Plasticity of the central nervous system in CRPS and RSI

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Observational non invasive

Summary

ID

NL-OMON31948

Source
ToetsingOnline

Brief title
fMRI in CRPS and RSI

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym
CANS, CRPS, CTD, RSI, WRUED

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Erasmus Fonds Pijnbestrijding

Intervention

Keyword: cortical organization, fmri, pain, rsi

Outcome measures

Primary outcome

With fMRI the blood oxygen level dependent (BOLD) response is measured. This response represents neuronal activation. When activity during rest is compared with activation during task performance, the specific areas involved in task performance can be identified. This way we will look at individual data but also at data from the three groups as a whole. Data from control subjects will be compared to affected hand and un-affected hand from the patients. Neuronal activation will be interpreted by looking at the size of the activation area, the contrast in activation between task and rest and the location of the activation. fMRI measurements will be performed using a 1.5 T MRI scanner at the Radiology department. The subjects will be lying on their back with the head inside the scanner for a period of 40-50 minutes. During this period the subject is required to lie still. Via an intercom system the subject can communicate with the researchers.

Secondary outcome

The data will be analyzed and linked to the questionnaires, like the SCL90 (fear and depression), kinesiophobia (TAMPA) and the McGill pain questionnaire. Correlations between the severity and location of complaints, the level of kinesiophobia, en the magnitude of plastic changes in cognitive and emotional areas will be calculated. The following data will be acquired in a Case Record Form:

• Demografic data

• Weight, height

• SCL90

• Pain Catastrophizing

• Tampa

• Pain anamnesis (see also appendix 2)

• Sensibele, autonomous en motor disorders

• Localization of pain according to patient

• Classification: neuropathic pain, non-neuropathic pain or combination of both

(*mixed pain*)

• Duration and intensity of pain (VAS-pain en McGill Pain Questionnaire)

• Assessment of origin based on medical file (if available)

• Inventory of used medication from medical file

Study description

Background summary

Background information CPRS
Complex regional pain syndrome (CPRS) is a complication after tissue damage, caused by surgery or trauma. Symptoms include pain, sensory, sudo and vasomotor disturbances, throphic changes and a decreased motor performance.

Yearly incidence is 26.2 per 100.000 person-years (95% CI: 23-29.7). CPRS most commonly occurs in the upper extremity. A bone fracture is often associated with the onset of complaints. Women are more prone (3.4 x) to develop these complaints then men. Highest incidence is found in females aged between 61 and 70 years (de Mos, 2007).

Until today, the pathofysiology of CRPS is still debated in the literature.
Afferent mechanisms such as inflammation, efferent mechanisms like deregulation of the vegetative nervous system, but also central mechanisms like specific

psychological profiles have been described (Huygen et al., 2001).

In a series of recent publications (2003-2007) the group of Maihofner has shown that the central representation of the hand in CPRS is dramatically altered. Tactile stimulation of the non-affected hand only leads to activation of the contralateral primary somatosensory cortex (S1), insula and bilateral secondary somatosensory cortex (S2), stimulation of the affected side leads to wide spread cortical activation, including contralateral S1 and motor cortex, parietal associative cortex (PA), bilateral S2, insula, frontal cortex and both anterior and posterior parts of the cingular cortex ((aACC and pACC). These results show that not only nociceptive areas are activated, but also cognitive, emotional and motor areas are activated during tactile stimulation.

In patients with CRPS a significant deterioration of the cortical hand representation is seen during performance of motor tasks with the affected hand. Also the location of this cortical representation is shifted towards the cortical representation of the lip. The level of performance during these motor tasks was related to the level of activation of the SMA, M1 and the posterior parietal cortex (Maihofner, 2007). After clinical improvement recovery off cortical organization is seen in CRPS patients.

