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Perspective

Exposure in Vivo as a Treatment Approach to Target Pain-Related Fear: Theory and New Insights From Research and Clinical Practice

Marlies den Hollander, PhD[1,2*], Rob J.E.M. Smeets, MD, PhD[2,3], Thijs van Meulenbroek, PT, PhD[1,2], Charlotte C.M. van Laake-Geelen, MD[1,2], Vera A. Baadjou, MD, PhD[1,2,†], Inge Timmers, PhD[2,†]

[1]Adelante Centre of Expertise in Rehabilitation and Audiology, Maastricht, the Netherlands
[2]Department of Rehabilitation Medicine, Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands
[3]CIR Revalidatie, location Eindhoven, the Netherlands

*Address all correspondence to Dr den Hollander at: marlies.denhollander@maastrichtuniversity.nl
†Denotes shared last authorship.

Abstract

Pain-related fear (PRF) can be a significant factor contributing to the development and maintenance of pain-related disability in individuals with persistent pain. One treatment approach to target PRF and related avoidance behavior is exposure in vivo (EXP). EXP has a long history in the field of anxiety, a field that is constantly evolving. This Perspective outlines recent theoretical advancements and how they apply to EXP for PRF, including suggestions for how to optimize inhibitory learning during EXP; reviews mechanistic work from neuroimaging supporting the targeting of PRF in people with chronic pain; and focuses on clinical applications of EXP for PRF, as EXP is moving into new directions regarding who is receiving EXP (eg, EXP in chronic secondary pain) and how treatment is provided (EXP in primary care with a crucial role for physical therapists). Considerations are provided regarding challenges, remaining questions, and promising future perspectives.

Impact. For patients with chronic pain who have elevated pain-related fear (PRF), exposure is the treatment of choice. This Perspective highlights the inhibitory learning approach, summarizes mechanistic work from experimental psychology and neuroimaging regarding PRF in chronic pain, and describes possible clinical applications of EXP in chronic secondary pain as well as in primary care.

Keywords: Chronic Secondary Pain, Exposure, Inhibitory Learning, Pain Neuroscience, Pain-Related Fear

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Introduction

Pain is inherently an emotional experience.[1] Persistent pain can be distinguished in chronic primary pain (ie, pain persisting for more than 3 months, associated with significant emotional distress and/or functional disability, and not better accounted for by another condition) and chronic secondary pain (ie, pain that may, at least initially, be conceived as a symptom secondary to an underlying disease).[2,3] Regardless of type of pain, a subset of individuals with chronic pain present with elevated levels of pain-related fear (PRF). There is a solid scientific base, supported by clinical experience, showing that PRF is an important factor in developing and maintaining disability. In fact, PRF contributes more to pain-related disability than pain intensity does[4,5] and hence should be an important therapeutic target. The fear avoidance model explains how patients with PRF may become trapped in a vicious circle of pain, worrying, fear, and avoidance behavior.[6,7] A treatment approach with a long history in a variety of anxiety-related problems is exposure in vivo (EXP). This approach, originally referred to as graded exposure, was adapted to target avoidance behavior in patients with PRF. Single-case experimental designs showed reductions in fear and disability in chronic low back pain,[8,9] work-related upper extremity pain,[10] and whiplash-associated disorders.[11] Its effectiveness has further been supported by randomized controlled trials[12–15] and extended to other diagnoses, such as complex regional pain syndrome type-I.[16] EXP is also suitable for youth with PRF and their parents[17–19] and is cost-effective compared with usual care.[20,21]

Since the early work in the late 1990s to early 2000s, there have been major advances in our understanding and applications of EXP. For instance, we have moved towards an inhibitory learning approach rather than a graded exposure approach. EXP is now applied more widely in a variety of clinical settings and other pain types. In addition, there has been more mechanistic work (eg, experimental psychology, neuroimaging) regarding (targeting of) fears in chronic pain. Here, we provide an overview of recent advances in theoretical understanding, research, and clinical applications of EXP. We focus on PRF and EXP for movements and activities (although many aspects may apply to EXP for pain sensations or other pain-related cues as well). These findings are relevant for clinicians, specifically those (interested in) working on improving functioning (ie, centered around movements and activities) in individuals with chronic pain.

An Inhibitory Learning Approach to Target Fears

Historically, the emotional processing theory provided the theoretical base for EXP,[22] stating that confrontation with a feared stimulus (conditioned stimulus [CS]; eg, movements, activities, or sensations) activates memories (unconditioned stimulus [US] representations; eg, harm or inability) and physiological reactions (conditioned responses [CRs]; eg, fear). Repeated confrontation with a feared stimulus was thought to result in a decrease of the CR through habituation, the long-presumed underlying mechanism of EXP. Consistent with this theory, former protocols of EXP for PRF aimed to reduce disability through the reduction of PRF in a gradual manner.

In the last 2 decades, insights from the field of anxiety-related disorders brought major advances in understanding how EXP works and how it should be optimized. It became clear that fear reduction during EXP is not a reliable indicator of learning,[23,24] and hence focusing on decreasing fear levels is no longer recommended. Instead, EXP is currently regarded as a method to dispute negative, fearful expectancies by establishing disconfirmation (mismatch) between the expectancy and the actual experience (ie, expectancy violation),[25] therewith decreasing learned responses such as avoidance behavior. The process of learning these new associations (ie, CSs that are not followed by US; resulting in new CS-non-US [CS-noUS] associations) is called inhibitory learning.[26] Specifically, this inhibitory learning mechanism may be hampered in anxious patients,[27] which may explain why some patients do not respond well to EXP. In patients with chronic pain, there is also support for alterations in classical conditioning (ie, associative learning) similar to those seen in anxiety-related disorders, including impaired safety learning and excessive generalization of fear.[28,29] Such alterations may not only contribute to acquisition and generalization of PRF, but reversely, elevated levels of PRF may also subsequently hamper extinction learning.

