Generalization of Exposure in Vivo in Complex Regional Pain Syndrome type I

Marlies den Hollander[* a,b,c], Jeroen de Jong[* b,d], Patrick Onghena [e], Johan W.S. Vlaeyen [a,f]

(* shared first co-authorship)

[a] Experimental Health Psychology, Maastricht University, Universiteitssingel 40, 6229 ER Maastricht, the Netherlands

[b] Department of Rehabilitation, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands

[c] Adelante Centre of Expertise in Rehabilitation, Zandbergsweg 111, 6432 CC, Hoensbroek, the Netherlands

[d] CAPHRI - School for Public Health and Primary Care, Department of Rehabilitation Medicine, Maastricht University, Universiteitssingel 60, 6229 ER Maastricht, the Netherlands

[e] Research Group on Methods, Individual and Cultural Differences, Affect and Social Behaviour, KU Leuven – University of Leuven, Tiensestraat 102, 3000 Leuven, Belgium

[f] Research Group Health Psychology, KU Leuven – University of Leuven, Tiensestraat 102, 3000 Leuven, Belgium

Correspondence concerning this article should be addressed to Marlies den Hollander, Department of Clinical Psychological Science, Maastricht University, PO Box 616, 6200 MD Maastricht, Netherlands. E-mail: marlies.denhollander@maastrichtuniversity.nl, T: +31433881481, F: +31433884155.

Abstract

Exposure in vivo has been found successful in reducing pain-related fear, disability, and experienced pain in chronic pain patients. Despite the success of exposure treatment, experimental studies show that extinction learning is fragile, raising doubts whether extinction of pain-related fear generalizes to new threatening activities after treatment. This study examined whether a particular exposure treatment, in which patients are exposed to a variety of activities (Multiple Exposure condition), promotes generalization of extinction to new threatening situations, compared to an exposure treatment in which subjects are repeatedly exposed to the same set of activities (Repeated Exposure condition). Generalization tests were combined with randomized replicated single case experimental designs (N=8). Included were patients with Complex Regional Pain Syndrome type I reporting elevated levels of pain-related fear. The Multiple Exposure treatment condition consisted of at least 15 activities to which patients were exposed once. The Repeated Exposure treatment condition exposed patients to only three activities during five sessions each. Generalization was tested by exposing patients to new fearful activities post-treatment and 6-months follow-up. Patients from both conditions performed equally well at both generalization tests. Daily measures showed that the Multiple Exposure condition is preferred to reduce fear of movement/(re)injury, pain catastrophizing and pain experience.

Introduction

Pain-related fear has been identified as one of the most important predictors of long-term disability in a variety of chronic pain conditions (Jensen, Karpatschof, Labriola, & Albertsen, 2010; Leeuw et al., 2007; Turk & Wilson, 2010; Vlaeyen & Linton, 2000; Zale et al., 2013). Protective behaviors, such as avoiding painful activities and guarding during movements after injury are adaptive, allowing the injury to heal and pain to subside. However, prolongation of these behaviors may have the paradoxical effect that fear, associated pain sensitivity and disability sustain (Vlaeyen & Linton, 2000, 2012; Vlaeyen, Crombez & Linton, 2016; van Vliet et al., 2018).

Classical conditioning is a potent learning mechanism in the context of pain, enabling the prediction of the occurrence of potential dangerous stimuli in the environment (Meulders, Vansteenwegen, & Vlaeyen, 2011; Vlaeyen, 2015). Due to pairing with inherently aversive experiences (unconditional stimuli, USs, such as pain and harm), emotionally neutral stimuli (conditional stimuli, CSs, for example proprioceptive stimuli such as movements or activities) can start to elicit protective responses (conditioned response, CR, such as avoidance behavior) on their own (Lissek et al., 2005). Individuals tend to not only avoid CSs that were originally paired with the US: US-expectancies generalize to novel CSs sharing perceptual or conceptual features with the original CS (Meulders, Vandael, & Vlaeyen, 2017). Generalization of fear acquisition enables the individual to conclude about the predictive value of similar stimuli, without having to experience these stimuli. Especially when it comes to avoiding harm, generalization is an adaptive process in the first place. Nevertheless, experimental studies show that individuals with chronic pain show impaired differential learning and excessive generalization (Meulders, Boddez, Blanco, Van Den Houte, & Vlaeyen, 2018; Meulders, Jans & Vlaeyen, 2015). The maladaptive and excessive spreading of protective responses may be a maintaining factor in chronic pain-related disability.

A method to reduce conditioned fear responses and associated protective behavior is exposure, which is generally regarded as the clinical analogue of fear extinction. Ample research has shown that extinction does not erase the original acquisition memory (CS-US), but creates a new extinction memory (CS-no US) that co-exists and competes with the originally acquired association (Bouton & King, 1983). Therefore, the current scientific opinion is that extinction is fragile. Individuals with anxiety disorders show hampered fear-extinction in conditioning procedures, compared to healthy controls (Wicking et al., 2016). Furthermore, the learning deficiencies shown in fear acquisition in chronic pain patients, seem to extend to slowed down extinction of generalization. In chronic pain patients, but not in healthy controls, CRs remained elevated to stimuli that are similar to, but have never been paired with the US, even despite corrective feedback (Meulders et al., 2018).

Although clinical studies have shown that exposure is a successful treatment for patients presenting with pain-related fear in chronic back pain (Leeuw et al., 2008; Linton et al., 2008; Vlaeyen, de Jong, Leeuw, & Crombez, 2004; Woods & Asmundson, 2008), post-traumatic neck pain (de Jong et al., 2008), work-related upper extremity pain (de Jong, Vlaeyen, van Eijsden, Loo, & Onghena, 2012), and Complex Regional Pain Syndrome type I (CRPS-I) (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; den Hollander et al., 2016), it is still unclear under what conditions extinction of fear and associated behavior (such as avoidance) generalizes to encounters with new threatening stimuli.

Generalization of extinction of pain-related fear from one CS to another CS (e.g. different movements) in chronic pain patients has been addressed in several experimental studies. Goubert et al. (2002) investigated if the effects of exposure to one movement generalized towards another dissimilar movement in low back pain patients. Participants were requested to perform two movements twice. Analyses revealed that pain was initially over-predicted, but after exposure the over-prediction was readily corrected. However, this exposure effect did not generalize from the first to the second movement, and this was particularly so for participants reporting high levels of pain catastrophizing (Goubert, Francken, Crombez, Vansteenwegen, & Lysens, 2002). In a subsequent study, ratings for perceived harm were also obtained, and similar results were reported (Crombez et al., 2002). Contrary to these studies, Trost et al. (2008) showed successful generalization of pain expectancy corrections across four adaptations of a reaching task, each introducing an element of increased intensity, in chronic low back pain patients reporting high levels of pain-related fear (Trost, France, & Thomas, 2008). However, these experimental were lab-based, and were not provided as a clinical treatment.

Therefore, the primary objective of this study was to investigate whether exposure treatment to multiple meaningful daily activities (e.g. CSs) promotes generalization of extinction to new threatening activities. We examined generalization following exposure treatment, which either consisted of exposure to multiple activities (Multiple Exposure condition), or repeated exposure to a limited number of activities (Repeated Exposure condition) in patients with CRPS-I reporting pain-related fear. We hypothesized that exposure to multiple stimuli would facilitate generalization of extinction.

Methods

Study design

We compared generalization of fear extinction of two exposure treatments that differed in the number of activities patients were exposed to. Generalization was evaluated with two behavioral tasks at post-treatment and at 6 months follow-up. A randomized replicated sequential single-case experimental

ABC phase design was used (Onghena & Edgington, 2005). Patients completed daily measures during a no-intervention baseline (period A), exposure treatment (period B) and at 6 months follow up (period C). The length of baseline was randomized between 12-16 days. The start date of the study depended on when pre-measurement session could be planned by the independent therapist, and the first exposure session was scheduled by an independent planner based on the availability of the treatment team.