Background information RSI
Complaints to the arm, neck and shoulder (CANS), otherwise known as repetitive strain injury (RSI), is a loose group of conditions associated with the excessive use of for instance a computer, guitar, knife or repetitive use of a tool. In the majority of cases (70-80%) no physical damage can be identified. However, recently inflammatory biomarkers have been identified that could give an indication on the severity of complaints (Carp, Barbe 2007). Moreover, there is evidence that micro-damage to muscles, tendons and nerves in arm and neck play a role (Barr 2003-2004). Changes in central sensitization in patients with chronic RSI have not been studied. Symptoms of RSI include pain, muscle weakness, numbness, changes in temperature and loss of motor coordination

In the Netherlands prevalence of complaints is around 10-30%, depending on profession (branch of industry). In 16 to 22% of the cases this leads to absence of work and medical consumption. In a small percentage (5-8%) complaints become chronic. Yearly costs at the societal level are estimated at 2.1 billion euros (TNO, 2004).

A number of factors have been associated with the occurrence of RSI. Besides physical factors like excessive force, working in (awkward) static positions en repetitive movement, also psychological factors such as deadlines, social atmosphere and stress can contribute to the complaints. Moreover, non-work-related factors like personality, coping strategies and kinephobia can elevate the risk of developing complaints. Complaints are approximately twice more common in women. These risk factors were recently confirmed in a longitudinal study (2004-2006) (Slijper, Richter 2007) using a precise exposure

analysis.

Plastic changes caused by chronic pain
Pain hyper-sensitivity can remain even when affected tissue is healed or can even occur without any tissue damage. In this case, pain is a manifestation of a pathological change in the central nervous system. This central sensitization is most commonly associated with an increased excitability of neurons in the central nervous system. Consequently normal input will induce an abnormal response. Despite the fact that the pain seems to originate in the periphery, it is actually a manifestation of abnormal sensory processing by the central nervous system.

Pain influences cognitive processing and demands attention (Eccleston & Crombez, 1999). This disruptive function of pain seems to be influenced by factors like pain-related fear and catastrophizing and can result in a continued focus on the pain instead of other stimuli (Crombez et al., 1999, Eccleston & Crombez, 1999, VanDamme et al., 2002). Patients with a strong focus on pain indeed report a higher level of pain intensity (McCracken et al, 1997; Rainville et al., 1997). Higher pain intensity is associated with kinesiophobia (Lundberg et al., 2006) and seen in 50% of patients with musculoskeletal complaints. In CRPS and other chronic musculo-skeletal complaints, kinesiophobia is a potential predictor for chronic constraints (De Jong et al., 2005, Swinkels-Meeuwisse et al., 2006, Buitenhuis et al., 2006). Furthermore, disruption of cognitive functioning and attention through pain is related to modulation of the anterior cingulated cortex (ACC), an area involved with pain perception and attention (Buffington et al., 2005). Changes in ACC activity during tasks in which continuous attention is demanded can be expected in patients with RSI, when chronic pain and pain related fear are present.

Study objective

The question, however, remains whether there are changes in pain processing in chronic RSI and whether the general process of pain sensitization is comparable to that seen in CPRS. In animal research (Byl, 1997) it has been shown that after repetitive pinching movements the representation in the somato-sensory cortex (S1-3b) was deteriorated. Although this has never been studied in humans, it suggests that recovery of the hand representation is important in the treatment of chronic RSI. Our hypothesis is that in patients with CPRS en RSI pain sensitization plays an important role. The process of pain sensitization could be a possible explanation for the widespread cortical activation seen in CRPS patients. Fear for damage through movement (kinesiophobia) and the tendency to catastrophize could enhance this process.

The aforementioned hypothesis is in accordance with the findings of Mainus & van Hilten (2006). In a systematic review they found some striking similarities in the patho-physiology and etiology of these complaints:
• Tissue damage of the musculoskeletal system is the origin of the complaints

• The progression of complaints that start in the periphery induce a cascade of reactions leading to changes in the excitability of the central nervous system.
• Loss of coordination in the distal musculature
• The severity and progression of complaints is linked to psychological characteristics and gender of the patient.