To compensate for potential learning deficits and to neutralize return of fear after EXP, suggestions to optimize inhibitory learning have been proposed.[25,30] These suggestions are also relevant to the area of PRF, and most can be easily integrated into treatment. We will provide some recommendations on how to provide EXP for PRF according to these new insights from the general field of anxiety disorders. A critical note here is that the number of studies in PRF evaluating providing EXP after inhibitory learning is still scarce. First, there is evidence that the more pronounced the mismatch between expectancy and actual outcome, the stronger the inhibitory learning of the CS-noUS association is, varying levels of fear during extinction learning predict lower fear at retest,[31] and arousal enhances the storage of memory.[32] Therefore, strictly following a fear hierarchy (ie, “graded” exposure) is suboptimal, and behavioral experiments (ie, testing the validity of negative and alternative thoughts for movements/activities in real-life situations) should be as “extreme” as possible (yet feasible) to maximize the mismatch. Second, because the expectancy-outcome mismatch is crucial for learning CS-noUS associations, techniques that potentially decrease the “surprise value” of the mismatch should be avoided. Therefore, we abandoned the formulation of alternative thoughts or modeling the activity by the therapist. All preexposure attempts to make the CS less aversive before the actual exposure should be refrained from. Third, retrieval cues (eg, a picture taken during a successful EXP session) or the instruction to mentally reinstate the exposure context in case of return of fear facilitates extinction learning, as does performing EXP in multiple contexts,[33] and with a variety of fear levels (instead of following a fear hierarchy) and durations. Fourth, the associative inhibitory processes are strengthened by affect labeling (ie, verbalizing the current emotional experience). In spider phobia, greater use of anxiety and fear words was associated with greater reductions in fear responding.[34] During the behavioral experiments, patients should explicitly reflect on their emotional state while performing activities, which is thought to help regulate emotions. Fifth, advising patients to focus on the non-occurrence of the expected outcome is another relevant suggestion that will facilitate CS-noUS learning. Any distraction, for example by “small talk” with the therapist, is counterproductive for CS-noUS learning and should be refrained from. During the experiment, the therapist may ask questions to help the patient to focus on this non-occurrence of the US. After each behavioral experiment, the patient should reflect on the non-occurrence of the US, because rehearsal of the CS-noUS association enhances storage of memory.[35] Lastly, the therapist should be aware of safety behaviors, also referred to as contextual avoidance behavior,[36] which are defined as actions performed to prevent, escape, or minimize feared catastrophes and/or associated distress.[37] During EXP for PRF, complete avoidance of movements and activities is omitted, but patients might still use overt and covert strategies "to keep themselves safe" and/or control experienced fear during confrontation with CSs (eg, tense muscles in the back, wear a corset under their clothes, or taking extra rest or medication prior to EXP). Instead of experiencing non-contingency between the activity and the feared outcome (eg, the US does not occur when confronted with the CS), the non-contingency may be attributed to the safety behavior (eg, "Because I tensed the muscles in my back, I was able to lift a heavy weight" instead of "Nothing bad happens to my back when I lift a heavy weight"). Also, a patient may use relaxation techniques or mental distraction, hindering full contact with the occurring natural contingencies (CS-noUS). Safety behavior may be allowed in case the patient is not willing to engage in EXP otherwise but is best to be omitted as soon as the patient has encountered enough encouraging experiences to raise curiosity about what would happen without dependence on safety behaviors.[38]

Insights From Neuroimaging on (Chronic) Pain and Its Modulation

The brain is undoubtedly the most crucial organ when it comes to pain because pain is inherently an output of the brain, and our brain is ultimately responsible for learning the (often implicit) associations discussed above (eg, CS-US and CS-noUS). A broad understanding of how the brain is involved in pain is at the foundation of pain neuroscience education that is widely available,[39,40] sometimes as a therapeutic (or preventive) approach on its own.[41,42] At its core, pain neuroscience education aims at reconceptualizing pain from being a marker of tissue damage to a marker for a perceived need to protect our body.[43] A basic understanding of evidence from neuroimaging research will contribute to a better comprehension of mechanisms underlying EXP. In addition, it could yield a powerful tool because it can be incorporated into clinical practice, providing a language to illustrate and justify the biopsychosocial approach to chronic pain rehabilitation.

Whether pain is perceived as a threat is subject to many factors and hence highly malleable. Pain processing is carried out in a widely distributed network of brain regions.[44–47] (Note that we refer to pain processing for simplicity, although this does not imply that all nociceptive signaling leads to pain, nor that nociceptive signaling is required for a pain experience.) Crucially, though, the flow of information across networks is bidirectional, meaning that different regions can impact one another and can even modulate signaling at the level of the spinal cord via a descending pathway[44,48] that either facilitates or inhibits experienced pain. Such crosstalk is crucial in establishing placebo/nocebo, the "pain inhibits pain" phenomenon, in pharmacological pain control (eg, through opioid signaling) but also in modulating pain experiences by expectations, mood, fears, worries, prior experiences, and appraisals.[48,49] One recent study showed that pain can be modulated (exacerbated) by negative emotions, but that the extent is highly variable across individuals and that connectivity between the amygdala (core threat center) and sensorimotor regions predicted this pain-facilitatory effect.[50] Similarly, studies showed that pain experience is exacerbated by (anticipatory) anxiety through hippocampal mechanisms.[51] Such emotional modulation of pain is thought to facilitate subsequent learning. In particular, when a stimulus is perceived as a threat while we are stressed, encoding and consolidation of information about that threat is prioritized, facilitating learning of threat-related information (eg, acquisition of PRF) at the cost of other functions (eg, memory updating, goal-directed behavior).[52]

When pain persists, it loses its alarming function and the behaviors it motivates may become maladaptive, as outlined in the fear avoidance model. The crucial role of cognitive and affective factors in persistent pain is supported by a shift in brain regions that code for pain, shifting from being more sensory dominated in the sub-acute stages to more affective/motivational in the chronic stages.[53] In addition, corticolimbic circuitry are crucially involved in the chronification of pain,[54–56] with a key role for the nucleus accumbens (reward/motivation center) and its communication with the prefrontal cortex (i.e., regulating of emotions, including inhibitory learning). The amygdala plays a central role in threat processing and regulation, and amygdala connectivity has been found to be altered in chronic pain and normalized after successful pain rehabilitation.[57,58] The amygdala is also important for learning to distinguish between threat and safety cues and for the subsequent extinction through inhibitory learning via connectivity with the prefrontal cortex.[59,60] In individuals with chronic pain, there are alterations in threat-safety discrimination learning, including more resistance to extinction learning (the experimental analogue of EXP).[28] In one study, altered threat-safety learning was found to be underlaid by aberrant amygdala activation but was only present in individuals with elevated pain-related worries.[61] Thus, corticolimbic circuitry seems to play a crucial role in persistence of pain, with important interactions with PRF and altered threat learning, potentially extending towards inhibitory learning.

