Utrecht University
Master Neuropsychology

THESIS

Neuroplasticity after Physical Therapy

A Pre- Study:

Test- Retest- Effects in Healthy Participants

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16th june, 2012

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Abstract

P300 event-related potentials have frequently been used to study maladaptive neuroplasticity in chronic pain patients. It has not only been found that this patient group shows a significant increase in P300 latency, but furthermore that successful pain therapy is able to normalize this latency. Pain exposure physical therapy (PEPT) is a new treatment for patients with complex regional pain syndrome type I (CRPS-I). An important question is whether PEPT is able to reverse the maladaptive neuroplasticity of CRPS- I patients, which is thought to be the cause of the chronic pain. Using the P300 as an objective parameter to assess pain relief and as a measure of neuroplasticity, this question could be answered. However, before testing the assumption that the P300 changes due to the pain relieving effects of the PEPT in patients, we investigated, whether there is a general effect of physical therapy ('sham' PEPT) on the P300 in healthy controls and how the individual differences are. The values of peak latency and amplitudes of the P300 were recorded in 15 healthy participants before and after a 'sham' therapy. No test- retest effects were observed. In a coming study with pain patients we will investigate whether this measure can be used to evaluate pain relief and neuroplasticity following PEPT in CRPS-I patients.

The most frequently studied ERP waveform in the cognitive domain is the P300 or P3 component (Sochurkova, Brázdil, Jurák & Rektor, 2006). The P300 wave is a positive deflection in the human event-related potential, which is commonly elicited in an 'oddball' paradigm. In this paradigm, trains of stimuli that are usually auditory or visual are used to assess the neural reactions to unpredictable but recognizable events. The electrophysical brain- reaction to those events, thus the P300, is known to be smaller and later in patients with decreased cognitive ability than in age- matched healthy subjects (Picton, 1992).

The P300 has also frequently been used to study maladaptive neuroplasticity in chronic pain patients. Maladaptive neuroplasticity is generally defined as any form of disadvantageous neuroplasticity (Antal & Paulus, 2010). A study of Tandon and Kumar (1993) found a significant increase in the auditory P300 latency in patients suffering from chronic pain. This indicates a delay in cognitive processing and furthermore suggests changes in interaction between different brain regions, thus neuroplasticity (Tandon & Kumar, 1993).

Another study by Tandon and colleagues (1997) not only found an increase in the auditory P300 latency in patients suffering from chronic low back pain, but furthermore showed that pain therapy is able to normalize this increased latency. After an epidural methylprednisolone therapy, the peak latency of the P300 of those patients decreased significantly. Therefore, it has not only been shown that the P300 can be used as a measure for maladaptive neuroplasticity in patients suffering from chronic pain, but furthermore that pain treatment can help to bring the P300 latency back to normal. In addition, a high correlation between a subjective measure of pain relief and a reduction of the P300 latency

suggested that the P300 can be used as an objective parameter to assess pain relief in chronic pain patients (Tandon, Kumar, Dhar & Battacharya, 1997).

Complex regional pain syndrome (CRPS) is a chronic pain condition that develops idiopathically after trauma, most commonly seen following injury to the limbs (Geha et al., 2008). The exact prevalence of CRPS is unknown, it is however estimated that in about 5% of all traumas or nerve lesions in the extremities, complex regional pain syndromes (CRPS) may develop (Maihöfner, Handwerker, Neundörfer & Birklein, 2003). This chronic pain syndrome is characterized by spontaneous pain or hyperalgesia that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event. Further characteristics are abnormal regulation of blood flow in the affected areas, as well as autonomic, trophic and motor abnormalities (Charlton, 2005). Additionally, CRPS can be subdivided into two different types. The symptoms of both diseases are identical. The difference between those two types is the origin of the disease. In type I, minor injuries or fractures of a limb precede the onset of the symptoms, whereas type II CRPS develops after injury to a major peripheral nerve (Charlton, 2005).

Even though not much is known about the possible causes or maintenance of CRPS-I it has already been found that, as in other chronic pain conditions, there is a decrease in cognitive functioning (Kang et al., 2010) as well as altered brain morphology located in areas related to pain processing in patients suffering from CRPS (Geha et al., 2008). Furthermore, neuroimaging studies have shown a reduction in the size of the representation of the CRPS-affected limb in the somatosensory cortex compared to the unaffected side (Maihöfner, Handwerker, Neundörfer & Birklein, 2003; Maihöfner et al, 2007). In patients suffering from CRPS type I, those findings cannot be explained by injury to possibly connected peripheral nerves. The only possible explanation for the altered brain morphology in this patient group is that those changes are due to the pain syndrome itself (Geha et al., 2008). It is therefore suggested that these changes are a consequence of maladaptive neuroplasticity.

Pain exposure physical therapy (PEPT) is a new treatment for patients suffering from complex regional pain syndrome type I (CRPS-I) which is already found to be a safe and effective treatment for patients with longstanding CRPS-I (mean duration of 55 months) (Ek et al., 2009). It consists of a progressive-loading exercise program (loading the extremities beyond pain limitations) and management of pain-avoidance behavior without the use of specific CRPS-I medication or analgesics (Ek et al., 2009). Thus, this treatment focuses on psychological and behavioral factors that maintain pain avoidance and disuse. Furthermore, it

aims to decrease pain behavior and to increase self-confidence in the patients' own physical possibilities (Ek et al., 2009).

The study of Ek and colleagues (2009) already found that PEPT is tolerated by patients with CRPS-I and can therefore be considered a safe treatment. Additionally, this study found indications that PEPT increases the level of activity, walking and quality of life. Further studies are necessary to demonstrate the efficiency of PEPT treatment. The assumption, that a progressive-loading exercise program will reduce peripheral and central sensitization and may restore the local autonomic deregulation and cortical representation in CRPS-I, needs further verification, especially at a neural level.

A relevant question therefore is whether PEPT, as the epidural methylprednisolone therapy in patients suffering from chronic low back pain, is able to reverse the maladaptive neuroplasticity of patients suffering from CRPS type I, which is thought to be the cause of the chronic pain of this patient group. This can be done by comparing the P300 latencies and amplitudes of CRPS-I patients before and after treatment. If a difference is found between pre- and post- treatment measures, it would provide further evidence for a central role of cortical mechanisms in the maintenance of the pain syndrome and could furthermore be interpreted as effectiveness of the therapy.

Before testing the assumption that the P300 of CRPS-I patients changes due to PEPT, we intended to find out, whether there is a general effect of physical therapy ('sham' PEPT) on neuroplasticity in healthy controls. The primary aim of this pre-study is thus to answer the question whether in healthy participants there is a change in the auditory P300 latency and/ or amplitude after one hour of physical therapy ('sham' PEPT). Because in healthy participants PEPT is no more than mild movements, no functional reorganization and thus no generalized changes in the P300 are expected. We do however expect individual differences in the pattern of changes in the P300. Even though it has repeatedly been shown, that there is a good test-retest reliability for the P300 amplitude as well as a good, but lower test-retest reliability for the P300 latency in healthy controls (Simons et. al, 2011), it is already known, that there are inconsistencies of test-retest measures of the P300 at individual level (Trejo et. al, 1991). However, in order to be a reliable measure for the effects of therapy we expect that in healthy volunteers the first and second measurements show good till excellent test- retest reliabilities, even though inconsistencies at individual level are anticipated.