After baseline, patients were randomly assigned to one of the two exposure conditions: Multiple Exposure or Repeated Exposure (period B). Both conditions received 18 one-hour sessions of treatment over a 3-month period. The first three sessions were the same for both conditions: psychological intake, administration of Photograph Series of Daily Activities of the upper extremities (PHODA-UE (Dubbers, Vikström, & de Jong, 2003)) and an educational session. The subsequent 15 sessions consisted of exposure in the assigned condition. In the Multiple Exposure condition, treatment consisted of at least 15 activities to which patients were exposed only once. In the Repeated Exposure condition, treatment consisted of 3 activities only, to which patients were exposed during five sessions each. After treatment, two generalization tests were conducted to test generalization of extinction. An independent and blinded therapist asked patients to perform two novel activities: one was standardized for all patients (headlong fall), one was selected based on the highest perceived harmfulness at baseline (see also paragraph Generalization Tests in Outcomes). At 6-months follow-up, participants completed daily measures for a period of two weeks (period C), and the generalization tests were repeated. Additionally, questionnaires were completed and an observation of functional disability was conducted at baseline, post-treatment and at 6 months follow-up.

Participants

Although the power of individual randomization tests with ABC designs is usually low, combining these designs in a multiple baseline setup increases the power considerably. Simulation studies have shown that under most conditions, the power to detect large treatment effects (d equal to 1.5 or larger) is already adequate (>0.80) for designs with 4 participants and a total of 20 measurement occasions (Ferron & Sentovich, 2002). Therefore, eight patients with upper extremity CRPS-I were included. Patients were referred for outpatient rehabilitation at the department of rehabilitation, Maastricht University Medical Center. To be included, they had to be between 18 and 65 years old. A physiatrist confirmed CRPS-I at time of inclusion using the IASP Orlando criteria (Mersky & Bogduk, 1994). Patients reported pain for at least 6 months and substantial fear of movement/(re)injury (Tampa Scale for Kinesiophobia [TSK] score ≥ 39) (Miller, Kori, & Todd, 1991, Roelofs et al. 2004). No TSK norm data were available for CRPS-I patients at the time we started this study, and only 1 previous study was conducted in CRPS-I (de Jong et al., 2005). We kept our inclusion criteria consistent with this first study,

since the current study also served as a partial replication. Therefore, we used the median of the TSK distribution in chronic low back pain samples as cut-off (Crombez, Vlaeyen, Heuts, & Lysens, 1999; Goubert et al., 2004). This choice is supported by the high similarities between fear of movement and in both CRPS and CLBP patients (Bean et al., 2014). Exclusion criteria were illiteracy, pregnancy, impairment of the contralateral extremity (e.g. because of rheumatoid arthritis, prior sympathectomy of the affected extremity), involvement in a litigation procedure regarding CRPS-I, alcohol or drug abuse, and serious psychopathology based on the Symptom Checklist (SCL-90) (Arrindell & Ettema, 1986) of which Dutch norms were available.

Procedure and program overview

The Medical Ethics Committee of the University Hospital Maastricht approved the study protocol (MEC 08-4-001). Upon referral, patients were first evaluated by the physiatrist who conducted a full physical examination, evaluated previous diagnostic tests, and gave information about the study. When patients agreed to participate, the researcher sent additional written information, along with an informed consent form, TSK and SCL-90. If patients fulfilled the inclusion criteria, they were planned for a pre-measurement session by an independent occupational therapist, who observed patients' performance using the Radboud Skills Test (RST) (Cup, van de Ven-Stevens, & Corstens-Mignot, 1999). Additionally, patients completed the Radboud Skills Questionnaire (RASQ) and the PCS. After this measurement session, patients started to complete daily measures as a baseline measurement period (period A). After treatment and at 6-months follow up, patients performed the generalization tests under supervision of the same occupational therapist (who was not involved in delivering exposure treatment) to test whether the effects of exposure generalized to novel threatening activities that were not targeted during exposure. Besides these tests, the RST was administered and several questionnaires (TSK, PCS, RASQ, PHODA-UE) were completed, both at post-treatment and 6 months follow-up. Additionally, during exposure treatment (period B), two weeks after treatment (period C), and two weeks at 6-months follow-up (period D) patients completed daily measures at home.

Exposure in vivo treatment

The same outpatient therapist team provided both the Multiple and Repeated Exposure treatment. The team consisted of a behavioral therapist and an occupational therapist both experienced in the cognitive behavioral rehabilitation of patients with chronic pain. In both conditions, exposure was highly structured, individually tailored, and aimed to restore a normal pattern of daily functioning, including complete return to work. Pain reduction and decreasing observed or reported physiological signs of CRPS-I, were no direct goals of exposure treatment.

Exposure treatment started with the completion of a behavioral analysis of the pain problem with specific attention to patients' catastrophic (mis-)interpretations of the pain problem. In the next session, the PHODA-UE (Dubbers et al., 2003) was administered, to further identify which activities are perceived to be associated with extreme negative consequences, such as harm. Patients were requested to judge the harmfulness of 110 daily life activities and movements represented by photographs. Using a (harm) thermometer, each picture was given a rating between 0 (representing no expectancies to harm the upper extremity) and 100 (representing that the patient is convinced that the activity will cause harm to the upper extremity). Additional catastrophic thoughts mentioned by the patient were registered. Session three consisted of individualized education provided by the therapist team explaining the treatment rationale. Patients were given a careful explanation of the fear-avoidance model, using their own symptoms, beliefs and behaviors in relation to their pain complaints. The therapist team illustrated the paradoxical and dysfunctional effects of various safety behaviors, and offered the patient a new perspective on CRPS-I as a condition that can be self-managed, rather than as a condition that needs careful protection or a serious disease. One of the major goals of the educational component was to help patients understand that the consequences of pain are overestimated, and that avoidance of painful activities is not adaptive anymore in this chronic phase of CRPS-I. Based on the results of the PHODA-UE and the patients' goals, individually tailored behavioral experiments were developed for the remaining 15 sessions. For the Multiple Exposure condition these were at least 15 activities and for the Repeated Exposure condition only 3 activities. To be sure that all activities were sufficiently threatening in both conditions, only activities rated above 50 on the PHODA-UE were included. Patients were systematically exposed to these tailored activities in the following sessions. To enhance generalization and maintenance, exposure was provided to the maximum spectrum of contexts and natural settings that can be achieved in and around the hospital setting. A more detailed description of exposure in vivo treatment can be found in Vlaeyen, Morley, Linton, Boersma, & de Jong (2012).

Outcomes

Generalization tests

In order to test generalization, each patient performed a behavioral task post-treatment and at 6-months follow-up. Both tests consisted of two activities. The first activity was a fall forward on both hands on the ground, starting from an upright sitting position on the knees. This activity was standard for all patients and was done post-treatment as well as at follow-up. The second activity was a random selection out of four "not-likely to happen in daily-life" activities (boxing against a punching bag, doing push-ups, hanging on a climbing frame and receive a Chinese burn [giving a Chines burn involves gripping the top of somebody's forearm with both hands then rotating the hands in opposite

directions, thus stretching the skin. The second activity at the follow-up test was always different from the one selected post-treatment. The tests were performed under supervision of an independent occupational therapist. The perceived harmfulness of those activities was rated at baseline (pictures of these activities were added to the PHODA-UE that was administered in treatment session 2), and just before and immediately after performing the test at post-treatment as well as at 6-months follow-up. The activities (CSs) for the generalization tests were chosen by the research team, based on their experience with activities individuals with CRPS-I still report as somewhat threatening after successful treatment. Within the expectancy violation context (Craske et al., 2014), activities of which the feared outcome is judged most likely to occur were chosen. If CRPS-patients would be willing to perform those activities, they would certainly be willing to perform usual activities requested in daily life functioning, and therefore it was reasoned that those activities were a good measure of generalization. Video clips of the chosen activities are available at https://www.caphri.nl/exposure-vivo.