Just as brain circuitry shifts during chronification of pain, several studies have demonstrated brain plasticity following successful pain rehabilitation.[58,62–65] For instance, youth showed connectivity changes in fear circuitry following intensive interdisciplinary pain rehabilitation, which were correlated with improvements in PRF.[58] Only a few studies examined neural correlates of EXP specifically. In individuals with posttraumatic stress symptoms, functional connectivity of the amygdala and hippocampus was enhanced after EXP.[66] In chronic pain, we demonstrated that neural responses to fear-evoking visual stimuli in several regions (including hippocampus and prefrontal cortex) were altered following EXP in a way that was related to reductions in PRF.[67] More recently, we showed brain plasticity in the functional connectivity of subcortical nuclei amygdala and hippocampus during rest following EXP.[68] Interestingly, it seems that pretreatment brain patterns could potentially predict which individuals will benefit from treatment,[69–71] offering a promising outlook on a role for brain imaging in prognostics. Yet, more work is needed in this realm. For instance, many studies have not included a control treatment, precluding any inferences on whether changes in neural circuitry are specific for the treatment at hand or whether they reflect more general treatment (or time) effects. In addition, it is challenging to perform neuroimaging research in clinical settings with clinical populations, especially with individuals who are in pain and hence may be particularly uncomfortable lying still in a scanner for prolonged time. For that reason, sample sizes may be limited and interventions may be offered within research settings instead of within care settings by experienced clinicians, limiting its generalizability and potential clinical application. In addition, it would be quite relevant to examine whether brain plasticity changes following EXP are similar for individuals with chronic secondary pain and for different care settings (eg, EXP in primary care).

Clinical Applications of EXP in Chronic Pain Rehabilitation

EXP for PRF is commonly applied as (part of) an interdisciplinary rehabilitation program for individuals with chronic primary musculoskeletal pain carried out in tertiary care.[72,73] More recently, advances have been made in the application of EXP to chronic secondary pain and in primary care, which we will discuss below after presenting an overview of our current methods of patient selection, identification of treatment goals, and therapy approach.

Patients only enter treatment after an extensive assessment, starting with a consultation by a physiatrist, including medical history, current pain-related complaints, disabilities, and medication used followed by a physical examination to rule out red flags and evaluate the physical capacity to perform daily-life activities. When patients are receptive to focus on improving functioning despite pain, an interdisciplinary team screening starts. During this screening, the occupational therapist identifies motivation and treatment goals, the physical therapist observes various activities to identify behavioral responses indicative of fear and avoidance, and the psychologist determines whether PRF significantly contributes to the experienced disability. EXP only starts after the interdisciplinary team agrees that PRF is an important maintaining factor and the patient agrees with the proposed treatment after education by both physiatrist (ie, on achievable level of functioning based on biomedical status) and the psychologist (ie, on treatment rationale of EXP, including the fear-avoidance model). Therapists usually work in a duo: the psychologist together with the physical therapist or occupational therapist. Individualized treatment goals are approached with attention to the patient's system (eg, partners or parents).

EXP in the Treatment of Chronic Secondary Pain

In contrast to chronic primary pain, chronic secondary pain is considered a symptom of an underlying medical disease.[3] Examples include chronic secondary musculoskeletal pain, defined as pain that occurs as part of a disease directly affecting bone, joint, muscle, or other soft tissue,[74] such as rheumatoid arthritis (RA) or osteoarthritis. Another example is chronic neuropathic pain caused by a lesion or a disease of the somatosensory nervous system[75,76] that can be originated peripherally (eg, painful diabetic neuropathy, small fiber neuropathy) or centrally (eg, chronic central neuropathic pain associated with spinal cord injury). In addition to the more obvious nociceptive pain signaling pathways, it has been shown that PRF often conjunctly contributes to the pain experience and pain-related disability in these chronic secondary pain conditions as well[77–82] and hence could be targeted using EXP. Nevertheless, compared with EXP in chronic primary pain, some important considerations have to be considered.

Because there is an underlying medical disease in chronic secondary pain, it is of utmost importance that adequate medical history-taking and physical examination are performed prior to initiating EXP treatment. Realistic and safe treatment goals need to be determined, taking into consideration restrictions due to the primary disease, comorbidity, and/or deconditioning. But first, patients need to be willing and ready to participate in a rehabilitation program that addresses PRF and daily-life pain-related behavior (eg, avoidance behavior). In clinical practice, we have experienced that patients with chronic secondary pain may simply not believe or realize that their perception and burden of the complaints can be altered.[83] In addition, patients with secondary pain need more counseling to educate them about pain, create awareness of underlying mechanisms, and create readiness to change. It is hypothesized that in secondary pain, it is even more important and challenging to unravel whether PRF plays a role in maintenance of pain-related disability. With secondary pain, one needs to be very specific about the nature of the PRFs—because they may be less obvious and inherently entangled with the primary disease—to formalize the optimal individualized-treatment protocol. Also, if other significantly debilitating (co-)morbidity is present, targeting PRF alone may not result in a satisfactory improvement in daily-life functioning because the other medical problems are still present. Furthermore, it is essential that before EXP starts, it is clear to the patient and rehabilitation team which bodily signs may be indicative of newly induced nociception (eg, warm and swollen joints in case of an acute inflammation in RA) to prevent new harm. Also, potential risks (eg, hypoglycemia or pressure ulcer due to sensory deficits in painful diabetic neuropathy) and restrictions (eg, limited joint mobility leading to restricted movements in RA) need to be identified.