A second aim of this pre-study is to investigate the suitability of two different questionnaires for the application to the main study with CRPS-I patients. Because it has already been known that an excessively negative orientation toward pain (pain

catastrophizing) and fear of movement and/ or (re)injury (kinesiophobia) are important predictors of chronic pain (Picavet, Vlaeyen, & Schouten, 2002), an interesting subsequent question is whether those two variables also play a role in the development or even the recovery of CRPS-I. This information would be very valuable for developing effective prevention strategies. This pre-study will therefore try to answer the question whether there are any test- retest effects of pain catastrophizing and/ or kinesiophobia following 'sham' PEPT in healthy controls. This will be assessed by using the Dutch versions of the 'Pain Catastrophizing Scale' and the 'Tampa Scale for Kinesiophobia'. Because both questionnaires are already known to have a high test-retest reliability, 0.92 for the 'Pain Catastrophizing Scale' (Sullivan, Bishop, & Pivik, 1995) and 0.88 for the 'Tampa Scale for Kinesiophobia' (Koho, Aho, Pohjolainen, & Hurry, 2009) and in healthy participants PEPT is no more than mild movements, no changes between pre- and post- measure and high test- retest correlations are expected.

The final objective of this study is to investigate whether a high score on a depression scale correlates with the amplitude or the latency of the P300 in healthy participants before and after the 'sham' treatment. This will be done by using the Dutch version of the 'Hospital Anxiety and Depression Scale' (HADS) to screen for depression (Zigmond & Snaith, 1983). It has already been well-established that a depression by itself can lead to a number of cognitive deficits (Weingartner et. al, 1982). Furthermore, some studies have shown disturbances (changes in the amplitude and/ or latency) in auditory event related potentials in patients suffering from a major depression (Vandoolaege, Hunsel, Nuyten, & Maes, 1998). It therefore seems to be important to control for the covariate of having depressive symptoms. However, other studies could not find any disturbances to the P300 in patients suffering from mild to moderate depressions (Kraiuhin et al., 1990). As every participant with a history of a psychiatric disorder will be excluded from this study, no correlation between a higher score on a depression scale and disturbances to the P300 is expected.

Methods

Participants

For this pilot study, 15 healthy volunteers were tested. The mean age of the participant group, including 3 male and 12 female participants was 20.33 (range 17-25), with a standard deviation of 2.32. The participants were recruited via the Sona-System of the Radboud

University Nijmegen. For an overview of all collected information of the participants please see *appendix 1*.

All participants received extensive information about the background of the study and the PEPT treatment (for 'Patient information' please see *appendix 2*). Subjects were excluded from the study if they had a history of psychiatric or neurological disorder, used medications or suffered from pre-existing pain or an existing pain syndromes (for 'Exclusion Criteria's' please see *appendix 3*). All participants signed an informed consent form (please see *appendix 4)*. Subjects were allowed to leave the study at any time without giving any reason and without any consequences. Approval for the experiment was obtained from the local Ethical Committee (Ethical Committee of the Faculty of Social Sciences, Radboud University Nijmegen).

Materials

Demographic and health data, such as age, gender, education, any existence of chronic pain, and whether the participants are right- or left- handed was collected using a questionnaire designed by the authors. For the full questionnaire please see *appendix 5*.

In order to measure the auditory evoked potential, a multi-channel electroencephalogram (EEG; 32 channels, Brainproducts ActiCap system; Brainvision system) was recorded during the auditory 'oddball' task (see below) (band-pass 0.1- 100 Hz, sample frequency 2000 Hz). The electrodes were mounted in an elastic electrode-cap and arranged according to the international 10- 20 system. Two electrodes behind both ears were used as reference. Eye movements were detected by horizontal and vertical electrooculogram (EOG) recordings (Keegan, Burke & Condron, 2009). Horizontal EOG was measured from the outer canthus of the left eye, and vertical EOG supra orbital to the left eye. Impedence was kept under 20 kΩ for all leads.

Headphones were used to deliver the sounds of the auditory 'oddball' binaurally to the patients. A template was used for the auditory 'oddball' paradigm using 'Presentation', a stimulus delivery and experimental control program for neuroscience .

To obtain some test-retest measures about participants negative orientation towards pain and participants fear of movement and/ or (re)injury the Dutch versions of the 'Pain Catastrophizing Scale' and the 'Tampa Scale of Kinesiophobia' were used respectively. For the total list of items of those two scales, please see *appendix 7 and 8*. For the detailed responses please see *appendix 1*.

Furthermore, the Dutch version of the 'Hospital Anxiety and Depression Scale' (HADS) was used to screen for depression. For the entire list of items and the detailed responses participants gave please see *appendix 6* and *1* respectively.

Auditory 'Oddball' Paradigm

For this study an auditory 'oddball' paradigm was used. The 'oddball' paradigm is a commonly used method to induce a P300 (positive deflection of the human event-related potential). To induce an auditory P300 with this paradigm, two different sounds are delivered to the participants binaurally through headphones. The subjects are than asked to count incidences of target stimuli (high-pitched sounds) that are hidden as rare occurrences amongst a series of more common stimuli (low-pitched sounds), that do not need to be counted. Because of the randomization and the different frequencies of the tones (20% and 80%) the occurrence of the target stimuli is not predictable and a component of surprise is elicited to induce a P300 (Picton, 1992). Furthermore, because of the fact that the subjects were asked to count the sounds it was ensured that the recording of the P300 were taken in an active or attended state (Picton, 1992).

The script we used consisted of baseline tones of 500 Hz and 'oddball' tones of 1000 Hz. A total of 200 trials (frequent + rare) was collected for each subject and 40 target stimuli ('oddball' stimuli) ERPs were obtained from each subject and were averaged. The interval between the stimuli varied randomly between 1000 and 1500 ms and was unpredictable by the subjects within that range.

Procedure and Design

In this pre-study a pre-post test design without a control group was administered. There was only one condition. All participants were treated with a 'sham' PEPT (multiple-single case design).

Recording of EEG took place in a sound attenuated room at the UMC St Radboud in Nijmegen. Care was taken by the researcher to keep the patients alert during the whole recording. In the same room the participants had to sign the informed consent and completed the questionnaires. The researcher was present during this whole procedure to answer any remaining questions, before and after the recordings.

After completing the questionnaires, EEG-electrodes were placed on the scalp and the first EEG recording was conducted. Between the two EEG recordings the 'sham' treatment was administered. The 'sham' PEPT consisted of a standardized procedure of mild movements of hands, arms, feet and legs. Participants were treated randomly at either the left or the right side of their body. This procedure took one hour, the approximate duration of a regular PEPT. After the second EEG recording, the participant had to complete the 'Pain Catastrophizing Scale' and the 'Tampa Scale of Kinesiophobia' once more to be able to get some test- retest results.

Signal analysis

Evoked potential waveforms measured at the vertex (Pz electrode) were extracted from the EEG off-line with Brain Vision Analyzer software version 1.05.0005. The P300 was defined as the largest positive value between 300 and 400 ms (Roser et. al, 2009). The analysis was focused at recording site Pz since that site exhibits the maximum auditory P300 amplitude and consistency (Trejo et al., 1991).

As a first step the continuous EEG was high-pass filtered at 1 Hz and low-pass filtered at 30 Hz. Then the EEG was segmented, based on the onset of the stimulus, into epochs from -1000 ms pre-stimulus to 1000 ms post-stimulus with a total period of two seconds (2000 ms) and baseline correction (-200 - 0 ms) was applied. Segments were then inspected for artifacts, like ocular, muscle or jaw artifacts and line noise activity and were removed if necessary. As a last step all segments were averaged to get a subject-specific evoked potential waveform.

Statistical Analysis

For statistical analysis IBM SPSS v. 20.0 was used. Data was analyzed at an individual level for each participant and at group level. A paired t-test was conducted to test whether there are statistically significant differences regarding the P300 latencies and amplitudes with respect to the time of measurement (pre vs. post). In all tests the significance level was set at $p < .05$.

In order to test, whether the P300 is a reliable measure for the effects of therapy, analysis of correlation were conducted. It was decided a priori that a reliability coefficient of less than

.40 would be considered poor, coefficients between .40–.59 would be considered fair, coefficients between .60–.75 good and coefficients larger than .75 excellent, based on previous accounts of classifying the degree of reliability (Rentzsch et al., 2008).