Treatment expectancy and credibility

When the rationale of exposure was explained (educational session) and post-treatment, patients completed expectancy- and credibility ratings on a 10 cm VAS, with "not at all" and "very much" on the extremes: "*Do you expect that exposure in vivo will help you to cope better with your pain complaints*?" (Expectancy) and "*Do you believe that exposure in vivo offered to you is a meaningful treatment for patients with CRPS-I*?" (Credibility)(Borkovec & Nau, 1972).

Daily measures

To check whether exposure treatment indeed modified self-reported fear of movement/(re)injury, pain catastrophizing, achievement of personally relevant goals, and pain intensity, a brief diary was used consisting of 11 items with visual analog scales (VAS). The first 7 items (Table 1) represented the main factors of existing questionnaires for fear of movement/(re)injury (Tampa Scale for Kinesiophobia [TSK]) (Goubert et al., 2004; Roelofs et al., 2007) and pain catastrophizing (Pain Catastrophizing Scale [PCS]) (Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002). All items were scored on 10 cm VASs, anchored with "*totally disagree*" and "*totally agree*". Two main scores were derived, consisting of the mean scores (range 0 to 10) of the items from TSK and PCS. Pain intensity was measured with an additional VAS anchored with "*no pain at all*" at one extreme and "*worst possible pain*" at the other. The last three VASs referred to the ability to perform personally relevant activities representing three functional goals. Each scale was preceded by the same question: "*How difficult was it to perform this activity today?*" The scale was anchored with "*no problem at all*" at one extreme, and "*impossible*" at the other. The diary was completed during baseline, until two weeks after the end of treatment, and for two weeks at 6-months follow-up. The diary has been shown to be sensitive to the

effects of exposure in previous studies (de Jong et al., 2008; de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; de Jong et al., 2012).

Observation of functional disability

Functional disability was measured with the Radboud Skills Test (RST) (Cup et al., 1999). The aim of the RST was to observe and evaluate to what extent CRPS-I patients involved their affected arm/hand during bilateral activities: walking, putting a letter in an envelope, putting a pillow in a pillow-cover, putting on a shirt, closing a button, putting on a sock, drying up the dishes and folding a towel. The tasks were scored on a five-point Likert scale (0 = the task is performed bilaterally without observable problems, 4 = the task cannot be executed without help). Also, patients scored how difficult they experienced each task. This was scored on a three-point Likert scale (0 = no problem, 2 = serious problem). The RST provides a measure of functioning judged by an independent occupational therapist (performance score) and by the patient himself (difficulty score). The RST has shown good psychometric properties (de Boer et al., 2001).

Questionnaires

Radboud Skills Questionnaire

The Radboud Skills Questionnaire (RASQ) (Oerlemans, Cup, DeBoo, Goris, & Oostendorp, 2000) consists of 45 items to measure experienced disability in bilateral skills. Each item is scored on a five-point Likert scale (1 = “normal”, 5 = “I do not perform the activity anymore as a result of CRPS-I”, and there was an extra option for “not applicable”). A total mean score was computed by summing up relevant items (minus the number of items in which the category “not applicable” was chosen), divided by the number of items. A mean item score [1-5] was also calculated. This mean item score can be used to compare participants, since the score is not influenced by the number of items scored as “not applicable”. The RASQ has been found reliable in CRPS-patients, with good test-retest and inter-observer reliability (Oerlemans et al., 2000).

Fear of movement/(re)injury

The Dutch language version of the Tampa Scale for Kinesiophobia (TSK-DV) (Goubert et al., 2000) was used to measure fear of movement/(re)injury. The TSK-DV consists of 17 statements that have to be rated on a four-point scale (1 = strongly agree, 4 = strongly disagree). A total score was calculated after inversion of items 4, 8, 12, and 16 which are phrased in reversed key. The total score ranges from 17 to 68. The Dutch version of the TSK has been shown to be sufficiently reliable and valid (Goubert et al., 2004; Roelofs et al., 2007).

Pain catastrophizing

Pain catastrophizing was measured by the Dutch version of the Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995; Van Damme et al., 2002). Participants were requested to reflect on past painful experiences and to indicate the degree to which they experienced each of the thirteen thoughts or feelings when they were experiencing pain on a 5-point Likert scale (0 = not at all, 4 = all the time). The PCS-DV has been shown to be a highly reliable and valid (Van Damme et al., 2002).

The perceived harmfulness of daily activities

To measure the threat-value of daily activities, the Photograph Series of Daily Activities of the upper extremities (PHODA-UE) (Dubbers et al., 2003) was used. The PHODA-UE consists of 110 photographs from various daily activities. Patients indicate to what extent they perceive these daily activities to be harmful and/or threatening, focusing on patient's judgment about the consequences of certain movements. A "harm" thermometer, consisting of a vertical line anchored at the bottom with 0 (not harmful) and at the top with 100 (very harmful), was used to rate every picture according to the patients' perceived threat. A mean total score ranging from 0 to 100 was calculated as the sum of all ratings divided by 110. Five pictures (headlong fall, boxing against a punching bag, doing push-ups, hanging on a climbing frame and receive a Chinese burn) were added to provide baseline scores for the generalization tests. The PHODA has been used before in studies examining the effectiveness of exposure in patients with CRPS-I and pain-related fear (de Jong, Vlaeyen, Onghena, Goossens, et al., 2005; den Hollander et al., 2016).

Statistical analyses

For analyzing the data of the diary, randomization tests based on the random determination of the moments of phase change or intervention points to test a null hypothesis about treatment effects in single case experimental designs using the rationale of Edgington were conducted (Onghena & Edgington, 1994). Randomization tests have the advantage of being valid for single-case experiments without making distributional assumptions (Edgington & Onghena, 2007). In addition, they are easy to apply (Onghena & Edgington, 2005) and extremely versatile for even the most complex single-case designs (Onghena & Edgington, 2005; Persons & Silberschatz, 1998). The randomization tests in this study used the difference between means as (directional) test statistic. Replicated single-case experiments may be considered as multiple studies that can be combined using meta-analytical procedures. Because the replicated single-case experiments in this study provided independent tests of the same null hypothesis, the directional *P*-values of these tests were combined by calculating the sum of the *P*-values and comparing this sum with all other sums that arose under the general null hypothesis (if the null hypothesis is true, than the *P*-value is just a random draw from a uniform [0, 1]

distribution). A more detailed description of the randomization tests for single-case experimental designs can be found in Onghena and Edgington (2005).

Because exposure treatment was expected to be superior to baseline, the null hypothesis that there is no differential effect for any of the measurement times was tested using randomization tests on the differences between baseline and exposure treatment. While 6-months follow-up was expected to be superior to baseline, and not to change in relation to exposure treatment, differences between 6-months follow-up and baseline and 6-months follow-up and exposure in vivo were also tested using randomization tests. The analyses were performed using SCRT software (Bulté & Onghena, 2013; De, Michiels, Vlaeyen, & Onghena, 2017).

Effect sizes are calculated according to the ‘‘Non-overlap of All Pairs’’ (NAP) method (Parker & Vannest, 2009). NAP summarizes data overlap between each phase A data point and each phase B data point, in turn. A nonoverlapping pair will have a phase B data point larger than its paired baseline phase A data point. NAP equals the number of comparison pairs showing no overlap, divided by the total number of comparisons and can be obtained as the Area Under the Curve (AUC) percentage from a receiver operating characteristic analysis (Parker & Vannest, 2009). NAP is a probability score; results fall within a 0.50 to 0.1 scale, where 0.86 is considered a large effect and 0.50 is no effect. Statistically, it is similar to looking at the probability that a random score from an intervention will be improved over baseline. For deteriorating performance during treatment phase, one must take the extra step of specifying the Baseline phase as the high score in an AUC module (Parker & Vannest, 2009). By doing so, the AUC range is extended from 0 to 1. Any score from 0 to .4999 represents deteriorating performance.

