Electrical Brain Responses During Processing of Nociceptive Stimuli Around Detection Threshold: an Explorative Study in Pain Patients

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The aim of this study is to combine measurements of the NDT with EEG recording and analysis to observe neurophysiological activity during nociceptive processing in CRPS patients. In this explorative study, multiple types of stimuli are delivered....

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

Summary

ID

NL-OMON52779

Source
ToetsingOnline

Brief title
Electrical Brain Responses During Nociceptive Processing in Pain Patients

Condition

- Other condition
- Diabetic complications
- Peripheral neuropathies

Synonym
pain

Health condition

Chronische pijn, centrale sensitisatie, perifere sensitisatie

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Vanuit het TTW Perspectief programma 14-12 NeuroCIMT project 2: Nocicept

Intervention

Keyword: Chronic pain, Evoked potential, Intraepidermal electrical stimulation, Noceptive detection threshold

Outcome measures

Primary outcome

The nociceptive detection threshold

EEG signals

Secondary outcome

Current pain (NRS)

Average pain in the last seven days (NRS)

Questionnaire about symptoms of central sensitization: central sensitization

inventory (CSI)

Current medication intake

Participant characteristics: age, sex, BMI, handedness

Outcomes of neurological examination of the back of the hands: anamnesis

sensory integrity and physical examination (pin-prick test and test for light

touch) (for healthy controls with lidocaine model and diabetic patients)

DN4

SFNSL

Questionnaire about daily functionality: Oswestry Disability Index (ODI)

Study description

Background summary

The development of treatments for chronic pain requires a more profound understanding of the physiological and psychological aspects of chronic pain. Several types of chronic pain, including FBSS , CRPS, certain types of DPN, sarcoidosis, arthrosis in healthy BMI and (morbid) obesity and CIPN are linked to increased sensitivity of the central nervous system. Therefore, it is important to study the underlying mechanisms of this increased sensitivity. However, one major obstacle is the lack of an objective measure of peripheral and central sensitivity, and of adequate diagnostic means for the presumed causes of chronic pain (such as small fibre neuropathy, or SFN, in painful diabetic neuropathy) . Besides hampering the development of new treatments, this causes inaccuracies in chronic pain diagnoses, resulting in delayed or unnecessary treatments.

Tracking detection thresholds of nociceptive specific electrocutaneous stimuli can facilitate the investigation of the underlying mechanisms of sensitization. Recently, a subjective method was developed for tracking multiple psychophysical thresholds over time, referred to as multiple threshold tracking (MTT), which has been shown sensitive to central changes in nociception. An objective measure of nociception related activity in the central nervous system is the electroencephalographic (EEG) signal. Multiple-trial averages of this signal, referred to as evoked potentials (EPs), have been shown to reflect nociceptive sensitivity to changes in stimulus parameters. Since MTT has been shown to be effective in measuring the effect of stimulus parameters on stimulus detection, while the EP has been shown to reflect neurophysiological activity related to stimulus processing, a combination of both techniques might provide insight into the relation between neurophysiological activity and nociceptive stimuli. We have recently investigated this relationship in healthy subjects in a study at Biomedical Signals and Systems at the University of Twente (approved by the METC Twente numbered NL62721.044.17). In this research, it was shown that components of the EP are closely related to the stimulus detection.

However, we did not yet investigate the NDT and EPs in patients with altered pain processing mechanisms. Measurements of NDTs and EPs in chronic pain patients could aid the diagnosis and the development of new treatments in these patients in the future. To enable this, it is necessary to understand how the NDTs and EPs in these patients behave when compared to healthy subjects.

[Amendment *test-retest*]
Preliminary results from this study show values of NDTs and EPs, habituation and paired-pulse facilitation, which are in line with results from the University of Twente. Again, EPs are modulated by stimulus detection and amplitudes. Strikingly, we found higher NDTs in FBSS patients and EPs appeared modulated by stimulus detection, but not by amplitudes. Since similar phenomena in NDTs and EPs were observed during nociceptive stimulation in pain-free subjects at St. Antonius hospital, it can be concluded that results of MTT-EP method can be replicated in a hospital environment. Secondly, the observed altered behavior of NDTs and EPs in FBSS patients showing signs of central sensitization allows further hypotheses regarding responsiveness to mechanisms underlying chronic pain.