It is likely that there will be a large overlap in the areas involved and plastic changes in cortical, sensory, motor, frontal and emotional areas in both CPRS-1 and RSI. In this research we will therefore use fMRI to directly compare activation of brain areas in both diseases.

Study design

In this research, we will systematically investigate brain activity in patients with unilateral (chronic; >1 year) RSI, CPRS-1 and healthy control subjects using functional Magnetic Resonance Imaging (fMRI). An fMRI experiment consists of a detailed anatomical scan followed by functional scans. During the structural scan, the subject is asked to lie still in the scanner. During the functional scans subjects are offered motor and sensory tasks. In particular, the following tasks will be administered:

Task 1. Finger tapping with the affected hand: Serial movement of the fingers, starting with thumb touching index finger, middle finger, ring finger, little finger, ring finger, etc.

Task 2. Finger tapping with the un-affected hand: Serial movement of the fingers, starting with thumb touching index finger, middle finger, ring finger, little finger, ring finger, etc.

Task 3. Sensory stimulus to the affected hand: The hand will be stimulated with a soft brush (a pressure of 150-250 mN).

Task 4. Sensory stimulus to the unaffected hand: The hand will be stimulated with a soft brush (a pressure of 150-250 mN).

Task 5. As a reference for changes in the hand representation the lower lip will be stimulated with a brush, or the subject will be asked to purse the lips. This way a comparison can be made with the results of Maihofner et al. (2003), who used the same reference stimulus.

The motor tasks will first be practiced outside the scanner to ensure that a stable movement pattern is acquired. During the functional scan, periods in which one of the tasks is performed are followed with periods of rest. The duration of these episodes in such a block paradigm is between 20-30 s. A functional scan consists of 10-15 blocks, lasting 5 minutes in total. In the experiment, five functional scans will be made. The total duration of the fMRI experiment will last approximately 40 to 50 minutes. For statistical evaluation

we will use SPM5 and Matlab.

Study burden and risks

When patients are willing to participate in the experiment, they will be offered questionnaires to assess whether they are suited to participate. We will evaluate the inclusion and exclusion criteria such as the duration and laterality of complaints. Based on the answers, subjects will be invited for a physical examination to further assess whether they comply to our inclusion and exclusion criteria. The physical examination will be performed by a research nurse at the Pain Treatment Center of the Erasmus MC. The measurements and examinations that this nurse will perform are described in more detail in Appendix 1 and 2.

This research uses fMRI. The subject takes place inside the scanner consisting of a large cylindrical magnet. The tunnel inside the magnet has a diameter of 55 cm and is 2 m long. When a subject suffers from claustrophobia, he or she is recommended not to participate. During scanning a coil is placed over the subject*s head to avoid head movement. The scanning itself creates a significant amount of noise. Communication with the researchers is possible using an intercom system. The subject can stop the scanning at any point during the experiment and leave the scanner.

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

For selection of CRPS-1 subjects we will use the Modified research diagnostic criteria for CPRS-1 (Bruehl, 1999). For selection of chronic RSI subjects we will use exclusion criteria specified in the Satsa report (Sluiter, 2001). These criteria are described in Appendix 1 of the protocol. Further inclusion criteria are:
• Minimal duration of complaints of 1 year
• Complaints are unilateral and restricted to the upper extremity (including shoulder)
• Most recent complaints not longer then two weeks ago
• McGill questionnaire score over 25
• No contra indication for performing an fmri-scan (see checklist appendix 4)

Exclusion criteria

CPRS: Other musculoskeletal of neurological disorders
RSI: only subjects with a-specific RSI will be selected, to this end we will exclude all subjects with specific forms of RSI according to criteria of Sluiter (Saltsa report, 2001)
general: The subject does not agree to be informed about unexpected findings

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-08-2008
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO

Date:	04-06-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL22235.078.08