Physical deconditioning due to preexisting lower activity levels and/or long-term avoidance may have resulted in additional negative physical consequences, such as decreased muscle strength, cardiorespiratory fitness, and balance.[84] However, the real challenge for the physiatrist and physical therapist is to disentangle whether deconditioning is caused by the consequences of the underlying disease itself or whether performance is negatively affected by PRF; in other words, whether a submaximal performance is representative for the patient's actual physical capability or due to PRF.[85] It is important to note that when the physiatrist or physical therapist determines there is a satisfactory physical capacity level to perform personally relevant daily-life activities (even in the presence of some deconditioning), EXP can be started immediately. In case the assessment shows decreased physical functioning that interferes with the capability of performing of daily-life activities, a specific condition-creating physical training should be provided before EXP starts.

EXP is most powerful when the discrepancy between the expectation (ie, an irrational feared consequence) and the actual experience is as large as possible. However, fears that are inherently related to a medical condition are not always irrational, and a certain level of the patient's concern can be considered appropriate and adaptive, such as fear of falling in case of sensory deficits of the feet.[79,86] EXP should be applied only when the avoidance of feared activities is irrational or disproportional (ie, when certain activities are deemed safe and feasible and pain during such activities does not indicate harm) and context specific, such that they can be mimicked and challenged in a therapeutic setting.[83] Note that this pertains specifically to fears and behaviors in the context of movements and activities and not to fears about pain or other sensations. Moreover, a prerequisite for successfully diminishing PRF is that the patient learns that physical activity is not harmful. However, many catastrophic thoughts and dysfunctional beliefs about the performance of daily-life activities are based on often non-compatible or even contradicting advice a patient may have received from a variety of health care providers. Therefore, even more so than in chronic primary pain, communication and collaboration between treatment team members and other involved health care providers is crucial to create a common approach to pain management and being active despite pain.

Application of EXP in Primary Care

Recent research shows the effectiveness and feasibility of biopsychosocial primary care interventions as delivered by physical therapists.[87] Also, elements of EXP have been introduced in primary care physical therapy settings.[88,89] Lessons learned concern the need for appropriate training of physical therapists, adequate selection of patients, and recommendation to work within multidisciplinary primary care networks. Because physical therapists are typically trained to provide exercise training, extra education is necessary for providing EXP. Such education or training would include learning to identify fearful thoughts and avoidance behavior, to create awareness about their impact on the level of functioning, to address PRF in behavioral experiments, and to apply techniques to optimize inhibitory learning.[88] Patients suitable for EXP in primary care should have considerable awareness about their PRF and its influence on daily-life functioning, and should be motivated to change their behavior. When PRF is excessive or other significant psychological or psychiatric comorbidity is present[90,91] or in the case of relapse, the patient should be referred to tertiary care. To help identify PRF, questionnaires and/or observations may be a first step (see for examples[92–97]). In addition, assessment methods are currently being developed to match care from primary to tertiary perspective.[98] However, to optimally apply EXP in primary care, multidisciplinary primary care pain rehabilitation networks seem most appropriate. One example is the Network Pain Rehabilitation Limburg, in which general practitioners, physical therapists, and psychologists join forces with a tertiary pain expertise center.[99] The network facilitates additional training, supervision, and collaboration to provide optimal biopsychosocial pain treatment in primary care. A physiatrist can be involved in selection of appropriate patients for primary multidisciplinary care and is available for consultation during treatment. It is hypothesized that these networks facilitating the transition from tertiary to primary multidisciplinary biopsychosocial pain rehabilitation could help to more quickly identify patients with developing PRF, which might lead to the prevention of chronification and increased pain-related disability and as such contribute to less costly interventions.

Considerations and Future Directions

In this review, we aimed to give an overview of the theoretical considerations for EXP and to bridge such reflections towards clinical applications. It should be noted though that the review is not exhaustive (for further reading, see references[29,72,73]) and that there are other considerations to be taken into account, some of which will be described below.

Although the integration of inhibitory learning principles shows promise for optimizing EXP and preventing relapse after successful EXP treatment, it requires a fairly cognitive approach to EXP. Our clinical experience has taught us that not all patients are able to explicitly state their expectations, therefore limiting its use. Furthermore, previous work, including from our group, has shown that EXP can be successfully applied without this cognitive focus by emphasizing more basic principles of EXP and of conditioning in general.[12,19,100] These previous studies did not, however, specifically address relapse after EXP for PRF.

Most of the theoretical developments come from the broader anxiety literature, and not all theoretical principles have been specifically tested for PRF. Although principles of inhibitory learning are likely transdiagnostic, this warrants some caution and more research. Additionally, it is a challenge to integrate new insights into clinical practice. For instance, even though some teams are working from an inhibitory learning perspective, others are still working from the more historical habituation premise, which may be suboptimal. Therefore, continuing education is advised to stay updated on the current state of the art. More knowledge may also help with another complicating factor: so-called therapist drift. Research in the general anxiety field shows that therapists might not opt for EXP despite being convinced of its effectiveness.[101] Understandably, patients might be reluctant to confront their fears and might show resistance, which may cause (empathic) distress in the therapist.[102–104] Our experience is that delivering EXP jointly helps to deal with these issues: psychologists have knowledge about EXP and know how to engage patients in stressful situations and deal with emotions, while physical therapists or occupational therapists bring knowledge about what to expect physically. When taken together, these expertise profiles facilitate designing and carrying out behavioral experiments that enable learning yet are within the physical capacity of the patient.