We used the Leeds Reliable Change Indicator (RCI) to evaluate whether an individual's change on the non-daily measures (TSK, PHODA-UE, PCS and RASQ) is reliable and large enough to be regarded as important taking into account measurement error (Morley & Dowzer, 2014). For the RST, not enough information on the reliability of the measure was available to perform the RCI analyses. Therefore, we decided to formulate pre-set criteria to detect a clinically important change as the result of exposure. Based on the results of a previous single case study we estimated that a mean improvement of 50% could be considered as clinically relevant (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005).

Results

Eighteen patients were found eligible for this study and started treatment, but 10 patients dropped out due to various reasons. Of these, two patients declined participation to the study after initial inclusion, because they refused to terminate ongoing medical treatment. Four patients were excluded immediately after the psychological intake session because they still expressed pain-reduction to be their only treatment goal. Two patients dropped out during exposure treatment, of which heart problems were diagnosed in one patient and an escalating family conflict in the other. Finally, two patients were excluded at the end of exposure. Both patients had concealed their involvement in a litigation procedure at time of inclusion. Patients who dropped out from the study were replaced by new consecutive patients. Finally, eight patients were included in the study.

Patients randomized to the Multiple Exposure condition (N = 4) were all female with a mean age of 49.3 ± 5.6 (SD). Three patients suffered from CRPS-I in the dominant hand, and one in the non-dominant hand. Two patients presented with obvious limitations in active movements, visible by a deviating stand of the upper extremity in rest (claw-shaped fingers or hyper extension at inclusion). In the Repeated Exposure condition (N = 4), one patient was male and the other three were female. Their mean age was 39.5 ± 12.7 (SD). Three patients suffered from CRPS-I in the dominant hand and one in the non-dominant hand. In one patient there was a clear limitation of active movements at inclusion. At inclusion, the mean duration of the complaints was 3.5 years (range: 1.5 years – 8 years).

Generalization tests

At both generalization tests, all patients performed both activities regardless of treatment condition. An overview of the observed performance quality of the activities during both tests for all patients per condition is shown in Table 2 (standard activity: headlong fall) and Table 3 (specific activity).

During performance of the standard activity at the post-treatment test, the independent occupational therapist observed safety behavior in one patient from the Multiple Exposure condition (while performing the headlong fall, this patient flexed the elbow of the extremity diagnosed with CRPS-I in the wrist, putting more weight on the other arm). At 6-months follow-up no such behaviors were observed in any of the patients. The specific activities (hanging, boxing, Chinese burn and/or push-ups) were performed without observable safety behavior by all patients at both tests. Since all patients were willing to perform several new threatening activities at both generalization tests, irrespective of their assigned treatment condition, we conclude that the effect of exposure treatment generalizes to threatening activities to which patients were not exposed during treatment.

Mean perceived harmfulness scores (PHODA-UE) were high at baseline for the standard activity (headlong fall: Table 2) and the specific activity (Table 3). Just before performance of the post-treatment generalization test, the mean perceived harmfulness ratings were lower than at baseline for

both the standard activity and the specific activity, suggesting that extinction of pain-related fear indeed generalized towards new activities. During these tests, the experienced harmfulness was lower in the Repeated Exposure condition compared to the Multiple Exposure condition for both the standard activity and the specific activity. Particularly one patient in the Multiple Exposure condition still experienced falling forward as threatening, despite the observation that this patient performed the activity without safety behaviors. The mean score of the baseline-threat during the generalization test at 6 months follow-up decreased in the Repeated Exposure condition to almost 0 for both activities. For patients in this condition, no (partial) return of perceived harmfulness was observed at 6-months follow-up, not even for the specific activity that was not performed during treatment or post-test. By contrast, in the Multiple Exposure condition perceived harmfulness increased compared to generalization test 1 for both activities as compared to the Repeated Exposure condition, but all patients were still willing to perform both activities, and no safety behavior was observed.

Expectancy and credibility check

Mean expectancy- (Multiple Exposure: 7.8 ± 0.36 SD; Repeated Exposure: 7.1 ± 2.14 SD) and credibility ratings (Multiple Exposure: 6.6 ± 1.17 SD; Repeated Exposure: 7.7 ± 2.24 SD) were relatively high in both conditions, and higher as compared to a previous exposure in vivo study in CRPS-I patients (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005). Measurements at post-treatment showed a further increase of expectancy (Multiple Exposure: 8.2 ± 1.47 SD; Repeated Exposure: 9.4 ± 0.48 SD) and credibility ratings (Multiple Exposure: 8.0 ± 1.66 SD; Repeated Exposure: 9.2 ± 0.51 SD). The results imply that the differential effectiveness of both treatment conditions was not substantially influenced by differences in treatment expectancy and credibility.

Daily measures

Results of the randomization tests on the daily measures (fear of movement/(re)injury, pain-catastrophizing, pain experience and performance of three personally relevant activities) for each patient in both conditions are displayed in Table 4. For all patients in the Multiple Exposure condition, significant changes in fear of movement and pain catastrophizing were found post-treatment (all $p < 0.05$). Notably, in the Multiple Exposure condition all improvements remained until 6-months follow-up for each patient (all $p < 0.05$). In the Repeated Exposure condition, one patient showed significant changes in fear of movement/(re)injury and pain catastrophizing, both post-treatment (FOM $p < 0.05$; CAT $p = 0.04$) and at 6 months follow up (FOM $p = 0.04$; CAT $p = 0.04$) Another patient showed a significant change in pain catastrophizing between baseline and post-treatment ($p = 0.03$), but not at 6 months follow-up ($p = 1.00$).

With regard to personally relevant activities, three patients in the Multiple Exposure condition showed a significant change in all three activities post-treatment ($p < 0.05$), and these changes remained stable over the follow-up period ($p < 0.05$). In the fourth patient, only one activity showed a significant difference after treatment ($p < 0.05$), but not at follow-up ($p = 0.053$). In the Repeated Exposure condition, only one patient showed a significant change in all three activities after treatment ($p < 0.04$), and another patient in two activities ($p = 0.04$). At 6-months follow-up, two patients in the Repeated Exposure condition showed a significant change in all three activities ($p < 0.05$).

In line with previous findings (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005) significant decreases in patients' pain experiences were observed. In the Multiple Exposure condition a significant change was found for one patient directly after treatment ($p = 0.04$), and for three patients at 6-months follow-up ($p \leq 0.04$). In the Repeated exposure condition, only one patient reported a significant decrease in pain experience at 6-months follow-up ($p = 0.04$).

Table 4 also gives an overview of the NAP-scores on the diary data between baseline, post-treatment and 6-months follow-up for each patient in the Multiple and Repeated Exposure condition. In the Multiple Exposure Condition, large effect sizes (NAP scores ≥ 0.86) were found in all patients for the changes in fear of movement/(re)injury (NAP = 1.00) and pain catastrophizing (NAP = 1.00), both after treatment and at 6-months follow-up. In the Repeated Exposure condition, two patients showed large effects (NAP = 1.0) on fear of movement/(re)injury and pain-catastrophizing. One additional patient showed a large effect between baseline and post-treatment (NAP = 1.00), but deteriorated compared to baseline at follow-up (PCS: NAP = 0.04; TSK: NAP = 0.00). In the Multiple Exposure condition, patients reported large effects on all activities (NAP ≥ 0.89), except one patient who reported deteriorating performance in one activity (NAP = 0.42). At 6-months follow-up period, this patient shows a major change relative to baseline on this activity (NAP = 0.89). In the Repeated Exposure condition, personally relevant activities had a large effect in all the patients both immediately after the exposure and at 6-months follow-up (NAP ≥ 0.98). Most NAP-scores also showed a reliable change in pain experience in the Multiple Exposure condition (NAP ≥ 0.76), except for one patient post-treatment (NAP = 0.62) and for one patient at 6-months follow-up (NAP = 0.55). Pain intensity showed a large effect in one patient in the Repeated Exposure condition both post-treatment (NAP = 0.99) and at follow-up (NAP = 1.00), and for one patient a smaller effect was observed post-treatment (NAP = 0.70) compared to follow-up (NAP = 1.00). Two patients in this condition were constant in their pain-experience over time (NAP 0.50-0.54).

