The role of anticipation in nocebo effects on pain

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21903

Source
NTR

Brief title
TBA

Health condition

Healthy participants

Sponsors and support

Primary sponsor: Leiden University, Leiden, the Netherlands
Source(s) of monetary or material Support: NWO Vici Grant Number: 45316004

Intervention

Outcome measures

Primary outcome

Stimulus preceding negativity (SPN) during evocation: The primary outcome of the study is the measurement of SPN, an event related potential (ERP) component used as a measure of anticipatory processing. Late SPN, measured in the 500ms directly prior to the onset of the thermal pain stimuli, will be compared between control and nocebo evocation phase trials to measure whether learned nocebo effects correspond with changes in anticipatory processing

prior to experiencing pain. The mean signal of all evocation phase trials free of artifacts in the EEG data from included participants will be included in this analysis.

Secondary outcome

SPN during acquisition: In the same manner described for the primary outcome, SPN during the 500ms preceding thermal pain stimuli will be compared between control and nocebo acquisition trials.

Nocebo effect on pain: Behavioral nocebo effects are measured as the mean difference between control and nocebo evocation trials during the first half of the evocation phase (first 15 control- and first 15 nocebo evocation trials). Only the first half of the evocation phase is used for the behavioral outcome as extinction is expected to progressively reduce the magnitude of the nocebo effect over the course of the evocation phase. We aim to minimize the impact of extinction on the results by analyzing only the first half of the evocation phase for this outcome.

Granger Causality: Granger Causality analysis in EEG data can test whether information contained in the time series of electrode X improves the prediction accuracy of information contained in the time series of electrode Y as compared to prediction by the past time series of electrode Y alone (Friston, Moran & Seth, 2013). Should information recorded from electrode X improve the prediction accuracy of information in electrode Y, one can infer that something in the time series of electrode X Granger causes later occurrences in the time series of electrode Y. This method has previously been used on EEG data to model networks of pain processing (Tommaso et al., 2015, Ploner, Sorg & Gross, 2017). By applying this method to EEG data collected during the anticipation and evocation of nocebo effects on pain, we aim to model a network of neural activity underlying nocebo-augmented pain, and compare this model to one of pain experienced during control evocation trials, thereby developing a network model of how anticipatory processing leads to nocebo effects on pain. Specifically, we plan to test an a priori network in which EEG signal from frontal electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8) Granger Causes signal in temporoparietal electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8), representing the process of prior, learned expectancies for nocebo pain stimuli influencing processing at somatosensory cortex during the evocation phase of conditioning, and compare this network between control and nocebo evocation trials. Secondly, a data driven model will be tested in an exploratory analysis in which all possible electrode pairs are tested and pairs with a significant Granger Causal relationship are included in the model.

Fear of Pain: The relationship between fear of pain, magnitude of the (behavioral) nocebo effect, SPN during evocation, and Granger Causality from frontal to temporoparietal electrodes will be assessed with correlation analysis to investigate the degree to which fear of pain corresponds to anticipatory processing of nocebo-augmented pain during nocebo evocation trials, given potential extinction of the nocebo effect. The analysis will be repeated with the entire evocation phase as an exploratory analysis.

Study description

Background summary

In this study on healthy adult participants, we will use electroencephalography (EEG) to measure neural activity during the anticipation of ‘normal’ and ‘nocebo-augmented’ pain. By exploring the differences in how the brain anticipates pain under these conditions, we aim to better understand how learned expectations shape painful experiences. Nocebo effects on thermal pain will be induced in a single group of 42 participants (sample size derived from a power analysis of Morton et al., 2010) using a verbal suggestion and classical conditioning paradigm while EEG is recorded.

Study objective

Primary research question: Does the amplitude of late SPN in the 500ms preceding a pain stimulus differ between the anticipation of moderate pain versus heightened, nocebo augmented pain, during the evocation of nocebo effects on pain?
Primary hypothesis: Late SPN amplitudes in response to cues (colored text on a computer screen indicating the activation of a (sham) TENS device), measured in the 500ms preceding cued stimuli, will be increased in anticipation of nocebo trials, as compared to control trials, in the evocation phase.
2. Secondary (exploratory) research questions and hypotheses:
2a. Research question: Does the amplitude of late SPN in the 500ms preceding a pain stimulus differentiate between the anticipation of moderate, control pain and heightened pain, during the acquisition of nocebo effects on pain?
Hypothesis: Late SPN in response to cues 500ms preceding nocebo and control pain stimuli, will be increased during nocebo trials, as compared to control trials, in the acquisition phase.
2b. Research question: Will differences in late SPN amplitude between the first half of nocebo and control evocation trials correlate with the magnitude of self-reported nocebo augmented pain (i.e., noceboe effect) for the evocation phase?
Hypothesis: The magnitude of late SPN (nocebo minus control amplitudes) will correlate with the magnitude of the nocebo effect.
2c. Research question: Does anticipatory neural processing measured with Granger Causality Analysis in the 1000ms preceding pain stimuli differ between moderate pain and heightened, nocebo augmented pain during the acquisition and evocation of nocebo effects?
Hypothesis: Anticipatory neural processing measured 1000ms prior to nocebo pain stimuli in frontal electrodes will predict neural activity in the following 1000ms in temporoparietal electrodes, from the onset of the pain stimulus, modelled with Granger Causality analysis. This model will be compared to a model for control pain stimuli, separately for the acquisition and evocation phases.
2d. Research question: How does fear of pain relate to self-reported nocebo augmented pain during the first half of the evocation phase?

