Manipulating NMDA-dependent learning to alter nocebo effects: A pharmacological fMRI study on pain and itch.

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The primary objective is to test the role of NMDA receptor-dependent learning in an experimental model of conditioned nocebo effects on self-reported pain (sub-study 1) and itch (sub-study 2). Secondary objectives are to examine the role of NMDA...

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

Summary

ID

NL-OMON49103

Source
ToetsingOnline

Brief title
Nocebo and Learning

Condition

- Other condition

Synonym
Nocebo effects; Insufficiently explained pain and itch symptoms

Health condition

Nocebo effects (experimental model in healthy participants)

Research involving

Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: NWO Vici grant (grant number: 45316004)

Intervention

Keyword: Conditioning, Learning, Nocebo effects, Pharmacological fMRI

Outcome measures

Primary outcome

The main study parameter is the magnitude of induced nocebo effects on self-reported pain and itch in the evocation phase as compared between the pharmacological groups. The magnitude of the induced nocebo effects on pain and itch is measured as the difference between self-reported pain or itch on a Numeric Rating Scales (NRS) between conditioned and control evocation trials, in early trials of the extinction phase.

Secondary outcome

Secondary study parameters for both sub-studies:

- The classification accuracy (into pharmacological groups), indicating that patterns of activation in the network of a priori ROIs form a model that can detect differences in neural activations during the induction of nocebo effects.
- The classification accuracy (into pharmacological groups), indicating that patterns of activation in the network of a priori ROIs form a model that can detect differences in neural activations during the evocation phase.
- The classification accuracy, indicating that patterns of activation in the network of a priori ROIs form a model that can detect commonalities and

differences in neural activations between the experience of pain and itch.

- The classification accuracy, indicating that patterns of activation in the network of a priori ROIs form a model that can detect common neural activations between the experience of nocebo-augmented pain and nocebo-augmented itch, thereby indicating a signature of activations relevant to the manifestation of nocebo effects, independent from sensory input.
- The prediction accuracy, indicating that patterns of activation in the network of a priori ROIs form a model that can predict the magnitude of induced nocebo effects based on patterns of activations during the induction of nocebo effects.
- The moderation of the magnitude of induced nocebo effects in the evocation phase by scores on the psychological questionnaires.
- The magnitude of nocebo effects on pain and itch present after nocebo attenuation, between the pharmacological groups, as measured in early trials of the extinction phase relative to the last trials of the extinction phase.
- The classification accuracy (into pharmacological groups) indicating that patterns of activation in the network of a priori ROIs form a model that can detect differences in neural activations during the attenuation of nocebo effects.

Study description

Background summary

Nocebo effects, negative responses to inert or active treatments which are putatively induced by negative outcome expectations, have been shown to play a

significant role in pain and itch perception and putatively also in chronic pain and itch conditions. The underlying mechanisms of these effects remain largely unexplored. One important process proposed to be involved in inducing nocebo effects is conditioning, i.e., associative learning. Nocebo effects on pain or itch may thus be formed by learning an association between two stimuli, for example factors in the environment like the treatment setting, and a negative treatment outcome. Upon conditioning via repeated pairing of these two stimuli, an association is formed through neural plasticity in the brain. N-methyl D-aspartate (NMDA) receptor activity appears to mediate the neural plasticity processes which are thought to underlie learning. Crucially, NMDA receptors can be agonized with pharmacological agents such as D-cycloserine (DCS), to augment neural plasticity. The effects of pharmacological manipulations on NMDA receptor activity can be observed in changes in the blood oxygen level dependent (BOLD) signal at specific functional regions and in whole brain networks using functional magnetic resonance imaging (fMRI). By manipulating NMDA dependent plasticity with this pharmacological agent we will be able to demonstrate the role of NMDA dependent learning in nocebo effects on pain and itch.

Study objective

The primary objective is to test the role of NMDA receptor-dependent learning in an experimental model of conditioned nocebo effects on self-reported pain (sub-study 1) and itch (sub-study 2). Secondary objectives are to examine the role of NMDA manipulations and related neural correlates during the induction, evocation, and attenuation of nocebo effects using statistical learning models. We also aim to explore neural differences between control stimulations and nocebo-augmented pain and itch. Lastly, the moderating effects of psychological variables measured with questionnaires on the nocebo effect will also be explored.

Study design

This study will utilize a placebo controlled, double-blind design with respect to the pharmacological administration. We will use validated conditioning and verbal suggestion paradigms to induce and attenuate nocebo effects on pain or itch, and examine the pharmacological underpinnings. Participants will be told that the (sham) activation of electrical pulses is affecting their pain/itch perception. Experimental pain and itch will be administered using a standardized thermal heat pain application device (sub-study 1) or through histamine-evoked itch (sub-study 2). Each sub-study will consist of 2 pharmacological groups: 1) 80mg/70kg DCS oral capsule, 2) a placebo oral capsule.

Intervention

We will manipulate NMDA-mediated learning mechanisms with a pharmacological agent, namely, the NMDA receptor agonist D-cycloserine.

Study burden and risks

Risks are minimal. The pharmacological agents are not expected to cause adverse effects or discomfort to the participants in the doses administered in this study. Several studies have been conducted in humans with up to 1000mg of DCS that reported minimal (e.g. drowsiness) or no adverse side effects. All participants will be monitored by a medical doctor. Mild discomfort or increased anxiety may be experienced during the induction of heat pain or itch. The standardized pain application device (Pathway, Medoc) is frequently used in clinic and research and has built-in safeguards. No risks associated with topical administration of histamine to evoke itch are known. The fMRI acquisition is non-invasive and safe. Participants will be carefully screened for all contra-indications (e.g. metal parts, pregnancy). A medical exam (carried out by a medical doctor) and a psychiatric screening will be completed per participant prior to participation. A medical backup team will be on call to further support the study medical doctor, who will monitor participants at all times during the study. Participants will be asked to invest approximately five hours of their time across 2 sessions in order to complete this experiment and will be allowed to withdraw from the study at any point. Participants will receive a reimbursement of 90 euros for completion of this study.

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

To be eligible, participants must meet all of the following criteria:
1. Between 18 and 35 years of age
2. Good understanding of spoken and written English
3. Native Dutch speaker

Exclusion criteria

A potential subject who meets any of the following exclusion criteria will be excluded from participation in this study:
1. History of serious or chronic medical or psychiatric conditions
2. History of chronic pain or itch conditions
3. Experiencing pain or itch on the day of testing above the threshold of 1 out of 10 on the NRS
4. Currently using antihistamines, analgesic medication, or itch-reducing medication (in the 24 hours prior to testing)
5. Recent use of psychotropic drugs (including recreational drugs such as cannabis and psychotropic prescription-medication; in the past month)
6. Currently being (or intending to become) pregnant, or currently breastfeeding
7. Colour-blindness
8. Body Mass Index under 16 or over 30
9. Meeting any exclusion criteria for entering the MR scanner (e.g., permanent metal parts in the body)
10. Having a too high threshold for pain (where high pain cannot be induced with temperatures lower than 49.5 °C) or not responding to histamine (no itch response)
- A medical exam (carried out by a medical doctor) and a psychiatric screening will be completed per participant prior to participation. A medical backup team will be on call to further support the study medical doctor, who will monitor participants at all times during the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-02-2021
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	D-cycloserine
Generic name:	D-cycloserine

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-06-2020
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2018-002637-37-NL
CCMO	NL66693.058.18