Imaging fear of painful touch: unraveling relationships between neural correlates of pain-related fear, somatosensory neuroplasticity, and sensory impairments in the context of chronic pain.

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The overarching aim of this proposal is to unravel the neural correlates related to acquisition, generalization and extinction of fear of touch in individuals with upper limb CRPS compared to healthy controls (objective 1), and to examine...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON57155

Source
ToetsingOnline

Brief title
FABrIC: imaging FeAr of painful touch in the BraIn in Chronic pain patients

Condition

- Other condition

Synonym
complex regional pain syndrome; posttraumatic dystrophy

Health condition

chronische pijn: complex regionaal pijnsyndroom

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: In hoofdzaak financiering van Europese Unie;Marie Sk□odowska-Curie postdoctoral fellowship en financiering van CRPS patiëntenvereniging

Intervention

Keyword: Chronic pain, Complex regional pain syndrome, Fear conditioning, Functional magnetic resonance imaging

Outcome measures

Primary outcome

Primary outcome: functional MRI blood-oxygen-level dependent (BOLD) responses

in the brain to the tactile fear conditioning paradigm (acquisition,

generalization, extinction phase).

Secondary outcome

Secondary outcomes and correlates:

- in-scanner fear of touch self-reports

- fMRI finger mapping assessing finger representations in the primary

somatosensory cortex (S1)

- Quantitative Sensory Testing (QST) measurements at the non-affected and

affected upper limb examining tactile acuity, allodynia, and hyperalgesia

- self-reported validated questionnaires using the secure online survey

software Qualtrics assessing pain catastrophizing, pain-related fear, fear

avoidance, positive and negative affect, optimism, resilience, trait anxiety,

pain-related disability, quality of life, current pain, average pain (past

week, month), and pain diagram assessing pain spreading.

Study description

Background summary

Chronic pain affects 20% of people worldwide leading to enormous personal suffering and economic burden. A key factor contributing to chronic pain disability that thus far has been neglected is fear of painful touch - a core symptom in people with complex regional pain syndrome (CRPS) (Biggs et al. 2017). We will use a novel tactile fear conditioning paradigm to examine the neural correlates of the acquisition, generalization, and extinction of fear of painful touch and interrelationships with somatosensory neuroplasticity, and sensory impairments. In this study we will include people with CRPS and age- and gender matched healthy controls. They will be subjected to a pain-fear conditioning experiment in the scanner using vibrotactile stimulation to the fingers as a conditioned stimulus (CS) and a painful electrocutaneous stimulus as the unconditioned stimulus (US) at the wrist. We will also include questionnaires to examine self-reported outcomes, quantitative sensory testing measurements to examine sensory impairments at the non-affected and affected upper limb and anatomical and functional Magnetic Resonance Imaging (MRI) of the brain.
Fear of touch due to allodynia is understudied and poorly understood, yet it is a core symptom related to disability and suffering in CRPS. The project will provide opportunities to alleviate CRPS stigma and improve treatments based on newly gained insights in hypothesized intertwined underlying neural mechanisms of pain-related fear and symptoms. The results are expected to have extensive impact for CRPS patients, society, and healthcare providers. Our study will contribute significantly to pain-related fear research and pain science in general. CRPS patient and therapist partners have confirmed the project relevance and impact potential during the design stage of this study. The results can contribute to increased recognition of the suffering of individuals with fear of touch and allodynia and better understanding of neurobiological and psychological mechanisms. Patients are disbelieved and stigmatized for the described symptoms, causing negative emotions, and showing the need to deepen our understanding of the underlying mechanisms.

We hypothesize that fear of touch will (1) be acquired in both groups, but there will be less differential learning (due to impaired safety learning) in CRPS than controls, (2) generalize to new fingers in both groups, but CRPS will show excessive fear generalization (i.e., also to fingers closer to the one previously not paired with pain), and (3) extinguish slower in CRPS. (4) This compromised fear learning will relate to changes in the neural underpinnings of fear learning in our novel fMRI tactile fear conditioning paradigm in patients

compared to controls. We hypothesize that (5) impaired threat-safety learning will be associated with allodynia (perceiving innocuous stimuli as painful), hyperalgesia, and reduced tactile acuity, and (5) vulnerability and resilience factors will modulate fear learning influencing pain-related outcomes in patients, and (6) somatotopic imprecision in finger representations in the primary somatosensory cortex will predict reduced tactile acuity and excessive fear generalization. (6) Hence, the more *blurred or less precise* somatosensory stimuli are encoded by the brain, the more fear generalization will occur.

Study objective

The overarching aim of this proposal is to unravel the neural correlates related to acquisition, generalization and extinction of fear of touch in individuals with upper limb CRPS compared to healthy controls (objective 1), and to examine interrelationships with sensory disturbances including allodynia, hyperalgesia and reduced tactile acuity (objective 2), and somatotopic imprecision in finger representations in the primary somatosensory cortex (S1) (objective 3). Furthermore, we aim to investigate how vulnerability (e.g., fear avoidance beliefs) and resilience factors (e.g., positive affect, optimism) modulate fear learning, and how they subsequently affect pain-related outcomes such as pain severity and spreading, disability, and quality of life (objective 4).

