Health condition

neurosciences

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Provincie Groningen;Europese Unie IAG2 programma,Xendo Drug Development

Intervention

Keyword: benzodiazepine, cognition, divided attention, memory

Outcome measures

Primary outcome

A generally diminished subject performance is expected in the presence of the medication. The study design is such that it will be possible to numerically quantify the effects. Specifically: the working memory task should reveal an increased difficulty in successfully complete the n-back test, possibly due to interference in the underlying mechanism of constant update of the target letter; the episodic memory should reveal an increased difficulty in retrieving a reliable information, and that difficulty should be detectable both as a variation in the answers variance and in their accuracy; finally, the divided attention task could shed light on possible interference effects caused by the medication in successful coping with two different activities. The placebo sessions will provide a reference in order to attempt to disentangle the physical and the psychological components of the effects generated by the assumption of benzodiazepine.

These informations may concur in paving the way towards a better understanding of the interaction mechanisms between neuronal activity at a network level and medications, specifically concerning the localization of areas specifically affected by the benzodiazepine, thus setting parameters for future studies of the same kind and for development of novel psychoactive substances targeted at specific regions/functions.

Secondary outcome

n.a.

Study description

Background summary

A staggering volume of papers using fMRI explore the localization and/or cognitive anatomy associated with some cognitive task, however only a minority study the effect of drugs.
Most investigations contrast the changes is the blood-oxygen-level-dependent (BOLD) signal at baseline and following task administration. Task-dependent activation of the brain results in transient increases in cerebral blood flow and glucose utilization with little or no increase in oxygen consumption. Thus, a relative oxygen surplus exists during active states which is the basis for the BOLD signal. Combining BOLD fMRI, recording of local field potentials (LFPs) and single- and multiunit spiking activity from the visual cortex of Macaque monkeys, Logothetis et al demonstrated that the BOLD signal correlates with LFPs and hence that the BOLD contrast method reflects the input and intracortical processing of a given area rather than its spiking output.
Local cortical information processing which is measured with BOLD fMRI is supported by modules consisting of a mesh work of glutamate- and gamma-aminobutyric acid (GABA)-containing projection neurons and interneurons, respectively, that receive extensive projections from subcortical modulatory systems. Psychotropic drugs affect the function of these modules directly by acting on locally expressed neurotransmitter receptors and transporters, (catabolic) enzymes and/or ion channels and hence drug effects can be meaningfully investigated with BOLD fMRI as has been demonstrated for a variety of drug classes.
Functional MRI is an especially useful tool to investigate drug effects on uniquely human brain functions. Nevertheless, the potential of BOLD fMRI for

novel central nervous system (CNS) drug development has not yet been fully realized. One of the reasons may be that limited information is available on the stability of the signal across sessions. Although in theory this may be overcome by always testing subjects in a parallel-group design, the MRI scanning procedure itself may influence brain function and/or performance for example because of high noise level in the scanner. Pre-exposure may help to accommodate the subject to the testing environment and thereby diminish potential effects of the procedure on the study results.

Study objective

In order to set up paradigms for pharmaco-MRI studies for development of novel psychotropic medications.
The present study will investigate the effect of:
- low-dose benzodiazepine on brain activation and test performance on a testbed of well studied standard tasks. The testbed of standard tasks will be constituted by: a working memory task; an episodic memory task; a dual task combining a motor with an oddball paradigm, resulting in divided attention;
- first exposure to the MR scanner and test environment on brain activation and test performance during a second and third exposure following administration of the above-mentioned tasks;
- benzodiazepine on the resting state fMRI signal and the stability of this signal.

Study design

The proposed study will be a double-blind, 4-way crossover study in young healthy male, right-handed subjects between 18-25 y.o.a. . At least 20 volunteers will be recruited. For the statistical analysis it is obligatory to have twenty completed sessions.
After an initial training session (ca. 1 hour), each subject will be tested on 4 occasions which will be separated by approximately 1 week. Subjects will receive no study medication or a placebo for period 1; periods 2 and 3 will be randomized to receive 2mg lorazepam (Temesta) or placebo. Period 4 will consist of a placebo. All doses will be administered ca.30 minutes prior to the start of the testing procedures.