To examine whether there are any test-retest effects on the 'Pain Catastrophizing Scale' of Kinesiophobia' and the 'Tampa Scale of Kinesiophobia' a Wilcoxon signed ranks test for paired samples was used, with significance set at $P < 0.05$. Further analysis of correlation (pre vs. post) were conducted to confirm the clinical applicability of the two questionnaires.

Furthermore, analysis of correlation were conducted to answer the questions if there is a significant correlation between the P300 and scores on the depression-subscale (scores on depression-subscale and the amplitude of the P300; scores on depression-subscale and the latency of the P300).

Results

The data of one patient had to be excluded, because there was too much noise in the EEG signal to produce a reliable ERP waveform. The grand average evoked potential waveforms for both measurements (pre and post) are shown in *figure 1*. The means (and SEMs) of the P300 amplitudes and latencies are summarized in *figure 2*. The correlations between pre- and post- measure and the individual differences in the pattern of changes in the P300 for all subjects are shown in *figure 3*.

For the analysis of the test-retest effects of the two different questionnaires and the analysis of correlation between the two measures (pre vs. post) data of all participant were included.

Evoked potential P300 amplitude

The paired t- test analysis revealed no significant differences on the P300 amplitude (t = 0.187, df = 13, p = .855). There was no significant change between the P300 amplitude observed before (M = 23.77μV) and after treatment (M = 23.40μV) (*fig. 2A*). The correlation between pre- and post- measure was fair and only marginal significant (r = .518, p = .058) (*fig. 3A*). The individual differences in the pattern of P300 amplitude changes can be seen in *figure 3B.*

Evoked potential P300 latency

The paired t- test analysis revealed no significant differences on the P300 latency (t = -1.013, df = 13, p = .330). There was no significant change between the P300 latency observed before (M = 348.8) and after treatment (M = 355.57) (*fig. 2B*). Again, only a fair and marginal significant correlation was observed between pre- and post- measure (r = .520, p = .057). The individual differences in the pattern of P300 latency changes can be seen in figure 3D.

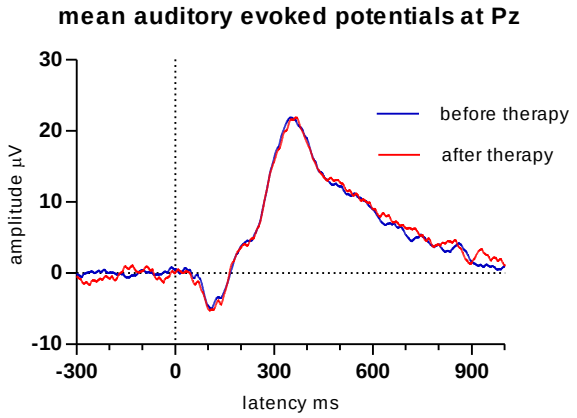
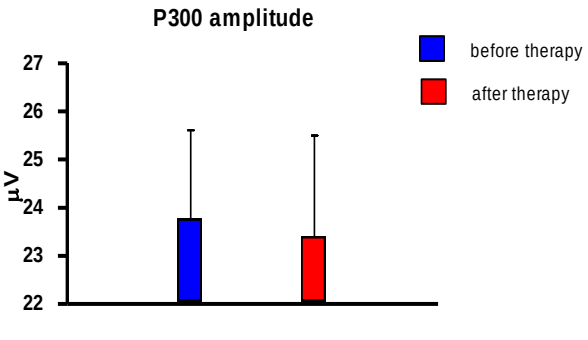


Figure 1.: Grand average evoked potential waveforms comparing the measurements (pre and post). The dotted line on the X-axis represents the stimulus onset.

A



B

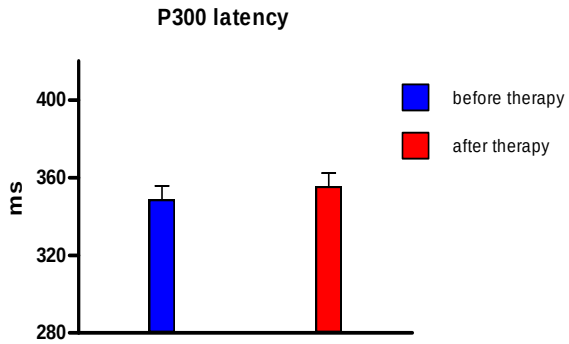
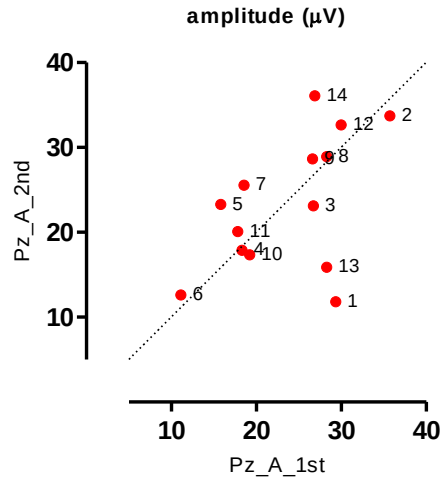
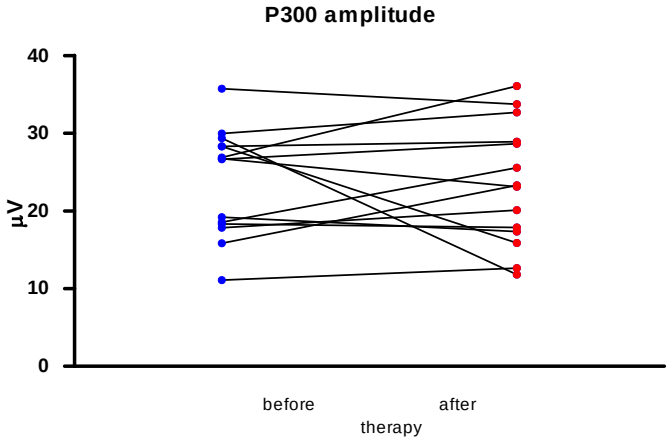


Figure 2A & 2B: Histograms representing the mean P300 potential amplitudes (A) and latencies (B) (and SEMs) for both measures (pre vs. post).

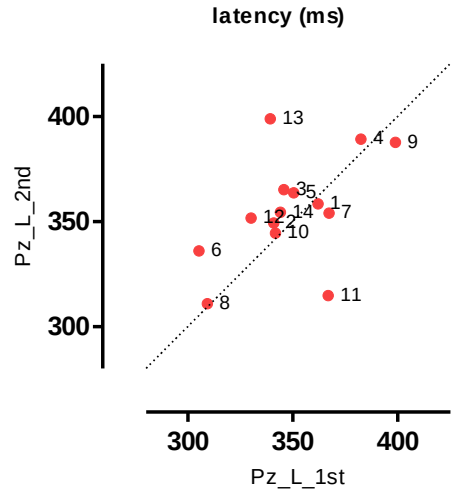
A



B



C



D

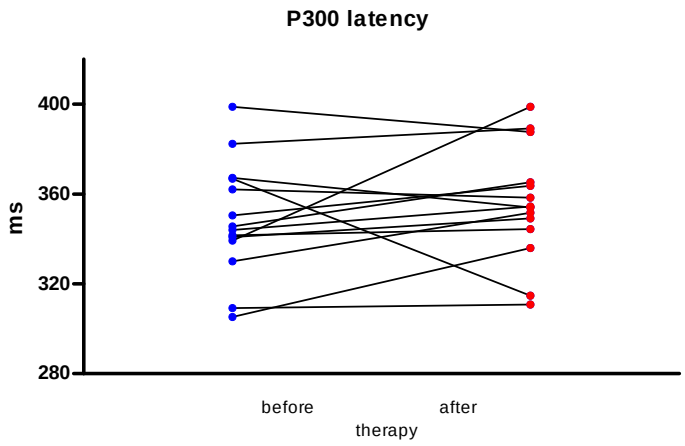


Figure 3A & 3B: Correlations between pre- and post- measures of the P300 amplitudes (A) and latencies (C). The dots represent the individual participants.