Hypothesis: Higher fear of pain will be correlated with higherself-reported nocebo augmented pain during the first half of the evocation phase. The analysis will be repeated with the entire

evocation phase as an exploratory analysis.
2e. Research question: How does fear of pain relate to networks of anticipatory neural processing preceding nocebo-augmented pain during the evocation phase?
Hypothesis: Higher fear of pain will be correlated with a larger difference in SPN and Granger Causality values between? nocebo and control evocation phase trials.

Study design

Participants complete the study in a single lab visit of approximately 2 hours in duration, during which the primary and secondary outcomes are measured.

Intervention

Verbal suggestions: Participants are told at the start of the experiment, and again just prior to the conditioning paradigm, that pulses from an electrical stimulation device attached to their aim via two electrodes will increase the intensity of the thermal pain stimuli when the electrical stimulation device is turned on.

Classical conditioning: Participants undergo a classical conditioning paradigm intended to form an association between the (sham) activation of the electrical stimulation device and increased pain intensity. The acquisition phase of the paradigm, during which time the association is learned, consists of 40 control and 40 reinforced nocebo pain stimuli trials. During control trials, a thermal stimulus calibrated to evoke moderate pain intensity (approximately 4 on a 0-10 pain scale) is paired with a message on a computer screen stating the electrical stimulation device is turned off. During reinforced trials, a thermal stimulus calibrated to evoke moderate pain intensity (approximately 7 on a 0-10 pain scale) is paired with a message on a computer screen stating the electrical stimulation device is turned on. The evocation phase of the paradigm, during which time the learned association is tested, consists of 30 control and 30 nocebo pain stimuli trials. These trials are identical to those of the acquisition phase with the distinction that now the pain stimuli for both trial types are set to the moderate pain intensity previously used only during control trials.

Contacts

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Eligibility criteria

Inclusion criteria

Adults ages 18-35
Strong understanding of written and spoken English
Normal or corrected to normal vision

Exclusion criteria

1. Ever having experienced serious medical or psychiatric conditions (e.g., heart or lung disease, panic attacks, alcohol addiction, clinical depression), including any present conditions thought to increase the risk of a serious COVID-19 infection (diabetes, severe obesity, HIV, severe kidney or liver diseases) and the presence of any condition or treatment that causes a reduced resistance to infections (autoimmune disorders, blood disorders, organ or stem cell transplant recipients, people without spleens).
2. Currently experiencing or having experienced in the last 48 hours any symptoms of COVID-19 (cough, sore throat, fever, trouble breathing, muscular pain, pain behind the eyes, excessive fatigue, diarrhoea, loss of sense of smell or taste).
3. Having tested positive for COVID-19 fewer than 7 days ago.
4. After testing positive for COVID-19 more than 7 days ago, not being symptom free for at least 48 hours.
5. Having a housemate/partner test positive for COVID-19 (or an untested but suspected COVID-19 infection) in the past month.
6. Ever having experienced chronic pain complaints (pain for more than 6 months).
7. Ever having experienced persisting painful health problems in the last 6 months.
8. Ever having experienced acute physical pain (more than 1 on the 0-10-point pain Numeric Rating Scale (NRS); e.g., mild headache), on the day of testing.
9. Having used pain medication or recreational drugs in the 24 hours prior to testing.
10. Having consumed more than 3 caffeinated drinks (coffee, tea, energy drinks, etc.) on the day of testing, any alcohol the day of testing, or more than 3 units of alcohol in the 24 hours before testing.
11. (Intended) pregnancy or breastfeeding.
12. Having recent injuries to the head, wrists or arms on the day of testing.
13. Previous participation in this or similar studies (e.g., using thermal pain).
14. On the day of testing: not being able to sufficiently distinguish between the different temperatures during calibrations and nocebo acquisition, or not reporting a pain of at least 6 (0-10 pain NRS scale) with the highest temperature used during calibrations.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-04-2021
Enrollment:	42
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
Coded, nonidentifiable, pseudoanonimized individual data relevant to all analyses reported in publications stemming from this project will be made available after the publication(s) are released. Data will be available upon request through an online database such as DataverseNL.

Ethics review

Positive opinion

Date:	21-10-2021
Application type:	First submission

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
NTR-new	NL9813
Other	Leiden University Psychology Ethics Committee : 2021-03-23-A.W.M. Evers-V2-2998

Study results