Approaches to chronic pain rehabilitation based on other principles, such as mindfulness or acceptance-commitment therapy (ACT), are rapidly growing.[105–108] Because PRF almost never presents in isolation, it begs the question whether rehabilitation programs should contain elements from multiple approaches (eg, EXP to target PRF, ACT to increase psychological flexibility and mindfulness-based stress reduction) and whether that would maximize effects. Based on inhibitory learning principles, however, some approaches may have contradictory effects. For instance, although relaxation could be an effect of mindfulness-based stress reduction, relaxation can also be conceptualized as a safety behavior when done in the context of EXP (ie, patients may distract themselves from bodily sensations during EXP). Additionally, efforts to reduce arousal (eg, relaxation) may result in poorer learning according to the inhibitory learning theory, because higher arousal is associated with better consolidation of the new CS-noUS memory trace.[32] Thus, it is important to consider the theoretical principles underlying different treatment approaches as well as their rationale and timing (e.g., relaxation might hamper full exposure to CS-noUS contingencies during EXP but may be beneficial prior to sleep to boost memory consolidation). In a broad sense, several elements from ACT are, however, already integrated into more recent theoretical models and clinical applications of EXP, especially the construct of psychological flexibility (ie, choosing values-based behavior in the presence of distressing experiences).[109] The fear avoidance model, for instance, nowadays incorporates the idea that goal setting is important and that prioritizing valued life goals goes hand in hand with recovery (while prioritizing immediate pain control is part of the vicious cycle of avoidance and disability).[7] This perspective may be especially relevant for chronic secondary pain, where the link between PRF, the pain experience, and disability is arguably more complex than in primary pain. Value-based actions can then form a crucial central component: activities and movement can be painful, but when they bring the patient closer to their values, they may choose to do them anyway.

Interestingly, it is not always clear what the exact CSs are. The Photograph Series of Daily Activities[95,96,110,111] can be used as a guide, addressing various movements and activities as potential fear-provoking stimuli (CSs), which patients may avoid or adjust (by using safety behavior). The concept of PRF, however, is broader than fear of movement or re-injury.[112] Some patients, for instance, describe that activities/movements are only avoided or adjusted when they feel pain or other bodily sensations. This illustrates the idea that the exact nature of the CS could also be proprioceptive or interoceptive in addition to exteroceptive. A thorough analysis of the exact nature of the CS, US, and its contingencies is therefore critical to select the appropriate focus for EXP. In fact, there have been studies showing beneficial effects of interoceptive exposure targeting fear of pain by explicitly focusing on bodily sensations in patients with chronic low back pain,[113,114] and adolescents with abdominal pain showing high fear of pain.[115] Furthermore, certain elements of other treatment approaches could be conceptualized as interoceptive exposure as well (eg, the focus of ACT on willingness to experience thoughts, feelings, and sensations).

In addition to applying EXP in other clinical settings, there have been many developments to digitize treatments (eg, internet delivery, smartphone applications)[116–118] or to incorporate digital technologies (eg, augmented or virtual reality [VR]). A meta-analysis showed that VR-EXP is as effective as EXP in anxiety disorders.[119] Within the pain field, VR is currently mainly applied as a distraction technique to reduce pain,[120,121] but there are several efforts to integrate VR into treatments (indirectly) targeting PRF.[122] For EXP specifically, VR has some promising potentials. For instance, VR could create specific fearful contexts to maximize the mismatch between the expectancy and actual experience. VR can help create as many activities as possible with a variety of fear levels, different durations, and multiple contexts to facilitate generalization of newly learned CS-noUS associations, therewith increasing effectiveness and sustainability. Some interesting work has also been done to manipulate the visual feedback (ie, enhanced VR) and hence manipulate the perceived range of motion (e.g., moving the neck).[123,124] This would theoretically aid the perceived mismatch between expectancy and actual experience (by exaggerating the actual experience), although first findings did not show differences between VR and enhanced VR.[123] It should be noted that there may be some important drawbacks to applying VR in EXP. For instance, explaining the use of VR as a safe way to challenge the patient's expectations could weaken the strength of mismatch, and the immersion and inherent distraction of the VR environment may hinder the testing of expectancies and/or the conscious experience of disconfirmation. Presence of a therapist (either physically or in the VR environment) would potentially circumvent such issues.

The last consideration concerns pain education. There is broad consensus that some level of knowledge is required prior to initiating EXP, but on the other hand the education may also provide knowledge that compromises the strength of the mismatch between expectancy and actual experience. Clearly, there is a precarious balance between effectuating readiness and willingness in the patient to engage in EXP while preserving the possibility to maximize the mismatch. In this context, we may have to distinguish a biomedical education (eg, the physiatrist explaining the achievable level of functioning) from a psycho-education (eg, the psychologist explaining the rationale of EXP). Some studies have found no support for effects of a psycho-educational session,[125] which may suggest that within the context of EXP, education should be conceptualized more as a prerequisite than an independent treatment element. Whether this is the case, and whether a distinction between biomedical and psychological education is meaningful, should be further investigated.

To conclude, the field of EXP is constantly changing, and its applications to target PRF for movements and activities are becoming well established in the context of chronic primary pain. In addition, its clinical applications are moving into new and compelling directions regarding both who is receiving EXP treatment and how the treatment is provided to even further improve functioning and hence quality of life of individuals living with persistent pain.

Author Contributions

Concept/idea/research design: M. den Hollander, R.J.E.M. Smeets, T. van Meulenbroek, C.C.M. van Laake-Geelen, V.A. Baadjou, I. Timmers

Writing: M. den Hollander, R.J.E.M. Smeets, T. van Meulenbroek, C.C.M. van Laake-Geelen, V.A. Baadjou, I. Timmers

Project management: R.J.E.M. Smeets

Consultation (including review of manuscript before submitting): R.J.E.M. Smeets, V.A. Baadjou, I. Timmers

All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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References

1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161:1976–1982.
2. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160: 28–37.

3. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). *Pain*. 2019;160: 19–27.
4. Zale EL, Lange KL, Fields SA, Ditre JW. The relation between pain-related fear and disability: a meta-analysis. *J Pain*. 2013;14: 1019–1030.
5. Crombez G, Vlaeyen JWS, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain*. 1999;80: 329–339.
6. Vlaeyen JW, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain*. 2012;153:1144–1147.
7. Vlaeyen JW, Crombez G, Linton SJ. The fear-avoidance model of pain. *Pain*. 2016;157:1588–1589.
8. Vlaeyen JW, de Jong J, Geilen M, Heuts PH, van Breukelen G. Graded exposure in vivo in the treatment of pain-related fear: a replicated single-case experimental design in four patients with chronic low back pain. *Behav Res Ther*. 2001;39:151–166.
9. Vlaeyen JW, De Jong JR, Onghena P, Kerckhoffs-Hanssen M, Kole-Snijders AM. Can pain-related fear be reduced? The application of cognitive-behavioural exposure in vivo. *Pain Res Manage Fall*. 2002;7:144–153.
10. de Jong JR, Vlaeyen JWS, van Eijsden M, Loo C, Onghena P. Reduction of pain-related fear and increased function and participation in work-related upper extremity pain (WRUEP): effects of exposure in vivo. *Pain*. 2012;153:2109–2118.
11. de Jong JR, Vangronsveld K, Peters ML, et al. Reduction of pain-related fear and disability in post-traumatic neck pain: a replicated single-case experimental study of exposure in vivo. *J Pain*. 2008;9:1123–1134.
12. Leeuw M, Goossens MEJB, van Breukelen GJP, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain*. 2008;138: 192–207.
13. Linton SJ, Boersma K, Jansson M, Overmeer T, Lindblom K, Vlaeyen JW. A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. *Eur J Pain (London, England)*. 2008;12:722–730.
14. Glombiewski JA, Holzapfel S, Riecke J, et al. Exposure and CBT for chronic back pain: an RCT on differential efficacy and optimal length of treatment. *J Consult Clin Psychol*. 2018;86:533–545.
15. Woods MP, Asmundson GJ. 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*. 2008;136: 271–280.
16. den Hollander M, Goossens MEJB, de Jong JR, et al. Expose or protect? A randomized controlled trial of exposure in vivo versus physiotherapy in patients with complex regional pain syndrome type 1. *Pain*. 2016;157:2318–2329.
17. Dekker C, van Haastregt JCM, JAMCF V, et al. Pain-related fear in adolescents with chronic musculoskeletal pain: process evaluation of an interdisciplinary graded exposure program. *BMC Health Serv Res*. 2020;20:213.
18. Simons LE, Vlaeyen JWS, Declercq L, et al. Avoid or engage? Outcomes of graded exposure in youth with chronic pain using a sequential replicated single-case randomized design. *Pain*. 2020;161:520–531.
19. Dekker C, Goossens M, Winkens B, Remerie S, Bastiaenen C, Verbunt J. Functional disability in adolescents with chronic pain: comparing an interdisciplinary exposure program to usual care. *Child Aust*. 2020;7:288.
20. Goossens ME, de Kinderen RJ, Leeuw M, et al. Is exposure in vivo cost-effective for chronic low back pain? A trial-based economic evaluation. *BMC Health Serv Res*. 2015;15:549.
21. den Hollander M, Heijnders N, de Jong JR, Vlaeyen JWS, Smeets R, Goossens M. Exposure in vivo versus pain-contingent physical therapy in Complex Regional Pain Syndrome Type I: a cost-effectiveness analysis. *Int J Technol Assess Health Care*. 2018;34: 400–409.
22. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. *Psychol Bull*. 1986;99:20–35.
23. Meuret AE, Seidel A, Rosenfield B, Hofmann SG, Rosenfield D. Does fear reactivity during exposure predict panic symptom reduction? *J Consult Clin Psychol*. 2012;80:773–785.
24. Baker A, Mystkowski J, Culver N, Yi R, Mortazavi A, Craske MG. Does habituation matter? Emotional processing theory and exposure therapy for acrophobia. *Behav Res Ther*. 2010;48: 1139–1143.
25. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. *Behav Res Ther*. 2014;58:10–23.
26. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. *Behav Res Ther*. 2008;46:5–27.
27. Craske MG, Liao B, Brown L, Vervliet B. Role of inhibition in exposure therapy. *J Exp Psychopathol*. 2012;3:322–345.
28. Harvie DS, Moseley GL, Hillier SL, Meulders A. Classical conditioning differences associated with chronic pain: a systematic review. *J Pain*. 2017;18:889–898.
29. Meulders A. Fear in the context of pain: lessons learned from 100 years of fear conditioning research. *Behav Res Ther*. 2020;131:103635.
30. Vervliet B, Craske MG, Hermans D. Fear extinction and relapse: state of the art. *Annu Rev Clin Psychol*. 2013;9:215–248.
31. Culver NC, Stoyanova M, Craske MG. Clinical relevance of retrieval cues for attenuating context renewal of fear. *J Anxiety Disord*. 2011;25:284–292.
32. Culver NC, Stoyanova M, Craske MG. Emotional variability and sustained arousal during exposure. *J Behav Ther Exp Psychiatry*. 2012;43:787–793.
33. den Hollander M, de Jong J, Onghena P, Vlaeyen JWS. Generalization of exposure in vivo in Complex Regional Pain Syndrome Type I. *Behav Res Ther*. 2020;124:103511.
34. Kircanski K, Lieberman MD, Craske MG. Feelings into words: contributions of language to exposure therapy. *Psychol Sci*. 2012;23:1086–1091.
35. Joos E, Vansteenwegen D, Hermans D. Post-acquisition repetitive thought in fear conditioning: an experimental investigation of the effect of CS-US-rehearsal. *J Behav Ther Exp Psychiatry*. 2012;43: 737–744.
36. Kirk A, Meyer JM, Whisman MA, Deacon BJ, Arch JJ. Safety behaviors, experiential avoidance, and anxiety: a path analysis approach. *J Anxiety Disord*. 2019;64:9–15.
37. Telch MJ, Lancaster CL. Is there room for safety behaviors in exposure therapy for anxiety disorders? In: Neudeck P, Wittchen H, eds., *Exposure Therapy: Rethinking the Model—Refining the Method*. New York, NY, USA: Springer; 2012:313–334.
38. Blakey SM, Abramowitz JS. The effects of safety behaviors during exposure therapy for anxiety: critical analysis from an inhibitory learning perspective. *Clin Psychol Rev*. 2016;49:1–15.
39. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain*. 2015;16:807–813.
40. Heathcote LC, Pate JW, Park AL, et al. Pain neuroscience education on YouTube. *PeerJ*. 2019;7:e6603.
41. Watson JA, Ryan CG, Cooper L, et al. Pain neuroscience education for adults with chronic musculoskeletal pain: a mixed-methods systematic review and meta-analysis. *J Pain*. 2019;20:1140 e1141–1140 e1122.
42. Wijma AJ, Speksnijder CM, Crom-Ottens AF, et al. What is important in transdisciplinary pain neuroscience education? A qualitative study. *Disabil Rehabil*. 2018;40:2181–2191.
43. Moseley GL. Reconceptualising pain according to modern pain science. *Phys Ther Rev*. 2007;12:169–178.