Individual differences in the pattern of changes of the P300 amplitudes (B) and amplitudes (D) for both measures (pre and post). The dots represent the latencies (A) and amplitudes (B) for every participant (blue→ pre; red→ post).

Pain Catastrophizing

There was a statistically significant difference between the means corresponding to the two measures of the 'Pain Catastrophizing Scale' (pre vs. post), after the application of the Wilcoxon signed ranks test for paired samples (p = .022). This indicates a significant decrease between the scores observed before (M = 16.6; SD = 7.4) and after treatment (M = 10.47; SD = 7.5) (*fig. 4*). The correlation between pre- and post- measure assessed by Pearson's r value was .911. This was highly significant (p = .000) (*fig. 5*).

Kinesiophobia

There also was a statistically significant difference between the means corresponding to the two measures of the 'Tampa Scale of Kinesiophobia' (pre vs. post), after the application of the Wilcoxon signed ranks test for paired samples (p = .043). Again, this indicates a significant decrease between the scores observed before (M = 30.93; SD = 6.9) and after treatment (M = 29.6; SD = 6.4) (*fig. 4*). The correlation between pre- and post-measure assessed by Pearson's r value was .943. This was again highly significant (p = .000) (*fig. 5*).

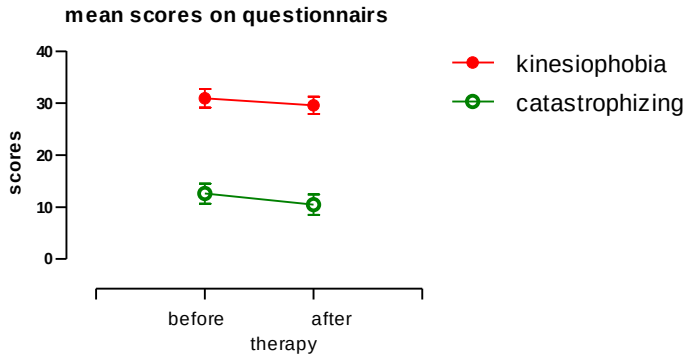


Figure 4: Mean scores with SEM of the two different questionnaires ('Pain Catastrophizing Scale' and 'Tampa Scale of Kinesiophobia') for both measures (pre vs. post), showing differences in answering pattern between the two different measures.

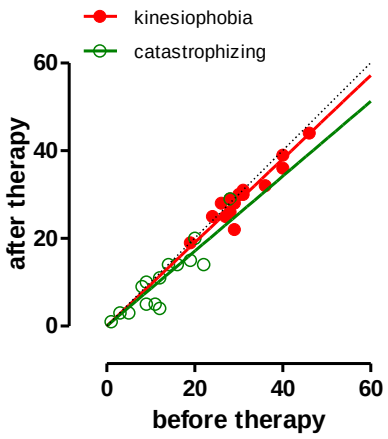


Figure 5: Individual scores on the two different questionnaires ('Pain Catastrophizing Scale' and 'Tampa Scale of Kinesiophobia') for both measures (pre vs. post), showing the correlation between the answering pattern of both measures. The dots represent the individual participants. Both regression lines are less steep then the line before =after, with slope 1 (dotted line).

Score on depression-scale and evoked potential P300

The average score on the depression- subscale of the HADS was 2.07 (*SD* = 2.12). No significant correlation was found between scores on the depression-subscale (HADS) and the P300 amplitude before (r = -.018, p = .950) and after treatment (r = .096, p = .745), as well as between the score of the depression-subscale (HADS) and the P300 latency before (r = .249, p = .391) and after treatment (r = .161, p = .583).

Discussion

The primary aim of this pre-study was to assess whether in healthy participants there is a change in the auditory P300 amplitude and/ or latency after one hour of physical therapy ('sham' PEPT) and whether these two measures do correlate. To answer this question EEG recordings were conducted during an auditory 'oddball' paradigm (commonly used method to induce a P300), before and after a 'sham' PEPT was administered to a group of healthy volunteers. The 'sham' PEPT consisted of a standardized procedure of mild movements of hands, arms, feet and legs. The analysis was focused at recording site Pz since that site exhibits the maximum P300 amplitude and consistency of the auditory event-related potential (Trejo et. al, 1991). It was hypothesized that there is no functional reorganization and thus no generalized changes to the P300 after the 'sham' PEPT.

Furthermore, in order to be a reliable measure of the effects of the therapy, it was hypothesized that in healthy volunteers the first and second measurements of the P300 amplitude and latency yield good till excellent correlations (coefficients above .60) (Simons et. al, 2011). Despite the expected good test- retest correlation for the P300 amplitude and the good, but lower test-retest correlation for the P300 latency in healthy controls (Simons et. al, 2011), individual differences in the pattern of changes in the P300 were expected (Trejo et. al, 1991).

In accordance with the first hypothesis no significant changes in the P300 amplitude or latency were found. This finding is consistent with the idea that in healthy participants PEPT is no more than mild movements and therefore does not induce functional reorganization, as shown by the P300. In accordance with the second hypothesis clear individual differences in the pattern of changes in the P300 were found. This confirms earlier findings about inconsistencies of test-retest measures of the P300 at individual level (Trejo et. al, 1991).

However, no good or excellent test- retest correlations (coefficients above .60) between the two measures (pre vs. post) for either the P300 amplitude nor for the latency were found. Both measures only showed fair test- retest correlations (coefficients between .40–.59). Those findings are however still in line with previous studies applying oddball paradigms, showing fair till excellent test-retest correlation coefficients for P300 amplitude (.50 - .80) and fair till good coefficients for P300 latency (.40–.70) in healthy controls (Polich, 1986; Fabiani et al., 1987; Segalowitz and Barnes, 1993). It is yet still possible, that the fair and only marginal significant correlations is a consequence of the rather small sample sizes (Trejo et. al, 1991).

The second aim of this pre-study was to investigate the suitability of two different questionnaires for the application to the main study with CRPS-I patients. The question was whether there are any test-retest effects of the negative orientation toward pain (pain catastrophizing) and the fear of movement and/or (re)injury (kinesiophobia) following ‘sham’ PEPT in healthy participants. This question was tried to be answered by using the Dutch versions of the ‘Pain Catastrophizing Scale’ and the ‘Tampa Scale for Kinesiophobia’. No changes between pre- and post- measure and high and significant test- retest correlations were expected.

For both questionnaires high and highly significant correlations between the test- and the retest- measure were recorded. Those findings are in accordance with the hypothesis and earlier reliability studies of those two questionnaires (Sullivan, Bishop, & Pivik, 1995; Koho,

Aho, Pohjolainen, & Hurry, 2009) and furthermore indicate their suitability for clinical practice.

However, contrary to the hypothesis, significant difference between the means corresponding to the two measures of the 'Pain Catastrophizing Scale' and the two measures of the 'Tampa Scale of Kineosophobia' were recorded. On both questionnaires participants scored significant lower on the second measure.

One possible reason for the decline in answering pattern on the 'Pain Catastrophizing Scale' is given by the explanation that this scale highly correlates with emotional distress (Sullivan, Bishop, & Pivik 1995). The first measure of the questionnaires was taken at the beginning of the experiment. None of the participants had earlier participated in an EEG experiment and therefore did not know what to expect. It is already known that uncertainty about a situation can lead to emotional distress (Gilovich, Keltner, & Nisbett, 2006). The second measure was taken at the end of the experiment. There was therefore no more uncertainty about the experiment. Uncertainty about the situation leading to emotional distress might therefore explain why healthy participants scored significantly lower on the 'Pain Catastrophizing Scale' after a 'sham' physical therapy.