Study design

In this study we will include people with complex regional pain syndrome (CRPS) (n=20) and age- and gender matched healthy controls (n=20). Participants will come to the lab for two consecutive test days if possible (or test days with maximum 72 hours in between).
Duration: The first session will take approx. 50 minutes. The second session will take approx. 1h45 minutes.
Setting: Testing of participants will take place in person. Only the questionnaires will be filled out using the secure online survey software Qualtrics.
MRI scans will take place using the cutting-edge neuroimaging facilities (3.0 Tesla MRI scanner) through Scannexus (https://scannexus.nl/), the scanner facility of the Maastricht Brain Imaging Centre (M-BIC). The QST measurements will take place in a psychophysiology lab room at Scannexus or for patients if they prefer at home.

Study burden and risks

Feasibility, burden and risks of the fMRI paradigm: based on previous experience, we expect that vibrotactile stimulation at the affected hand could be painful in some patients. Therefore, we will calibrate the intensity of the

mini-piezo tactile stimulation (mPTS) stimuli so that each patient and healthy person perceives the stimuli above the sensation threshold but below the pain threshold (VAS < 2/10), which increases feasibility of the experiment (for healthy controls, the subjective intensity will be matched). This calibration also serves as a familiarization, and a familiarization will also be included for the US (unconditioned stimuli). We hypothesize that the fMRI fear conditioning paradigm at the non-affected hand will always be possible and this serves as a risk mitigation. Representative patient partners confirmed this hypothesis.

Test day 1:
1. Completing a number of questionnaires about their complaints (30 minutes), no risks.
2. Measuring sensitivity to stimuli (20 minutes), no risks.

Test day 2:
1. Completing questionnaires (15 minutes), no risks.
2. MRI scan during which vibration stimulation is given (25 minutes), risk of incidental findings.
3. The MRI scans (vibration and electrical stimuli) (65 minutes), chance of incidental findings.

A potential source of discomfort is represented by the use of painful stimuli. However, these stimuli will be based on a calibration procedure during which participants will be explicitly explained that they can choose their tolerance intensity (defined as a stimulus that is painful, and demanding some effort to tolerate). It will be made explicitly that this intensity can be chosen by them, and no higher stimulations will be delivered during the experiment. Participants are informed that they are able to stop the experiment at any point with no further consequence.

Furthermore, MRI and related techniques such as fMRI, have been used extensively for both clinical and research purposes. Scans pose no particular risks outside general MRI Health and safety requirements. All scanning protocols are approved by a safety officer. There is risk of physical injury from MRI if a participant has metal in his/her body or other medical circumstances that contraindicate exposure to a strong magnetic field. Thus, all participants are carefully screened (verbally during a personal screening interview and in writing using a detailed health check-screening questionnaire) before being able to enter the MRI scanner environment. The operation of the scanners is limited to qualified MRI certified users who have been trained and accredited by the scanning facility. Measures, such as pillows, table padding, are taken to minimize discomfort whilst lying in the scanner. Although participants are pre-screened for claustrophobia, it is possible that some individuals may experience claustrophobia in the scanner. Scanning will be immediately discontinued if a participant reports feeling claustrophobic.

UM has its own standard operating procedures to deal with incidental findings arising from brain imaging (i.e., detection of an unexpected brain abnormality on a scan). Concerning incidental findings policies, UM stipulates that if the researcher becomes aware of a potential abnormality he or she obtains a review by a physician with the relevant qualification who will then inform the participant and/or their general practitioner (or equivalent) if further investigations are needed. Any such contact will previously have been authorized by the participant who is informed that these are not clinical scans and therefore do not provide a guarantee that abnormalities, if present, will be detected.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients: adult patients with upper limb CRPS who have chronic pain (> 3

months) in the left or right upper limb (i.e., unilateral problems) diagnosed by a physician. Age between 18 and 65 years. BMI < 30.
Heathy pain-free persons: age- and gender-matched with the patients.
Patients and healthy persons: right-handed, left-handed or ambidextrous (as indicated by the Edinburgh Handedness Inventory) because of the MRI brain outcomes. Without contraindications for MRI participation (including pregnancy).
Inclusion criteria for healthy pain-free controls: without any injury to the fingers/hands, without clinical depression or anxiety (current or past), without acute or chronic pain (current or past).

Exclusion criteria

Exclusion criteria for participation in MRI studies for patients and healthy persons include: claustrophobia, active medical implants, passive implants deemed unsuitable, pregnancy; previous experience with metalworking without eye protection.
Exclusion for patients and healthy persons: Cardiovascular, psychiatric, and/or neurological disease. Diagnosed with (another) chronic pain syndrome (e.g. fibromyalgia, whiplash associated disorders, chronic migraine). < 18 year or > 65 year.
Exclusion for healthy persons: injury at the fingers/hands, clinical depression or anxiety (current or past), acute or chronic pain (current or past).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2024

Enrollment:	40
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	14-10-2024
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL86098.068.24