In conclusion, the randomization tests for all diary data between baseline and post-treatment, and baseline and 6-months follow-up, showed somewhat better results for all variables for patients in the

Multiple Exposure condition. NAP scores show large effects for personally relevant activities in both the Multiple Exposure condition and the Repeated Exposure condition, but for the variables fear of movement/(re)injury, pain catastrophizing and pain experience, larger effects can be observed in the Multiple Exposure condition.

When combined p-values per condition are calculated, only in the Multiple Exposure condition fear of movement/(re)injury (TSK pre-post: $p < 0.01$, pre-FU: $p < 0.01$), pain catastrophizing (PCS pre-post: $p < 0.01$, pre-FU: $p < 0.01$) and pain experience (pre-post: $p = 0.03$, pre-FU: $p < 0.01$) are significantly reduced, between baseline and post-treatment as well as between baseline and 6-months follow-up. The meta-analytical procedure shows that, regardless of condition and timespan (pre-post treatment or pretreatment-follow-up), significant changes occurred in the performance of personally relevant activities (Multiple Exposure: pre-post: $p < 0.01$, pre-FU: $p < 0.01$; Repeated Exposure: pre-post: $p < 0.01$, pre-FU: $p < 0.01$).

Observation of functional disability

Table 6 displays the results of the Radboud Skills Test (RST). At baseline, the independent occupational therapist observed more restrictions in the performance of ten daily life activities in patients in the Multiple Exposure condition, than in patients in the Repeated Exposure condition. After treatment, the observation scores decreased in both conditions, indicating less restrictions in performance, although a minor decline was observed 6 months follow-up. This decrease was of the same size for both conditions and clinically relevant according to the pre-set criteria (> 50%). At baseline, patients in the Multiple Exposure condition rated the standardized activities as more difficult than patients in the Repeated Exposure condition, although perceived difficulty was generally low. After treatment, patients in both conditions evaluated the standardized activities of the RST as less difficult compared to baseline. The change in mean difficulty scores was comparable over conditions and changes remained until 6 months follow-up.

Self-reported functional disability

Based on the mean item score on the RASQ at baseline, patients in the Multiple Exposure condition reported to be more disabled than patients in the Repeated Exposure condition (Table 7). After treatment, the mean item score in both conditions showed a clear reduction of the reported disabilities, and these changes appear to maintain until 6 months follow-up. The results of the Leeds RCI (Figure 3) show a reliable change both from baseline to post-treatment and from baseline to 6 months follow-up, in all patients except one; this patient from the Repeated Exposure condition did not maintain the reliable change until 6-months follow-up.

Fear of movement/(re)injury

Table 8 displays the mean TSK-score at baseline, post-treatment and 6-months follow-up for patients in both conditions. Baseline mean scores were comparable for both conditions. Pain-related fear decreased post-treatment in both conditions, and remained constant over the follow-up period. The Leeds RCI (Figure 3) shows a reliable change from baseline to post-treatment in every patient, independent of condition. Between baseline and 6-months follow-up, no reliable change in TSK scores occurred for one patient in the Multiple Exposure condition, and for one patient in the Repeated Exposure condition.

Pain catastrophizing

The mean PSC-scores (Table 8) were comparable at baseline for both conditions. At post-treatment, pain catastrophizing decreased in both conditions. At 6-months follow-up, the mean PCS-score in the Multiple Exposure condition decreased a little further and the Repeated Exposure condition showed an increase in pain catastrophizing compared to post-test. The results of the Leeds RCI (Figure 3), indicate no reliable change in the Multiple Exposure condition for one patient between baseline and post treatment, and for another patient between baseline and 6-months follow-up, and in the Repeated Exposure condition for one patient between pre-treatment and 6-months follow-up.

The perceived harmfulness of daily activities

The results of the PHODA-UE are summarized in Table 8. At baseline, the mean total scores are comparable for both conditions. Both conditions reported a substantial reduction of the perceived harmfulness of activities after treatment, and these scores remained stable until 6-months follow-up. The Leeds RCI shows that all changes on the PHODA-UE are reliable, both from baseline to post-treatment, as from baseline to follow-up (Figure 3). Given that the PHODA consisted of 110 photographs, and that in both conditions, patients were not exposed to all these activities, it might be concluded that in both conditions, extinction of pain-related fear generalized well to activities not performed during exposure treatment.

Discussion

This study was designed to test the hypothesis that exposure treatment to multiple daily life activities promotes generalization of extinction to new threatening activities in patients with CRPS-I reporting pain-related fear. Two variants of exposure treatment were compared; one during which patients were exposed once to at least 15 different activities (Multiple Exposure condition), and one during which patients were exposed to 3 activities only, 5 sessions each (Repeated Exposure condition).

The results of this preliminary study with eight patients can be summarized as follows: *first*, contrary to our hypothesis, all participants performed several new threatening activities (e.g. falling forward,

doing push-ups, receive a Chinese burn, boxing) during both generalization tests equally well, irrespective of treatment condition. Those activities were not addressed during treatment, indicating successful generalization of extinction of pain-related fear to a new activity (CS) after exposure treatment. *Second*, both conditions showed significant improvements in the performance of personally relevant activities, based on effect-sizes as well as meta-analytical procedures over the daily measures. From the diaries, exposure to multiple stimuli seems to be preferred over repeated exposure to favorably change fear of movement and pain catastrophizing, both immediately after exposure treatment and at 6-months follow-up. Indeed, when individual p-values are combined in a meta-analysis, exposure to multiple stimuli significantly reduced fear of movement and pain-catastrophizing, whereas repeated exposure did not. *Third*, all patients reported a reliable change on the standardized questionnaires in functional disability, fear of movement, and perceived harmfulness of daily activities post-treatment, and most patients (all except one) in pain-catastrophizing. At 6-months follow-up, one patient in each condition no longer showed a reliable change compared to baseline on fear of movement and pain-catastrophizing, as well as one patient in the repeated exposure condition for functional disabilities. *Finally*, and although exposure treatment is not primary directed towards pain itself, reported pain intensity decreased for all patients who were exposed to multiple activities, despite increased engagement in various physical activities. In the repeated exposure condition, 50% of the patients reported a significant decrease in reported pain intensity. Additionally, meta-analytical procedures showed that a significant decrease in the reported pain intensity was found in the Multiple Exposure condition, where patients were exposed to a broad variety of activities.

Based on the current findings, we conclude that after exposure treatment, patients perform new threatening activities as well as personally relevant activities, regardless if they were exposed to many different or only a few activities. Nevertheless, exposure to multiple stimuli seems preferable over exposure to repeated stimuli, to positively change fear of movement, pain-catastrophizing and pain intensity. We will first compare our findings with previous experimental studies on generalization, and then provide possible explanations for these preliminary findings.