However, the reproducibility of the MTT-EP method is never assessed within the same subject. Therefore, it would be interesting to investigate the effects of a test-retest in the same pain-free subjects, because it yields unique results on the reliability of this MTT-EP experiment. Second, future work should be performed in the same FBSS patient as well, but then when they are just treated by neuromodulation. This chain of results would facilitate new insights into the underlying mechanisms of the CNS and reveal possibly a new approach to current treatment.

However, it is unknown if EPs can be seen using this MTT-EP experiment in FBSS patients who are treated by neuromodulation. Therefore, it is also recommended to measure the same FBSS patients again. But then, when the neuromodulator is turned off and on. This is relevant, because then we should measure the efficacy of the treatment in chronic pain patients in future.

[Amendment *Uitbreiding groep diabeten lidocaïne model']
Additionally, the MTT-EP approach could play a role in (early and more objective) neurophysiological, nociceptive characterization of diabetes patients with chronic painful DPN and without neuropathic pain complaints. To find out, exploration and evaluation of (the results of) the MTT-EP method in a lidocaine model of SFN is also necessary. Outcomes, compared to those of other research groups (e.g. healthy subjects and other chronic pain patient populations), will expectedly grant insight in potential applicability within a broader clinical perspective.

[Amendement 'Uitbreiding gezonde controlegroep']
Subject characteristics, such as age and gender, may affect the detection threshold and stimilus-related response. However, this is unknown yet. It is important to know their relationship, so that we can match the healthy controls in a good way to the characteristics of the pain syndromes.

[Amendement *Pijn bij sarcoïdose en (morbide) obesitas*]:
The group will be expanded further to examine the influence of BMI on the measurements. This is done by adding (morbid) obesity patients with and without

chronic arthrogenic pain. The effect of BMI on the measurements will become more visible if morbidly obese patients with / without chronic pain are measured before and after bariatric surgery. Moreover, the MTT-EP approach could play a role in neurophysiological characterization of sarcoidosis patients with chronic pain and symptoms of SFN. These results can be compared with other research groups and are expected to provide insight into the possible applicability.

[Amendement 'Toevoeging onderzoeksgroep: CIPN']:
The MTT-EP approach could play a role in neurophysiological characterization of CIPN patients with chronic pain and symptoms of SFN. These results can be compared with other research groups and are expected to provide insight into the possible applicability.

[Amendment *FBSS-SCS*]
It is essential to explore the reproducibility and feasibility of the MTT-EP method to be able to investigate whether the MTT-EP method can be used to determine the effect of spinal cord stimulation in patients with FBSS.

[Amendment 'Meetlocatie voet']:
Exploring the feasibility of the MTT-EP method when stimuli are applied to the foot in FBSS patients with implanted spinal cord stimulator is important to further investigate whether the MTT-EP method can be used to determine the effect of spinal cord stimulation. By changing the location where stimuli are applied, the MTT-EP method could provide an objective evaluative measure of the effectivity of spinal cord stimulation and may lead to more insight into underlying mechanisms of FBSS and spinal cord stimulation.

Adding a healthy control group where stimuli will be applied to the foot, provides the possibility to compare the FBSS-SCS-f group to a pain-free population. Additionally, this control group could be used as a comparison for other patient groups where the foot appears to be a more appropriate location for stimulus application.

Study objective

The aim of this study is to combine measurements of the NDT with EEG recording and analysis to observe neurophysiological activity during nociceptive processing in CRPS patients. In this explorative study, multiple types of stimuli are delivered. The NDT and EEG are measured and analysed with respect to the stimulus parameters.