A similar explanation might hold for the decline in the answering pattern on the 'Tampa Scale of Kineosophobia'. The participants, that were uncertain about what to expect of an EEG experiment and how painful it might be, might have experienced pain related fear, which is already known to highly correlate with the answering pattern of the 'Tampa Scale of Kineosophobia' (Roelofs et. al, 2012). Because all participants were informed, that connecting the electrodes to the scalp might be unpleasant or sometimes even painful, pain related fear might have been induced. This has possibly led to a higher score on the kineosophobia scale.

The last objective of this study was to investigate whether a high score on a depression scale correlates with the amplitude or the latency of the P300 in healthy participants before and after the 'sham' treatment. It was hypothesized that the subjects who participated at this pre-study do not show a correlation between a higher score on a depression scale and disturbances to the P300.

Consistent with this last hypothesis, no significant correlation between a higher score on a depression scale and changes to the P300 was found both for latencies and amplitudes before and after treatment. Although some studies have already shown disturbances (changes in the amplitude and/ or latency) in auditory event related potentials in patients suffering from a major depression (Vandoolaege, Hunsel, Nuyten, & Maes, 1998), those disturbances could

not be found in patients suffering from mild to moderate depressions (Kraiuhin et al., 1990). As in this pre- study all participant with a history of a psychiatric disorder (thus also with a major depression) were excluded, our findings provide further evidence for the idea that only those individuals suffering from a major, not from a mild or moderate depression show disturbances of the P300.

In this pre-study not all hypothesizes were confirmed. This has various implications for the coming study with CRPS-I patients. The first and main hypothesis was confirmed. There was no general effect of physical therapy ('sham' PEPT) on the P300 in healthy controls. This indicates that there was no functional reorganization, thus no neuroplasticity following 'sham' PEPT in healthy participants. However, we did not find good test- retest correlations for either the P300 amplitude or the latency in healthy volunteers. Both measures only showed fair test- retest correlations, that were only marginal significant. Those two outcomes, together with the observed individual differences in the pattern of changes in the P300, indicate that the P300 amplitude as well as the latency should not be interpreted at individual level. Changes at individual level should thus not be interpreted as an effect of the therapy.

In a coming study we will investigate whether changes to the P300 amplitude and/ or latency do occur in patients suffering from CRPS-I following PEPT. We will do this by comparing the mean amplitudes and latencies of the groups before and after therapy. No conclusion will be taken by comparing the amplitudes and/ or latencies at individual level. If there will be differences in either the mean P300 amplitudes or latencies of the group following PEPT, changes to the P300 can be interpreted as effectiveness of this therapy.

A second implication of this pre-study relates to the test-retest findings of the two different questionnaires. It is already known that an excessively negative orientation toward pain (pain catastrophizing) and fear of movement and/or (re)injury (kinesiophobia) are important predictors of chronic pain (Picavet, Vlaeyen, & Schouten, 2002). An important question for the coming study with CRPS-I patients is therefore whether those two variables also play a role in the development or even during the recovery of CRPS-I.

In this pre- study for both questionnaires high and highly significant correlations between the test- and the retest- measure were recorded. Those findings indicate their suitability for clinical practice. However for both questionnaires significant difference between the means corresponding to the two measures were recorded. In the coming study with CRPS- I patients those questionnaires can therefore not reliably be used by comparing

scores between pre- and post- measures, to answer the question whether PEPT decreases pain catastrophizing and kinesiophobia.

One possibility to still assess whether those two variables also play a role in the development or even during the recovery of CRPS-I, is by using a control group in the coming study. We would therefore be able to not simply compare pre- and post- measures, but furthermore to compare the pattern of scoring on the two questionnaires between healthy controls and CRPS-I patients. By doing this we can investigate whether changes in the pattern of scoring can simply be explained by uncertainty or whether the patient group shows a stronger decrease on the post- measure. If an interaction was found between time of measurement and scores of the questionnaires, this would indicate that PEPT changes the negative orientation toward pain (pain catastrophizing) and the fear of movement and/or (re)injury (kinesiophobia) in CRPS-I patients.

The final implication of this pre-study is related to the lack of significant correlation between scores on the depression scale and P300 measures. If in the coming study with CRPS-I patients participants with a psychiatric disorder will be excluded, no depression scale needs to be administered. Nevertheless, it is already known that chronic pain and depression co-occur in 30 to 50% of the patients (Moitra et. al, 2011). It might therefore be difficult to find enough participants without any history of a depressive episode. When working with patients suffering from CRPS-I, having a depression might not be used as exclusion criteria, and it is therefore important to control for the covariate of having a depression.

In consideration of all the findings of this pre- study, in the coming study with CRPS-I patients we will try to answer the question whether PEPT is able to reverse the maladaptive neuroplasticity of patients suffering from CRPS type I, as was shown with epidural methylprednisolone therapy in patients suffering from chronic low back pain (Tandon, Kumar, Dhar & Battacharya, 1997). If PEPT is able to reverse this maladaptive neuroplasticity, it would provide further evidence for a central role of cortical mechanisms in the maintenance of this pain syndrome and could furthermore be interpreted as effectiveness of the therapy.

Acknowledgement

This project would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study.

First and foremost I offer my sincerest gratitude to my supervisor, Dr Tineke van Rijn, who has supported me throughout my thesis with her great enthusiasm and knowledge. With your help and support during the last years, and especially because of your persistent optimism you taught me how great it is to be a scientist.

My gratitude also goes to Dr Jan van Egmond and Jan Willem Ek to let me be part of this wonderful project. I think that the work you are doing is wonderful and I hope that you will achieve everything that you wish for.

During my work concerning this project I have been blessed with a friendly and inspiring group of fellow students and workers of the Radboud University Nijmegen and the Radboud Hospital Nijmegen. I am thanking all of you for the great company and especially for accompanying me to my first international congress where I had the pleasure to present my first results. My special thank goes to Dr Emanuel van den Broeke, who did not only accompany and support me during the whole project, but without your help, I wouldn't have been able to achieve any of this.

I furthermore want to thank Dr Chris Dijkerman and Tanja Nijboer for supervising this project and for all the ideas and suggestions that gave me the chance to optimize many of my own ideas.

Last but not least I want to thank all the participants. Thank you for your time and patience. This project couldn't have been accomplished without your help.

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Appendix

Appendix 1: Overview of all collected information of the participants

Table 1. *Detailed information of all participants*

Subject	Gender	Age	Further Education	Depression score	Pain Catastrophizing (1^{st} vs. 2^{nd})	Kinesiophobia (1^{st} vs. 2^{nd})
1	Female	21	WO	0	1 vs. 1	19 vs. 19 .
2	Female	21	WO	0	9 vs. 10	36 vs. 32
3	Female	18	WO	1	28 vs. 29	46 vs. 44
4	Female	20	WO	5	16 vs. 14	30 vs. 30
5	Female	18	WO	0	5 vs. 3	28 vs. 29
6	Female	19	WO	0	11 vs. 5	24 vs. 25
7	Male	19	WO	3	12 vs.11	40 vs. 39
8	Male	24	WO	4	20 vs. 20	40 vs. 36
9	Male	22	WO	2	3 vs. 3	29 vs. 28
10	Female	20	WO	7	9 vs. 5	26 vs. 28
11	Female	23	WO	0	22 vs. 14	27 vs. 25
12	Female	17	WO	3	14 vs. 14	31 vs. 31
13	Female	19	WO	2	8 vs. 9	28 vs. 26
14	Female	25	WO	3	12 vs. 4	29 vs. 22
15	Female	19	WO	1	19 vs. 15	31 vs. 30