Four previous experimental studies have investigated whether exposure to different movements enhanced generalization of extinction of pain-related fear in chronic low back pain patients (Crombez et al., 2002; Goubert, Crombez, & Lysens, 2005; Goubert et al., 2002; Trost et al., 2008). Only Trost et al. (2008) showed successful generalization of pain-expectancy corrections: during four similar movements of increasing intensity, patients corrected their pain-expectancy ratings from one movement to another. The other studies provided no support for the hypothesis that varied exposure

facilitates generalization of extinction. Several differences with the aforementioned studies provide possible explanations why we found generalization regardless of exposure condition.

First, exposure was provided as a treatment instead of an experimental test, which induces a difference in patients' expectancies. Patients who actively seek improvement of their health condition, as our sample, might be more open to experience a mismatch between what they expect (harm) and what they experience (the activity could be performed without harm, despite pain), and such a prediction error is crucial for inhibitory learning (Craske et al., 2008). *Second*, the experimental studies tested whether extinction of pain-related fear for a simple movement (e.g., bending forward, straight leg rising) generalized towards another dissimilar movement. In the current study, patients were exposed to functional, individually tailored activities (e.g., gardening, vacuum cleaning, golfing). Patients might be more motivated to perform relevant daily activities since these provide reward, and this is particularly relevant since the activities might also be painful (e.g. Claes et al. 2014). *Third*, patients might consider the absence of an aversive outcome as an "exception to the rule" originally learned during fear acquisition (the assumption that movements hurt or harm). Repeated disconfirmatory evidence is required to correct these harm-expectancies, and the current research shows that in the experimental studies, not enough repetitions might have been provided to serve as disconfirmatory evidence. *Fourth*, since pain-related fear is a general, overarching construct, encompassing various predictors (CSs) for various feared outcomes (USs), patients do not only learn to correct harm-expectancies over the course of treatment. Additional experiences with different pain intensities as well as other physiological symptoms of CRPS-I can be conceived as interoceptive exposure, which is also to result in new inhibitory learning. Variations in pain intensity will cause variations in pain-related fear during exposure; research has shown that inhibitory associations are strengthened and return of fear is less likely when different fear levels have been reported during treatment (Kircanski et al., 2012). *Fifth*, exposure was provided to a wide spectrum of contexts and natural settings that can be achieved in and around the hospital setting. Generalization of extinction is facilitated when participants are exposed to the conditioned stimuli in a variety of daily life contexts (Rowe & Craske, 1998). Despite that generalization tests consisted of activities that differed in terms of content (the test-activities were not addressed during exposure), physical environment (the activity was provided in a room that was not used during exposure), social environment (presence of an independent observer, instead of the therapists), and time (at post-treatment and at 6-months follow-up), all patient performed the activities.

We found some differences between both exposure conditions. Strategies to maximize inhibitory learning in order to prevent relapse have been described (Craske et al., 2008). One of the mechanisms described is contextual variation during exposure treatment, and another is to maximize the mismatch

between expectation and actual experience during exposure. Because of larger variation, we hypothesized that exposure to multiple activities would be more successful to counter renewal during the generalization test. Unexpectedly, patients from both conditions performed all requested activities. Nevertheless, in the long run, it seems that exposure to multiple stimuli is to be preferred since patients receiving this condition seem to better retain their improvements in pain-related fear measures. A possible explanation might be in differences in the prediction error, which might have been more pronounced in the multiple exposure condition. All selected activities in both conditions were scored 50 or higher on the PHODA, so it seems likely that patients exposed to many different activities repeatedly experienced a prediction error more often than patients who were exposed to the same activities several times. The latter might have been less surprised that no harm occurs after being exposed to the same activity on several occasions. Another and additional explanation might be that multiple exposures connect inhibition or safety with more "elements" of the exposure stimuli that might be in common with the new generalization stimuli, thereby creating stronger generalization.

The current study has several strengths. First, whereas previous studies evaluated generalization in an experimental setting, the current study evaluates generalization of extinction in patients with pain-related fear after exposure treatment. Studies on generalization of extinction after exposure treatment are scarce (but for a study in spider phobia see Preusser et al., 2017), and we are not aware of any other study on this subject in pain-related fear. Second, since fear serves as a motivator for avoidance behavior, it is intuitive to assume that after extinction of fear, avoidance behavior will automatically be refrained from (Vervliet & Indekeu, 2015). However, an experimental study showed that avoidance behavior can persist irrespective of fear-extinction in rats (Bravo-Rivera, Roman-Ortiz, Montesinos-Cartagena, & Quirk, 2015). In humans, especially avoidance behavior with reduced costs may persist and maintain anxiety in the long run (Vervliet & Indekeu, 2015). Therefore, a strength of the current study is that not only measures of fear extinction were included, but also a measure of behavioral performance (generalization tests). Third, the use of a repeated single case experimental design, analyzed with randomization tests and meta-analytic procedures, as well as the additional use of NAP (Parker & Vannest, 2009) as effect-size, and the Leeds Reliable Change Index (Morley & Dowzer, 2014) to measure reliable change, enabled us to compare both variations of exposure, and to check whether results are comparable with a previous SCEDs in CRPS-I (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005).

Some limitations and weaknesses should be mentioned as well. First, it would have been valuable to collect additional behavioral data such as latency time to starting the movement, avoidance of starting etc. Adding these measures in future replications of the current study would certainly help to detect

more subtle differences between conditions, which might have been missed in the current way of observing the performance of the generalization test. A second limitation of the study is that we used a cut-off score for inclusion that was based on the TSK distribution in individuals with chronic low back pain (CLBP). Although this may threaten the internal validity of our study, the clinical utility of TSK in CRPS-I seems supported by Bean et al. (2014) showing that CRPS patients and patients with chronic low back pain had remarkably similar scores on TSK. In future studies, PHODA (PHOtograph series of Daily Activities; Leeuw et al., 2007) might be a preferred instrument to select patients for exposure treatment. A later study from our group (de Jong et al., 2011) revealed that PHODA was superior in identifying highly fearful patients with CRPS-I than TSK. In the current study, the mean pre-treatment PHODA scores were >50, indicating that we included a sufficiently fearful group of CRPS-I patients. Third, we used a diary from a previous study (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005), which did not include specific questions to measure generalization. It would have been interesting to measure the perceived harmfulness and willingness to perform some of the activities that would be used for the generalization test. Exposure treatment, as delivered in this study, consisted of 15 sessions; daily measures would have enabled us to evaluate at what point in treatment patients change the threat value of activities they have not performed yet, or from when they would be willing to perform such activities. Fourth, even though we measured performance during the generalization test, it is still questionable if this test has ecological validity to mimic avoidance behavior in daily life situations. If avoidance or approach behavior is prioritized depends on a complex interplay of stimuli (Claes, Crombez, & Vlaeyen, 2015; Vlaeyen, Morley, & Crombez, 2016). The presence of the observer might increase motivation to perform activities, that would probably be absent in a real-life context. Additionally, the test was performed in the same clinical setting as exposure treatment (although in another room that was never used during exposure treatment), and not in the patients' home or work situation. A more prominent switch in "contexts" could have contributed to renewal. Even though we studied generalization after exposure treatment as it is clinically delivered, the generalization test might still be an invalid context for performance in real life situations. Finally, another limitation of the study is that we cannot generalize the current findings to other chronic pain syndromes, as we only included adult patients with CRPS-I. It would be helpful to extend the current study question towards adults with other pain diagnoses and children with chronic pain.