44. Schweinhardt P, Bushnell MC. Pain imaging in health and disease—how far have we come ? *J Clin Invest*. 2010;120: 3788–3797.
45. Wager TD, Atlas LY, Ma L, Roy M, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. *New Engl. J Med*. 2013;368:1388–1397.
46. Coghill RC. The distributed nociceptive system: a framework for understanding pain. *Trends Neurosci*. 2020;43:780–794.
47. Xu A, Larsen B, Baller EB, et al. Convergent neural representations of experimentally-induced acute pain in healthy volunteers: a large-scale fMRI meta-analysis. *Neurosci Biobehav Rev*. 2020;112:300–323.
48. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo, and reappraisal effects in humans. *Nat Med*. 2010;16: 1277–1283.
49. Ploghaus A, Becerra L, Borras C, Borsook D. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. *Trends Cogn Sci*. 2003;7:197–200.
50. Gandhi W, Rosenek NR, Harrison R, Salomons TV. Functional connectivity of the amygdala is linked to individual differences in emotional pain facilitation. *Pain*. 2020;161:300–307.
51. Ploghaus A, Narain C, Beckmann CF, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci*. 2001;21:9896–9903.
52. Timmers I, Quaedflieg CWEM, Hsu C, Heathcote LC, Rovnaghi CR, Simons LE. The interaction between stress and chronic pain through the lens of threat learning. *Neurosci Biobehav Rev*. 2019;107:641–655.
53. Hashmi JA, Baliki MN, Huang L, et al. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain*. 2013;136:2751–2768.
54. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci*. 2012;15:1117–1119.
55. Vachon-Presseau E, Tétreault P, Petre B, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*. 2016;139:1958–1970.
56. Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain*. 2018;159:2421–2436.
57. Simons LE, Erpelding N, Hernandez JM, et al. Fear and reward circuit alterations in pediatric CRPS. *Front Hum Neurosci*. 2016;9:703.
58. Simons LE, Pielech M, Erpelding N, et al. The responsive amygdala: treatment-induced alterations in functional connectivity in pediatric Complex Regional Pain Syndrome. *Pain*. 2014;155: 1727–1742.
59. Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. *Neurosci Biobehav Rev*. 2006;30:188–202.
60. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*. 2005;48:175–187.
61. Heathcote LC, Timmers I, Kronman CA, et al. Brain signatures of threat-safety discrimination in adolescent chronic pain. *Pain*. 2020;161:630–640.
62. Seminowicz DA, Shpaner M, Keaser ML, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain*. 2013;14:1573–1584.
63. Nahman-Averbuch H, Schneider VJ 2nd, Chamberlin LA, et al. Alterations in brain function after cognitive behavioral therapy for migraine in children and adolescents. *Headache*. 2020;60: 1165–1182.
64. Yoshino A, Okamoto Y, Okada G, et al. Changes in resting-state brain networks after cognitive-behavioral therapy for chronic pain. *Psychol Med*. 2018;48:1148–1156.
65. Rogachov A, Bhatia A, Cheng JC, et al. Plasticity in the dynamic pain connectome associated with ketamine-induced neuropathic pain relief. *Pain*. 2019;160:1670–1679.
66. Zhu X, Suarez-Jimenez B, Lazarov A, et al. Exposure-based therapy changes amygdala and hippocampus resting-state functional connectivity in patients with posttraumatic stress disorder. *Depress Anxiety*. 2018;35:974–984.
67. Timmers I, de Jong JR, Goossens M, Verbunt JA, Smeets RJ, Kaas AL. Exposure in vivo induced changes in neural circuitry for pain-related fear: a longitudinal fMRI study in chronic low back pain. *Front Neurosci*. 2019;13:970.
68. Timmers I, van de Ven V, Vlaeyen JWS, et al. Cortico-limbic connectivity in chronic pain tracks pain intensity relief following exposure in vivo. *Biol Psych Glob Open Sci*. 2021;1:28–36.
69. Davis KD. Imaging vs quantitative sensory testing to predict chronic pain treatment outcomes. *Pain*. 2019;160:S59–S65.
70. Bosma RL, Cheng JC, Rogachov A, et al. Brain dynamics and temporal summation of pain predicts neuropathic pain relief from ketamine infusion. *Anesthesiology*. 2018;129:1015–1024.
71. Harris RE, Napadow V, Huggins JP, et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. *Anesthesiology*. 2013;119:1453–1464.
72. Verbunt J, Smeets R. *Graded Exposure: Een cognitief gedragsmatige aanpak van chronische pijn*. Houten, the Netherlands: Springer; 2016.
73. Vlaeyen JWS, den Hollander M, de Jong JR, Simons LE. Exposure in vivo for pain-related fear. In: Turk DC, Gatchel RJ, eds., *Psychological Approaches to Pain Management, a Practitioner's Handbook*. New York, NY, USA: Guilford Press; 2018: 177–204.
74. Perrot S, Cohen M, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain*. 2019;160:77–82.
75. Jensen TS, Baron R, Haanpaa M, et al. A new definition of neuropathic pain. *Pain*. 2011;152:2204–2205.
76. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain*. 2019;160:53–59.
77. Bulbena A, Gago J, Pailhez G, Sperry L, Fullana MA, Vilarroya O. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: a 15-year follow-up cohort study. *Gen Hosp Psychiatry*. 2011;33:363–370.
78. Celletti C, Castori M, La Torre G, Camerota F. Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Biomed Res Int*. 2013;2013:580460.
79. Geelen CC, Smeets R, Schmitz S, van den Bergh JP, Goossens M, Verbunt JA. Anxiety affects disability and quality of life in patients with painful diabetic neuropathy. *Eur J Pain (London, England)*. 2017;21:1632–1641.
80. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *J Pain Symptom Manag*. 2005;30:374–385.
81. Jia X, Jackson T. Pain beliefs and problems in functioning among people with arthritis: a meta-analytic review. *J Behav Med*. 2016;39:735–756.
82. Simmonds JV, Herbland A, Hakim A, et al. Exercise beliefs and behaviours of individuals with joint hypermobility syndrome/Ehlers-Danlos syndrome—hypermobility type. *Disabil Rehabil*. 2019;41:445–455.
83. van Laake-Geelen CCM, Smeets RJEM, Goossens MEJB, Verbunt JA. Effectiveness of exposure in vivo for patients with painful diabetic neuropathy: a pilot study of effects on physical activity and quality of life. *J Rehab Med Clin Comm*. 2021;4:1000046.
84. van Meulenbroek T, Huijnen IPJ, Simons LE, Conijn AEA, Engelbert RHH, Verbunt JA. Exploring the underlying mechanism of pain-related disability in hypermobile adolescents with chronic musculoskeletal pain. *Scand J Pain*. 2020;21:22–31.
85. Huijnen IPJ, Verbunt JA, Wittink HM, Smeets RJEM. Physical performance measurement in chronic low back pain: measuring physical capacity or pain-related behaviour? *Eur J Phys*. 2013;15: 103–110.