Each period, images will be acquired at rest and when performing a simple motor task or tests for working and episodic memory, and attention. Blood flow measurements will be made using arterial spin labeling (ASL) immediately prior to and following the test procedures. Tests will be performed in blocks. The encoding- and recall phases of the episodic memory task will be separated by the acquisition of a structural MR of the brain for alignment of the activation parameters and will be treated as 1 block (block A). Block order (block A, plus working memory = block B; plus divided attention + motor function = block C) will be randomized for each subject and the block order remains fixed all 4

periods.
Between blocks, subjects will focus for ca. 5 minutes on a neutral fixation point and a resting state MRI will be obtained. Each block will approximately last 15 - 20 minutes. The total scanning time will be approximately 90 minutes.

For the working memory a predefined sequence of stimuli (pictures, letters, sounds) will be presented to the subject, whose task is to decide if the current stimulus matches the one which was administered n steps back.
The episodic memory, the memory of unique events in time and place, will be tested using the software package Presentation and a set of pictures selected from the International Affective Picture System (IAPS)
During the dual task(Attention & motor), two effects are integrated. The attention part will consist of a Choice Reaction Task (CRT), i.e., an auditory oddball paradigm. The subject is presented with two stimuli occurring at different frequencies and it is asked to discriminate them. For the motor part the subject is requested to produce a constant force by abducting the index finger of the left hand.

Intervention

Each subject will be tested at 4 different periods, each period will be separated by ca. 1 week.
The first time the subjects will not receive medication or a placebo.
During the 2nd and 3rd visit the subjects will be given a placebo or once-only 2 mg lorazepam (Temesta).
During the 4th visit the subject will receive placebo medication.
All doses will be taken ca. 30 minutes prior to the start of the tests

Study burden and risks

Participants will thoroughly be examined before they will be included in the study. Therefore, the experiment will not entail more than minimal risk to the participants. The study is not intended to benefit the subjects directly However, the data collected during this study will give the possibility to set up paradigms for the development or of new psychotropic medication.
The burden associated with cognitive tests is minimal as is the effect of the benzodiazepine (lorazepam) that will be employed for this study. Lorazepam is characterized by a medium duration of action (0.4 to 3 hours). After each visit, a companion or a taxi will take the subjects home.

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

Healthy, right-handed male individuals between 18-25 year -o.

Exclusion criteria

•Female sex.
•Previous participation in a study with MRI.
•Clinically significant history of drug allergies (benzodiazepines).
•Recent history (within previous 6 months) of alcohol or drug abuse.
• History of or current significant medical illness including cardiac arrhythmias or other cardiac disease, hematological disease, bronchospastic respiratory disease, dyspnea, diabetes mellitus, renal or hepatic insufficiency, thyroid disease, infection, or any other illness that the investigator considers clinically significant.
• History of or current psychiatric or neurological illness.
• Smoking cigarettes (or equivalent) or the use of nicotine based products, within 3 months prior to study drug administration
• Positive urine screen for drugs of abuse at screening or admission.
• Use of any prescription or over-the-counter psychotropic medication (including herbal

medications) within 2 weeks of dosing with the study drug.
• Visual disorder that cannot be corrected through the use of corrective lenses
• Claustrophobia and/or a panic disorder
• Those suffering from phobiae of physical restraint, specifically concerning the head and the hand/finger complex
• Participants who do not fulfill the criteria for participating in an fMRI assessment (e.g. people who have metal implants (pacemaker, heartvalves, vascular clips, eye-implants or red tattoos, piercing)
• Psychological and/or emotional problems, which limit the ability of the subject to comply with the study requirements.
• Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-07-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lorazepam / Temesta
Generic name:	benzodiazepine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-04-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2009-010894-19-NL
CCMO	NL27170.042.09