Appendix 2: Patient- information

EEG- Informatie voor Deelnemers

Het doel, de voorbereiding en werkwijze van het onderzoek

Doel van het onderzoek

Het doel van een Elektro-EncefaloGram (EEG) is de elektrische activiteit van de hersenen te meten. Dit EEG onderzoek maakt onderdeel van een grotere studie over neuroplastische veranderingen in het brein van patiënten met het chronisch complex pijnsyndroom (CRPS). De onderzoeksgroep die dit onderzoek doet is van mening dat de oorzaak van de ziekte gezocht moet worden in de hersenen, in tegenstelling tot de algemene opvatting dat het gaat om een uit de hand gelopen ontstekingsreactie van het ledemaat.
Door EEG metingen willen wij veranderingen op brein niveau aantonen die tot het ontstaan en de instandhouding van de ziekte bij kunnen dragen. Verder willen wij verandering op brein niveau voor en na een fysiotherapeutische behandeling (PEPT) meten, om aan te tonen dat een verbetering van de klachten samenhangt met een verandering op brein niveau.
Voordat het onderzoek met CRPS patiënten uit wordt gevoerd willen wij naar de test- hertest effecten van de verschillende maten kijken, die in later onderzoek gebruikt zullen worden. Dit zijn verschillende, aan chronische pijn gerelateerde vragenlijsten, een event- related potential (het P300) en het resting state EEG.

Het onderzoek

Voor het onderzoek wordt gedaan, wordt de procedure ook nog uitlegt. Aan het onderzoek is geen enkel risico verbonden: er wordt geen elektrische activiteit naar de hersenen gestuurd maar de spontane activiteit van de hersenen zelf wordt gemeten. Deze activiteit wordt gemeten met elektroden die in een muts zitten. Het aanbrengen van de muts duurt ongeveer 30 minuten. Om de geleiding tussen de electroden en de hoofdhuid te bevorderen, brengen we onder de elektroden een contactgelei aan en wat over de hoofdhuid krassen we met een stomp pennetje. Dit krassen kan wat vervelend zijn. De registratie van het EEG neemt ongeveer 30 minuten in beslag. De activiteit van de hersenen wordt in een computerprogramma opgeslagen en later geanalyseerd.
De hele procedure zal dus ongeveer een uur duren en twee keer uit worden gevoerd (test-hertest effecten). Tussen de twee metingen zal er een pauze van 60 minuten worden gehouden. In deze tijd wordt u gevraagd om een aantal opdrachten uit te voeren. Het gehele onderzoek zal maximaal 3 uur in beslag nemen.

Voorbereiding

- Was uw haar de dag vóór het onderzoek grondig. Gebruik geen haarvet of -gel. Dit kan de geleiding tussen de elektroden en de hoofdhuid negatief beïnvloeden.
- Oorbellen moet u vóór het onderzoek verwijderen.
- U mag de periode voorafgaand aan het onderzoek gewoon eten en drinken (behalve 3 uur van tevoren geen koffie of donkere thee drinken)