The first primary objective is to compare NDTs and EPs of healthy subjects in a hospital with the results of healthy subjects from previous study at the University of Twente. Another primary objective is to describe how the NDTs for electrical stimuli behave in healthy subjects, in chronic pain patients (FBSS, CRPS-I, painful DPN, sarcoidosis, CIPN, (morbid) obesity with chronic

arthrogenic pain and arthrogenic pain patients with healthy BMI) and in diabetes patients without neuropathic pain and pain-free (morbid) obese patients, using a multiple threshold tracking paradigm, and how neurophysiological responses (EPs) are related to the delivered electrocutaneous stimuli properties in healthy subjects and these patients. A third primary objective is exploration of the reproducibility of the MTT-EP measurement in healthy subjects and FBSS patients (when spinal cord stimulator is turned off) by a test-retest at the St. Antonius hospital Nieuwegein. Also, the applicability of the MTT-EP method in FBSS patients who are treated by neuromodulation (when the spinal cord stimulator is turned on) needs to be explored by analyzing whether the evoked potentials can be induced during spinal cord stimulation, and in FBSS patients treated by neuromodulation when stimuli are applied to the foot. Furthermore, the primary objective is to explore the influence of subject characteristics on the detection theshold and stimulus-related responses in healthy subjects. A last primary objective is exploration of the MTT-EP capabilities for neurophysiological mapping of nociception in (pain-free) healthy subject with a lidocaine SFN model.

Secondary objectives are to confirm the hypothesis that FBSS patients, CRPS-I patients, diabetes patients with painful DPN, sarcoidosis patients, CIPN patients, (mobid) obese patients with chronic arthrogenic pain (retest for the morbid obesity) and chronic arthrogenic pain patients with healthy BMI are appropriate populations to study (chronification of) pain and pain physiology, and to analyze how the NDT and EEG are related to sensitization in these chronic pain patients (compared to matched healthy subjects).

Study design

Mono-center, cross-sectional study.

Study burden and risks

The participants are asked to come to the St. Antonius Hospital for one session. Half of the FBSS patients with spinal cord stimulator (FBSS-SCS) will be asked to turn of the stimulator 4 hours prior to the experiment, and half of the FBSS-SCS-f patients will be asked to turn off the stimulator 12 hours prior to the experiment. If this is not tolerated, patients can switch the stimulator on again. Participants are not allowed to consume alcohol or use drugs during the 24 hours prior to the session (they are allowed to take medication). At the start of the session, the participant fills in a questionnaire. This is followed by a short, orienting neurological examination (*pin-prick test* for sharp sensations, *gauze test* for subtle sensations) of diabetes patients and healthy subjects that will receive the lidocaine SFN model. Then, two patches (active and placebo) will be applied on the back of both hands of participants in the lidocaine SFN model group. As these participant are allowed to continue their activities at the St. Antonius Hospital, the burden of this waiting time

is estimated to be minimal. Subsequently, the participant is familiarized with the stimuli by stepwise application of increasing stimuli until stimulus detection. During the experiment, the participant will receive randomized stimuli around the detection threshold according to the multiple threshold tracking (MTT) paradigm, first on one hand and then on the other. The burden during the session is minor, as the stimuli are expected to stay below the pain threshold* but participants will undergo the experiment for two hours in total, of which they need to be very concentrated for one hour. For this, the participants will be compensated with a voucher.. In healthy participants with lidocaine SFN model, there is a chance (approximately 16%) of skin reactions, such as redness or itch, directly under or around the patch. These normally do not persist for more than a day. Risks of allergic reactions or systemic adverse events are negligible, as are risks of the stimulation method for all research groups.

*The pain threshold in healthy subjects lays around 2 mA for intra-epidermal stimulation, see the IMDD of the AmbuStim (D2). The pain threshold in CRPS patients might be lower. However, using the MTT paradigm, stimuli are applied around the detection threshold estimated during the experiment. Therefore, the pain threshold will not be reached unless the subject fails to respond adequately to the applied stimuli.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Healthy subjects:
Age between 18 and 75.
No history of pathological pain.,
Healthy subjects (with lidocaine model):
Age between 18 and 65.
No history of pathological pain.
Patients:
FBSS:
Age between 18 and 65.,
CRPS-1 following injury in arm/hand:
Age between 18 and 65.,
Chronic painful DPN:
Age between 18 and 75.
Type 1 or 2 diabetes mellitus (DM); including subtypes.
An official diagnosis for diabetic polyneuropathy (DPN).
Duration of neuropathic pain >3 months (i.e. chronic).,
DM without neuropathic pain:
Age between 18 and 75.
Type 1 or 2 diabetes mellitus; including subtypes.
Absence of pathological pain complaints.
Sarcoidosis patients:
Age between 18 and 75
A score above 30 on the Small Fiber Neuropathy Screening List (SFNSL)
An experienced neurologist will judge whether there is a possibility / probability of SFN
Obesity patients, pain-free:
Age between 18 and 75
BMI between 30 and 40 kg/m2
obesity patients with chronic arthrogenic pain:
Age between 18 an 75
BMI between 30 and 40 kg/m2
Chronic arthrogenic pain
Duration of arthrogenic pain at least 3 months
morbid obesity patients, pain-free (test-retest):
Age between 18 and 75
BMI at least 40 kg/m2
morbidobesity patients with chronic arthrogenic pain (test-retest):
Age between 18 an 75