Concluding, the current findings suggest that irrespective of exposure treatment condition (multiple versus repeated activities), extinction of pain-related fear generalized to the performance of new activities that were not addressed during treatment, and that patients considered to be harmful before the start of treatment. Both exposure treatments had favorable effects on self-reported functional disability, pain-related fear, pain catastrophizing, perceived harmfulness of daily activities and

experienced pain. Generalization of extinction appears facilitated when participants are exposed to a variety of individually tailored threatening activities, to experience optimal mismatches between what they expect (harm, increased or unbearable pain) and actually experience during exposure ("I can do this without injuring my body"). Our study provides clinical evidence that exposure treatment may mediate generalization of extinction across different fear-evoking stimuli, irrespective of whether a multiple or a repeated exposure was offered. Both forms of exposure showed favorable results, with the multiple exposure outperforming the other one on a number of outcome variables, including pain report. Nevertheless, an experimental demonstration of superiority of one form of exposure over another in order to maximize generalization of extinction of pain-related fear remains more than welcome. One possibility would be to make the generalization test more stringent. Rather than exposing participants to novel activities in the same context (the hospital), as done in the current study a better test would be to present these novel activities in novel contexts as well (home or job context). Our prediction would be that the multiple exposure condition would not only outperform the repeated exposure on extinction of pain-related fear, but also on the generalization of pain-related fear towards novel contexts.

References

Arrindell, W. A., & Ettema, J. H. M. (1986). *SCL-90: Manual for a multi-dimensional psychopathology indicator.* Lisse: Swets & Zeitlinger.

Bean, D. J., Johnson, M. H., & Kydd, R. R. (2014). Relationships between psychological factors, pain, and disability in complex regional pain syndrome and low back pain. *Clin J Pain, 30*(8), 647-653. doi:10.1097/AJP.0000000000000007

Borkovec, T. D., & Nau, S. D. (1972). Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry, 3*(4), 257-260. doi: https://doi.org/10.1016/0005-7916(72)90045-6

Bouton, M. E., & King, D. A. (1983). Contextual control of the extinction of conditioned fear: tests for the associative value of the context. *J Exp Psychol Anim Behav Process, 9*(3), 248-265.

Bouton, M. E., & Ricker, S. T. (1994). Renewal of extinguished responding in a second context. *Animal Learning & Behavior, 22*, 317-324. doi: https://doi.org/10.3758/BF03209840

Bravo-Rivera, C., Roman-Ortiz, C., Montesinos-Cartagena, M., & Quirk, G. J. (2015). Persistent active avoidance correlates with activity in prelimbic cortex and ventral striatum. *Front Behav Neurosci, 9*, 184. doi: 10.3389/fnbeh.2015.00184

Bulté, I., & Onghena, P. (2013). The single-case data analysis package: Analysing single-case experiments with R software. *Journal of Modern Applied Statistical Methods, 12*(2), 450–478. doi: 10.22237/jmasm/1383280020

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014). Competing goals attenuate avoidance behavior in the context of pain. *J Pain, 15*(11), 1120-1129. doi:10.1016/j.jpain.2014.08.003

Claes, N., Crombez, G., & Vlaeyen, J. W. (2015). Pain-avoidance versus reward-seeking: an experimental investigation. *Pain, 156*(8), 1449-1457.

Craske, M., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behav Res Ther, 46*(1), 5-27. doi: 10.1016/j.brat.2007.10.003

Craske, M., Treanor, M., Conway, C., Zbozinek, T., & Vervliet, B (2014). Maximizing exposure therapy: an inhibitory learning approach. *Behav Res Ther 58*, 10-23.

Crombez, G., Eccleston, C., Vlaeyen, J., Vansteenwegen, D., Lysens, R., & Eelen, P. (2002). Exposure to physical movements in low back pain patients: restricted effects of generalization. *Health Psychol, 21*(6), 573-578.

Crombez, G., Vlaeyen, J., Heuts, P., & Lysens, R. (1999). Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain, 80*(1-2), 329-339.

Cup, E. H., van de Ven-Stevens, L., & Corstens-Mignot, M. (1999). Radboud Skills Test (RST): A specific disease-related functional hand-test for patients with Complex Regional Pain Syndrom type 1 of one upper extremity (translated from Dutch). *Nederlands Tijdschrift voor Ergotherapie, 27*, 152-156.

de Boer, I., van Drie-Verschoor, P., Huijmans, A., Corstens-Mignot, M., Cup, E. H., & Berendsen, E. (2001). Intra- and interrater reliability of the Radboud Skills Test (translated from Dutch). *Nederlands Tijdschrift voor Ergotherapie, 29*, 15-19.

de Jong, J. R., Vangronsveld, K., Peters, M. L., Goossens, M. E., Onghena, P., Bulte, I., & Vlaeyen, J. (2008). Reduction of pain-related fear and disability in post-traumatic neck pain: a replicated single-case experimental study of exposure in vivo. *J Pain, 9*(12), 1123-1134. doi: 10.1016/j.jpain.2008.06.015

de Jong, J. R., Vlaeyen, J., Onghena, P., Cuypers, C., den Hollander, M., & Ruijgrok, J. (2005). Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. *Pain, 116*(3), 264-275. doi: 10.1016/j.pain.2005.04.019

de Jong, J. R., Vlaeyen, J., Onghena, P., Goossens, M. E., Geilen, M., & Mulder, H. (2005). Fear of movement/(re)injury in chronic low back pain: education or exposure in vivo as mediator to fear reduction? *Clin J Pain, 21*(1), 9-17; discussion 69-72.

de Jong, J. R., Vlaeyen, J., van Eijsden, M., Loo, C., & Onghena, P. (2012). Reduction of pain-related fear and increased function and participation in work-related upper extremity pain (WRUEP): effects of exposure in vivo. *Pain, 153*(10), 2109-2118. doi: 10.1016/j.pain.2012.07.001

De, T. K., Michiels, B., Vlaeyen, J. W., & Onghena, P. (2017). Shiny SCDA [Computer software].

den Hollander, M., Goossens, M., de Jong, J., Ruijgrok, J., Oosterhof, J., Onghena, P., . . . Vlaeyen, J. (2016). Expose or protect? A randomized controlled trial of exposure in vivo vs pain-contingent treatment as usual in patients with complex regional pain syndrome type 1. *Pain, 157*(10), 2318-2329. doi: 10.1097/j.pain.0000000000000651

Dubbers, A. T., Vikström, M. H., & de Jong, J. R. (2003). The Photograph series of Daily Activities (PHODA-UE): cervical spine and shoulder. Heerlen/Maastricht, the Netherlands: Zuyd University, Institute for Rehabilitation Research (iRv), Maastricht University.

Edgington, E. S., & Onghena, P. (2007). *Randomization Tests* (4 ed.). Boca Raton: Chapman & Hall/CRC, Taylor & Francis Group.

Ferron, J., & Sentovich, C. (2002). Statistical Power of Randomization Tests Used with Multiple-Baseline Designs. *The Journal of Experimental Education, 70*(2), 165-178. doi: 10.1080/00220970209599504

Goubert, L., Crombez, G., & Lysens, R. (2005). Effects of varied-stimulus exposure on overpredictions of pain and behavioural performance in low back pain patients. *Behav Res Ther, 43*(10), 1347-1361. doi: 10.1016/j.brat.2004.10.006

Goubert, L., Crombez, G., Van Damme, S., Vlaeyen, J., Bijttebier, P., & Roelofs, J. (2004). Confirmatory factor analysis of the Tampa Scale for Kinesiophobia: invariant two-factor model across low back pain patients and fibromyalgia patients. *Clin J Pain, 20*(2), 103-110.

Goubert, L., Crombez, G., Vlaeyen, J., Van Damme, S., Van den Broeck, A., & Van Houdenhove, B. (2000). The Tampa Scale for Kinesiophobia: Psychometric characteristics and standardization (translated from Dutch). *Gedrag en Gezondheid, 28*, 54-62.

Goubert, L., Francken, G., Crombez, G., Vansteenwegen, D., & Lysens, R. (2002). Exposure to physical movement in chronic back pain patients: no evidence for generalization across different movements. *Behav Res Ther, 40*(4), 415-429.