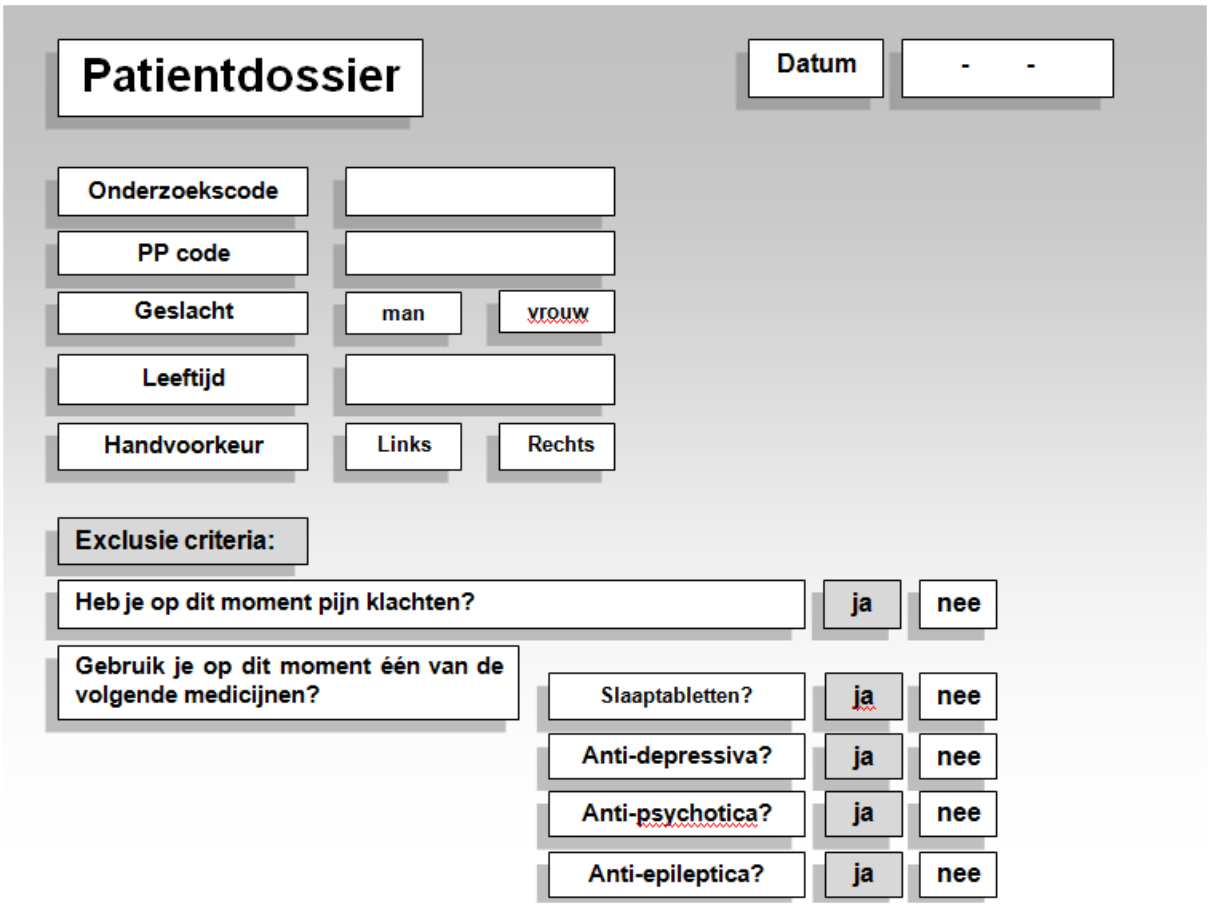
Tijdens het onderzoek

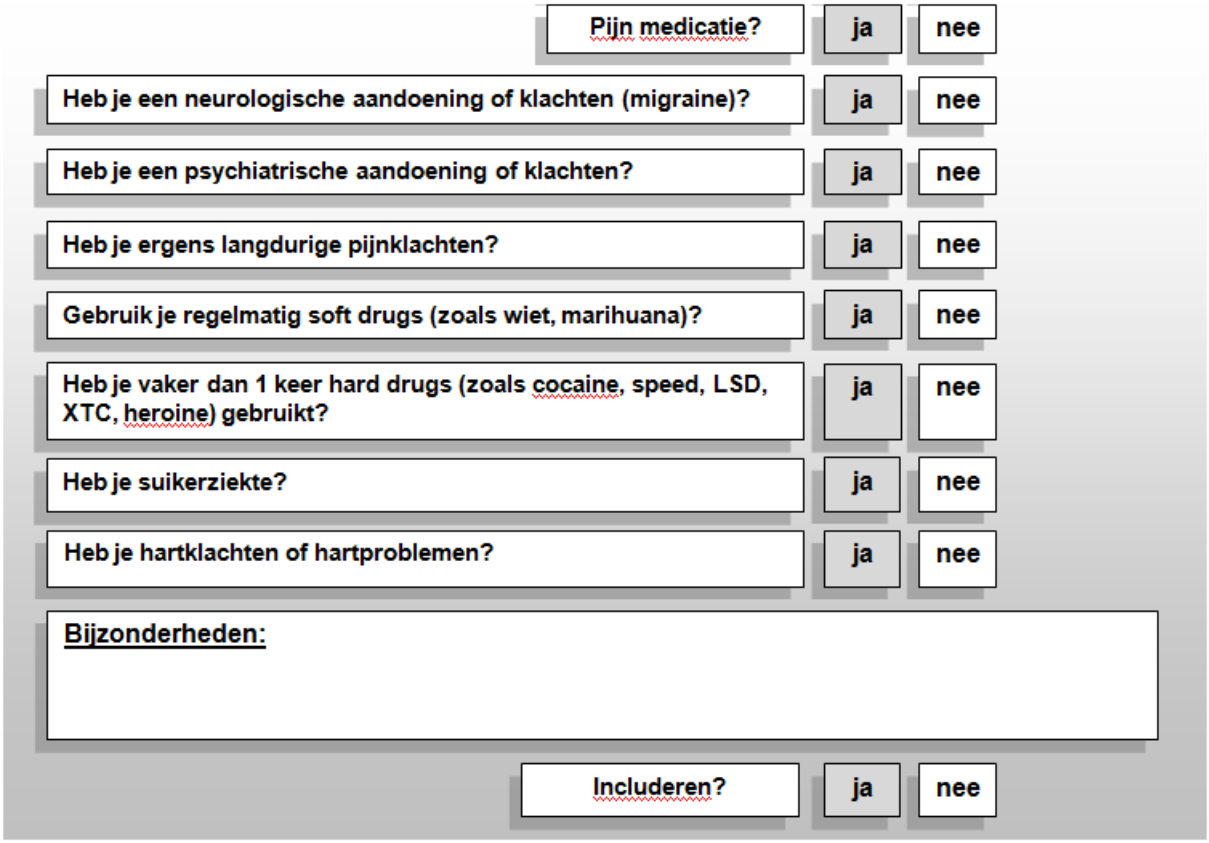
Tijdens het onderzoek zit u op een makkelijke stoel; de meeste tijd met de ogen dicht. Het is van belang dat u het hoofd zo min mogelijk beweegt, omdat anders storingen in de EEG-opname kunnen ontstaan. U krijgt auditieve stimuli aangeboden en krijgt bepaalde opdrachten die nodig zijn om veranderingen in de hersenfunctie op te wekken.

Na het onderzoek

Na afloop van het onderzoek verwijdert de laborant de elektroden. Na het onderzoek kunt u op eigen gelegenheid naar huis gaan en uw werkzaamheden hervatten.

Appendix 3: Exclusion Criteria




Pijn medicatie?
ja
nee
Heb je een neurologische aandoening of klachten (migraine)?
ja
nee
Heb je een psychiatrische aandoening of klachten?
ja
nee
Heb je ergens langdurige pijnklachten?
ja
nee
Gebruik je regelmatig soft drugs (zoals wiet, marihuana)?
ja
nee
Heb je vaker dan 1 keer hard drugs (zoals cocaine, speed, LSD, XTC, heroine) gebruikt?
ja
nee
Heb je suikerziekte?
ja
nee
Heb je hartklachten of hartproblemen?
ja
nee
Bijzonderheden:
Includeren?
ja
nee

Appendix 4: Informed Consent Form

TOESTEMMINGSVERKLARING

voor deelname aan het wetenschappelijk onderzoek:

Neuroplasticity after physical therapy

A pre- study:

test- retest- effects in healthy participants

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen over het onderzoek te stellen. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef op te geven.

Ik stem toe met deelname aan het onderzoek.

Naam :

Geboortedatum :

Handtekening : Datum:

Ondergetekende verklaart dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Zij verklaart tevens dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, voor haar, verder geen gevolgen heeft.

Naam :

Functie :

Handtekening : Datum:

Appendix 5: General questionnaire

Geachte deelnemers,

Voor een correcte verwerking van de onderzoeksresultaten is het noodzakelijk om een aantal gegevens over de deelnemers te verzamelen. We vragen u in verband hiermee deze vragenlijst in te vullen. Alle informatie die wij hiermee verzamelen wordt vertrouwelijk behandeld, de gegevens worden dus anoniem verwerkt.

Alvast bedankt voor uw medewerking!

1) Geslacht: **M / V** *(Omcirkel het alternatief dat voor u van toepassing is).*

2) Leeftijd: ____ jaar *(invullen aub)*

3) Heeft u last van (chronische) pijn? **JA** **NEE** *Als u deze vraag met **JA** hebt beantwoord ga verder met vraag **3**. Als u deze vraag met **NEE** hebt beantwoord ga verder met vraag **14.***

4) Hieronder ziet u enkele lijnen met links de woorden "helemaal geen pijn" en rechts de woorden "ondragelijke pijn".
De bedoeling is dat u op elke lijn een streepje zet om aan te geven hoeveel pijn u heeft. Dus hoe meer pijn u heeft, hoe meer u het streepje naar rechts zet. Lees goed de bijhorende tekst, want het gaat over bepaalde momenten.

a) Wilt u op onderstaande lijn een streepje zetten om aan te geven hoeveel pijn u **nu, op dit moment** hebt.

helemaal geen pijn ——————————————— ondraagelijke pijn

b) Het is mogelijk dat de pijn niet altijd even erg is. Wilt u daarom op onderstaande lijn aangeven hoe hevig uw pij is als hij het **minst erg is.**

helemaal geen pijn ——————————————— ondraagelijke pijn

c) Wilt u tenslotte op onderstaande lijn een streepje zetten om aan te geven hoe hevig uw pijn is als hij **op zijn ergst** is.

helemaal geen pijn ——————————————— ondraagelijke pijn

5) Hieronder ziet u twee lijnen met links de woorden "heel goed" en rechts de woorden "helemaal niet".

De bedoeling is dat u op elke lijn een streepje zet om aan te geven hoe goed u op het moment **thuis** en, als u nog werkt **op werk** kunt functioneren. Dus hoe beter u functioneert, hoe meer u het streepje naar rechts zet.

a) Wilt u op onderstaande lijn een streepje zetten om aan te geven hoe goed u **thuis** kunt functioneren.

heel goed ——————————————— helemaal niet

b) Wilt u op onderstaande lijn een streepje zetten om aan te geven hoe goed u **op werk** kunt functioneren (als u op het moment niet werkt, hoeft u hier niks in te vullen).

heel goed ——————————————— helemaal niet

6) Bent u in staat om u pijn te lokaliseren (bv. rugpijn, hoofdpijn)? **JA** **NEE**

*Als u deze vraag met **JA** hebt beantwoord ga verder met vraag **6***
*Als u deze vraag met **NEE** hebt beantwoord ga verder met vraag **7***

7) Waar liggen de hoofdpunten van uw pijn (locatie van pijn)?

_____

8) Hoe lang heeft u (ongeveer) al pijn? _____ jaar

9) Hoe lang is het (ongeveer) geleden dat bij u de diagnose CRPS-I werde gesteld? _____ jaar

10) Wie heeft de diagnose gesteld? _____

11) Gebruikt u medicaties (tegen de pijn)? **JA** **NEE**

*Als u deze vraag met **JA** hebt beantwoord, aub lijst met soort medicaties en dosering inleveren bij onderzoeker*

12) Gebruikt u op dit moment medicaties? **JA** **NEE**

13) Welke behandelingen heeft u al gehad? _____

_____

14) Bent u rechts- of linkshandig? **rechts** **links** **beide**

15) Welk soort vervolgopleiding heeft u gevolgd?

geen vervolgopleiding **LBO** **MBO** **HBO** **WO**

16) Wat is de naam en het adres van u huisarts? _____

_____

Bedankt voor uw deelname!