BMI at least 40 kg/m2
Chronic arthrogenic pain
Duration of arthrogenic pain of at least 3 months
chronic arthrogenic pain patients:
BMI between 18.5 and 25 kg/m2
Chronic arthrogenic pain
Duration of arthrogenic pain of at least 3 months
CIPN patients:
Age between 18 and 75
Mammary carcinoma treated with Paclitaxel
FBSS-SCS patients:
Age between 18 en 65 years old
Spinal cord stimulator implanted at least 3 months ago
(Initial) Implantation considered successful, at least 50% pain relief determined by NRS or VAS
FBSS-SCS-f patients:
Age between 18 en 65 years old
Spinal cord stimulator implanted at least 3 months ago
(Initial) Implantation considered successful, at least 50% pain relief determined by NRS or VAS

Exclusion criteria

General exclusion criteria:
Participant*s refusal during the study.
Communication problems or incapable of following the instructions.
Diabetes, except for diabetes mellitus patients.
Implanted stimulation device, except the neurostimulator in case of FBSS-SCS patients
Pregnancy.
Consumption of alcohol or drugs within 24 hours before the experiment.
Medical history of chronic pain (for healthy subjects)
Skin on (at least) one of the hand dorsa non-intact, inflamed or otherwise affected (e.g. injured, wounded).
Additional exclusion criteria for healthy subjects with lidocaine model:
Use of drugs based on or containing amyl nitrite, sodium nitrite, sodium thiosulfate, epinephrine and/or prilocaine (topical)
(Known) hypersensitivity to lidocaine or other amide-type local anaesthetics, with allergic reactions such as urticaria or anaphylaxis.
(Known) hypersensitivity to any other component in the lidocaine or placebo patch, with allergic reactions such as urticaria or anaphylaxis.
Additional exclusion criteria for the patients with chronic painful DPN:
Chronic pain complaints other than due to DPN.
Known possible other causes of polyneuropathy.
Central or peripheral nerve disorders other than diabetic polyneuropathy (e.g.

spinal stenosis, radiculopathy, multiple sclerosis, carpal tunnel syndrome).
Additional exclusion criteria for the diabetes patients without neuropathic pain:
Central or peripheral nerve disorders other than diabetic polyneuropathy (e.g. spinal stenosis, radiculopathy, multiple sclerosis, carpal tunnel syndrome).
Additional exclusion criteria for sarcoidosis patients:
Severe or chronic non-neuropathic pain complaints.
Known possible other causes of polyneuropathy.
Central or peripheral nerve disorders other than sarcoidosis with symptoms of SFN (e.g. spinal stenosis, radiculopathy, multiple sclerosis, carpal tunnel syndrome).
Additional exclusion criteria for (morbid) obesity group with/without chronic pain and the chronic arthrogenic pain group:
Underwent bariatric surgery (except in the retest of the morbid obesity groups)
Rheumatoid arhritis
Chronic painful form of diabetic polyneuropathy
Additional exclusion criteria for CIPN patients:
Severe or chronic non-neuropathic pain complaints.
Known possible other causes of polyneuropathy.
Central or peripheral nerve disorders other than CIPN with symptoms of SFN (e.g. spinal stenosis, radiculopathy, multiple sclerosis, carpal tunnel syndrome).
Additional exclusion criterion for HC-f group and FBSS-SCS-f patients:
Skin on (at least) one of the foot dorsa non-intact, inflamed or otherwise affected (e.g. injured, wounded).

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-10-2018
Enrollment:	440

Type:	Actual

Ethics review

Approved WMO Date:	27-08-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-12-2020
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL66136.100.18