Jensen, J. N., Karpatschof, B., Labriola, M., & Albertsen, K. (2010). Do fear-avoidance beliefs play a role on the association between low back pain and sickness absence? A prospective cohort study among female health care workers. *J Occup Environ Med, 52*(1), 85-90. doi: 10.1097/JOM.0b013e3181c95b9e

Kircanski, K., Mortazavi, A., Castriotta, N., Baker, A. S., Mystkowski, J. L., Yi, R., & Craske, M. G. (2012). Challenges to the traditional exposure paradigm: variability in exposure therapy for contamination fears. *J Behav Ther Exp Psychiatry, 43*(2), 745-751. doi: 10.1016/j.jbtep.2011.10.010

Leeuw, M., Goossens, M. E., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. (2007). The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med, 30*(1), 77-94. doi: 10.1007/s10865-006-9085-0

Leeuw, M., Goossens, M. E., van Breukelen, G. J., de Jong, J. R., Heuts, P. H., Smeets, R. J., . . . Vlaeyen, J. (2008). Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain, 138*(1), 192-207. doi: 10.1016/j.pain.2007.12.009

Linton, S. J., Boersma, K., Jansson, M., Overmeer, T., Lindblom, K., & Vlaeyen, J. (2008). A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. *Eur J Pain, 12*(6), 722-730. doi: 10.1016/j.ejpain.2007.11.001

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behav Res Ther, 43*(11), 1391-1424. doi: 10.1016/j.brat.2004.10.007

May, M., Junghaenel, D. U., Ono, M., Stone, A. A., & Schneider, S. (2018). Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. *J Pain, 19*(7), 699-716. doi:10.1016/j.jpain.2018.01.006

Mersky, H., & Bogduk, N. (Eds.). (1994). *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms* (2 ed.). Seattle, WA: IASP Press.

Meulders, A., Boddez, Y., Blanco, F., Van Den Houte, M., & Vlaeyen, J. (2018). Reduced Selective Learning in Fibromyalgia Patients Versus Healthy Controls. *Pain*. doi: 10.1097/j.pain.0000000000001207

Meulders, A., Jans, A., & Vlaeyen, J. (2015). Differences in pain-related fear acquisition and generalization: an experimental study comparing patients with fibromyalgia and healthy controls. *Pain 156*(1), 108-122.

Meulders, A., Vandael, K., & Vlaeyen, J. (2017). Generalization of Pain-Related Fear Based on Conceptual Knowledge. *Behav Ther, 48*(3), 295-310. doi: 10.1016/j.beth.2016.11.014

Meulders, A., Vansteenwegen, D., & Vlaeyen, J. (2011). The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. *Pain, 152*(11), 2460-2469. doi: 10.1016/j.pain.2011.05.015

Miller, R. P., Kori, S. H., & Todd, D. D. (1991). The Tampa Scale.

Morley, S., & Dowzer, C. N. (2014). Manual for the Leeds Reliable Change Indicator: Simple Excel® applications for the analysis of individual patient and group data. Retrieved from: http://medhealth.leeds.ac.uk/info/618/clinical_psychology_dclinpsychol/797/leeds_reliable_change_index

Oerlemans, H. M., Cup, E. H., DeBoo, T., Goris, R. J., & Oostendorp, R. A. (2000). The Radboud skills questionnaire: construction and reliability in patients with reflex sympathetic dystrophy of one upper extremity. *Disabil Rehabil, 22*(5), 233-245.

Onghena, P., & Edgington, E. S. (1994). Randomization tests for restricted alternating treatments designs. *Behav Res Ther, 32*(7), 783-786.

Onghena, P., & Edgington, E. S. (2005). Customization of pain treatments: single-case design and analysis. *Clin J Pain, 21*(1), 56-68; discussion 69-72.

Parker, R. I., & Vannest, K. (2009). An improved effect size for single-case research: nonoverlap of all pairs. *Behav Ther, 40*(4), 357-367. doi: 10.1016/j.beth.2008.10.006

Persons, J. B., & Silberschatz, G. (1998). Are results of randomized controlled trials useful to psychotherapists? *J Consult Clin Psychol, 66*(1), 126-135.

Roelofs, J., Goubert, L., Peters, M. L., Vlaeyen, J. W., & Crombez, G. . (2004). The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. *Eur J Pain, 8*(5), 495-502.

Roelofs, J., Sluiter, J. K., Frings-Dresen, M. H., Goossens, M., Thibault, P., Boersma, K., & Vlaeyen, J. W. (2007). Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain, 131*(1-2), 181-190. doi: 10.1016/j.pain.2007.01.008

Rowe, M. K., & Craske, M. G. (1998). Effects of varied-stimulus exposure training on fear reduction and return of fear. *Behav Res Ther, 36*(7-8), 719-734.

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment, 7*(4), 524-532.

Trost, Z., France, C. R., & Thomas, J. S. (2008). Exposure to movement in chronic back pain: evidence of successful generalization across a reaching task. *Pain, 137*(1), 26-33. doi: 10.1016/j.pain.2007.08.005

Turk, D. C., & Wilson, H. D. (2010). Fear of Pain as a Prognostic Factor in Chronic Pain: Conceptual Models, Assessment, and Treatment Implications. *Current Pain and Headache Reports, 14*(2), 88-95. doi: 10.1007/s11916-010-0094-x

Van Damme, S., Crombez, G., Bijttebier, P., Goubert, L., & Van Houdenhove, B. (2002). A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain, 96*(3), 319-324.

van Vliet, C. M., Meulders, A., Vancleef, L. M. G., & Vlaeyen, J. W. S. (2018). The Opportunity to Avoid Pain May Paradoxically Increase Fear. *J Pain, 19*(10), 1222-1230. doi:10.1016/j.jpain.2018.05.003

Vervliet, B., & Indekeu, E. (2015). Low-Cost Avoidance Behaviors are Resistant to Fear Extinction in Humans. *Front Behav Neurosci, 9*, 351. doi: 10.3389/fnbeh.2015.00351

Vlaeyen, J. (2015). Learning to predict and control harmful events: chronic pain and conditioning. *Pain, 156 Supplement 1:S86-S93*.

Vlaeyen, J., de Jong, J., Leeuw, M., & Crombez, G. (2004). Fear reduction in chronic pain; Graded exposure *in vivo* with behavioral experiments. In G. Asmundson, J. Vlaeyen & G. Crombez (Eds.), *Understanding and treating fear of pain* (pp. 313-343). Oxford: University Press.

Vlaeyen, J., & Linton, S. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain, 85*(3), 317-332.

Vlaeyen, J., & Linton, S. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain, 153*(6), 1144-1147.

Vlaeyen, J., Crombez, G., & Linton, S. (2016). The fear-avoidance model of pain. *Pain 157*(8), 1588-1589.

Vlaeyen, J., Morley, S., & Crombez, G. (2016). The experimental analysis of the interruptive, interfering, and identity-distorting effects of chronic pain. *Behav Res Ther, 86*, 23-34. doi: 10.1016/j.brat.2016.08.016

Vlaeyen, J., Morley, S., Linton, S. J., Boersma, K., & de Jong, J. R. (2012). *Pain-Related Fear: Exposure-Based Treatment for Chronic Pain*: IASP Press.

Wicking, M., Steiger, F., Nees, F., Diener, S. J., Grimm, O., Ruttorf, M., . . . Flor, H. (2016). Deficient fear extinction memory in posttraumatic stress disorder. *Neurobiol Learn Mem, 136*, 116-126. doi: 10.1016/j.nlm.2016.09.016

Woods, M. P., & Asmundson, G. J. G. (2008). Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: A randomized controlled clinical trial. *Pain, 136*(3), 271-280.

Zale, E., Lange, K., Fields, S., & Ditre J. (2013). The relation between pain-related fear and disability: a meta-analysis. *J Pain 14*(10), 1019-1030.