Appendix 6: Hospital Anxiety and Depression Scale (HADS)

Naam: Leeftijd:

Geslacht: Datum:

Het is bekend dat emoties bij de meeste ziektes een belangrijke rol kunnen spelen.
Deze vragenlijst dient als hulpmiddel om te weten te komen hoe u zich voelt. Lees iedere vraag en onderstreep het antwoord dat het beste weergeeft hoe u zich **gedurende de laatste week** gevoeld heeft.
Denk niet te lang na over uw antwoord. Uw eerste reactie op elke vraag is waarschijnlijk betrouwbaarder dan een lang doordacht antwoord.

1**. Ik voel me gespannen:**
Bijna altijd
Vaak
Soms
Nooit

2. Ik geniet nog steeds van de dingen waar ik gewoonlijk van kon genieten:
Zeker zo veel
Wat minder
Nauwelijks nog

3. Ik heb een angstig gevoel alsof er iets vreselijks gaat gebeuren:
Zeer zeker
Zeker
Een beetje
Helemaal niet

4. Ik kan lachen en de dingen van de vrolijke kant zien:
Net zoveel als gewoonlijk
Nu wat minder
Nu duidelijk minder
Helemaal niet meer

5. Ik maak me zorgen:
Heel vaak
Vaak
Niet zo vaak
Heel soms

6. Ik voel me opgewekt:
Nooit
Heel af en toe
Soms
Meestal

7. Ik kan me ontspannen:
Altijd
Meestal
Af en toe
Nooit

8. Ik heb het gevoel dat bij mij alles moeizamer gaat:
Bijna altijd
Heel vaak
Soms
Nooit

9. Ikheb een angstig, gespannen gevoel in mijn buik:
Nooit
Soms
Vrij vaak
Heel vaak

10. Het interesseert me niet meer hoe ik eruit zie:
Inderdaad, het interesseert me helemaal niet meer
Ik besteed minder aandacht aan mijzelf dan ik zou moeten
Ik besteed misschien iets minder aandacht aan mijzelf
Ik besteed minstens net zoveel aandacht aan mijzelf als gewoonlijk

11. Ik voel me ongerust:
Inderdaad, zeer vaak
Tamelijk vaak
Soms
Nooit

12. Ik kijk met plezierb uit naar dingen:
Net zoveel als gewoonlijk
Iets minder dan gewoonlijk
Veel minder dan gewoonlijk
Nauwelijks

13. Ik raak plotseling in paniek:
Inderdaad, zeer vaak
Tamelijk vaak
Soms
Nooit

14. Ik kan genieten van een goed boek of een radio- of televisie- programma:
Vaak
Regelmatig
Af en toe
Zelden

Wilt u controleren of u alle vragen beantwoord heeft?
BEDANKT.

Appendix 7: The Dutch version of the 'Pain Catastrophizing Scale'

Pijn Catastroferen Schaal (PCS)
M. Sullivan, S. Bishop, J. Pivik, 1995

Geautoriseerde Nederlandstalige vertaling G. Crombez en J. Vlaeyen

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Wij zijn geïnteresseerd in de soort gedachten en gevoelens die u ervaart als u pijn hebt. In de onderstaande lijst staan dertien beweringen die verschillende gedachten en gevoelens beschrijven die mogelijk met pijn te maken hebben. Probeer aan te geven in welke mate deze gedachten en gevoelens ook voor u van toepassing zijn. Maak daarbij gebruik van de volgende puntenschaal.

Omcirkel dat op u van toepassing is, hierbij geldt:

0=helemaal niet 1=in lichte mate 2=in zekere mate 3=in grote mate 4=altijd

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Als ik pijn heb …….

1. vraag ik mij voortdurend af of de pijn zal ophouden	0	1	2	3	4
2. voel ik dat ik zo niet verder kan	0	1	2	3	4
3. is dat verschrikkelijk en denk ik dat het nooit beter zal worden	0	1	2	3	4
4. is dat afschuwelijk en voel ik dat de pijn mij overweldigt	0	1	2	3	4
5. voel ik dat ik het niet meer uithoud	0	1	2	3	4
6. word ik bang dat de pijn erger zal worden	0	1	2	3	4
7. blijf ik denken aan andere pijnlijke gebeurtenissen	0	1	2	3	4
8. verlang ik hevig dat de pijn weggaat	0	1	2	3	4
9. kan ik de pijn niet uit mijn gedachten zetten	0	1	2	3	4
10. blijf ik eraan denken hoeveel pijn het wel doet	0	1	2	3	4
11. blijf ik denken hoe graag ik zou willen dat de pijn ophoudt	0	1	2	3	4
12. is er niets dat ik kan doen doen om de intensiteit van de pijn te verminderen	0	1	2	3	4
13. vraag ik mij af of er iets ernstigs kan gebeuren	0	1	2	3	4

Appendix 8: The Dutch version of the 'Tampa Scale of Kinesiophobia'

Naam: Geb.datum: Datum:

Tampa schaal voor Kinesiofobie

Miller, R.P., Kori, S.H. & Todd, D.D. (1991)
Geautoriseerde Nederlandse Vertaling
Vlaejen J.W.S., Kole-Snijders A.M.J., Crombez G., Boeren R.G.B. & Rotteveel A.M. (1995)

Geef van onderstaande beweringen door middel van een cijfer 1 en 4 aan in welke mate u het eens of oneens bent met deze bewering. De betekenis van de cijfers is als volgt;

1 = in hoge mate mee oneens
2 = enigszins mee oneens
3 = enigszins mee eens
4 = in hoge mate mee eens

1.	Ik ben bang om bij het doen van lichaamsoefeningen letsel op te lopen.	1	2	3	4
2.	Als ik me over de pijn heen zou zetten, dan zou hij erger worden.	1	2	3	4
3.	Mijn lichaam zegt me dat er iets gevaarlijk mis mee is.	1	2	3	4
4.	Mijn pijn zou waarschijnlijk minder worden als ik lichaamsoefeningen zou doen.	1	2	3	4
5.	Mijn gezondheidstoestand wordt door anderen niet serieus genoeg genomen.	1	2	3	4
6.	Door mijn pijnprobleem loopt mijn lichaam de rest van mijn leven gevaar.	1	2	3	4
7.	Mijn pijn betekent dat er sprake is van letsel.	1	2	3	4
8.	Als mijn pijn erger wordt door iets, betekend dat nog niet dat dat gevaarlijk is	1	2	3	4
9.	Ik ben bang om per ongeluk letsel op te lopen.	1	2	3	4
10.	De veiligste manier om te voorkomen dat mijn pijn erger wordt is gewoon oppassen dat ik geen onnodige bewegingen maak.	1	2	3	4
11.	Ik had wellicht minder pijn als er niet iets gevaarlijks aan de hand zou zijn met mijn lichaam.	1	2	3	4
12.	Hoewel ik pijn heb, zou ik er beter aan toe zijn als ik lichamelijk actief zou zijn.	1	2	3	4
13.	Mijn pijn zegt me wanneer ik moet stoppen met lichaamsoefeningen doen om geen letsel op te lopen.	1	2	3	4
14.	Voor iemand in mijn toestand is het echt af te raden om lichamelijk actief te zijn.	1	2	3	4
15.	Ik kan niet alles doen wat gewone mensen doen, omdat ik te gemakkelijk letsel oploop.	1	2	3	4
16.	Zelfs als ik ergens veel pijn door krijg, geloof ik niet dat dat gevaarlijk is.	1	2	3	4
17.	Ik zou geen lichaamsoefeningen hoeven te doen wanneer ik pijn heb.	1	2	3	4

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