86. Kanera IM, van Laake-Geelen CCM, Ruijgrok JM, et al. Living with painful diabetic neuropathy: insights from focus groups into fears and coping strategies. *Psychol Health*. 2019;34:84–105.
87. van Erp RMA, Huijnen IPJ, Jakobs MLG, Kleijnen J, Smeets R. Effectiveness of primary care interventions using a biopsychosocial approach in chronic low back pain: a systematic review. *Pain Pract*. 2019;19:224–241.
88. van Erp RMA, Huijnen I, Köke A, Verbunt J, Smeets R. Feasibility of the biopsychosocial primary care intervention 'Back on Track' for patients with chronic low back pain: a process and effect-evaluation. *Eur J Physiother*. 2020. https://doi.org/10.1080/21679169.2020.1840627.
89. van Erp RMA, Huijnen IPJ, Ambergen AW, Verbunt JA, Smeets RJEM. Biopsychosocial primary care versus physiotherapy as usual in chronic low back pain: results of a pilot-randomised controlled trial. *Eur J Physiother*. 2019;23:3–10. https://doi.org/10.1080/21679169.2019.1630855.
90. Arrindell WA, Ettema JHM. *SCL-90. Handleiding bij een Multidimensionele Psychopathologie-Indicator*. Lisse, The Netherlands: Swets & Zeitlinger; 2003.
91. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale—preliminary report. *Psychopharmacol Bull*. 1973;9:13–28.
92. Crombez G, Bijttebier P, Eccleston C, et al. The child version of the Pain Catastrophizing Scale (PCS-C): a preliminary validation. *Pain*. 2003;104:639–646.
93. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess*. 1995;7:524–532.
94. Miller RP, Kori SH, Todd DD. The Tampa Scale (unpublished report). *Clin J of Pain*. 1991;7:51.
95. Leeuw M, Goossens ME, van Breukelen GJ, Boersma K, Vlaeyen JW. Measuring perceived harmfulness of physical activities in patients with chronic low back pain: the Photograph Series of Daily Activities–short electronic version. *J Pain*. 2007;8:840–849.
96. Verbunt JA, Nijhuis A, Vikstrom M, et al. The psychometric characteristics of an assessment instrument for perceived harmfulness in adolescents with musculoskeletal pain (PHODA-youth). *Eur J Pain (London, England)*. 2015;19:695–705.
97. Holzapfel S, Riecke J, Rief W, Schneider J, Glombiewski JA. Development and validation of the Behavioral Avoidance Test-back pain (BAT-back) for patients with chronic low back pain. *Clin J Pain*. 2016;32:940–947.
98. Bier JD, Sandee-Geurts JJW, Ostelo R, Koes BW, Verhagen AP. Can primary care for back and/or neck pain in the Netherlands benefit from stratification for risk groups according to the STarT back tool classification? *Arch Phys Med Rehabil*. 2018;99:65–71.
99. Lamper C, Kroese M, Koke A, Ruwaard D, Verbunt J, Huijnen I. Developing the Network Pain Rehabilitation Limburg: a feasibility study protocol. *BMJ Open*. 2019;9:e025962.
100. Hedman-Lagerlof M, Andersson E, Hedman-Lagerlof E, Wicksell RK, Flink I, Ljotsson B. Approach as a key for success: reduced avoidance behaviour mediates the effect of exposure therapy for fibromyalgia. *Behav Res Ther*. 2019;122:103478.
101. Pittig A, Kotter R, Hoyer J. The struggle of behavioral therapists with exposure: self-reported practicability, negative beliefs, and therapist distress about exposure-based interventions. *Behav Ther*. 2019;50:353–366.
102. Deacon BJ, Lickel JJ, Farrell NR, Kemp JJ, Hipol LJ. Therapist perceptions and delivery of interoceptive exposure for panic disorder. *J Anxiety Disord*. 2013;27:259–264.
103. Waller G. Evidence-based treatment and therapist drift. *Behav Res Ther*. 2009;47:119–127.
104. Waller G, Turner H. Therapist drift redux: why well-meaning clinicians fail to deliver evidence-based therapy, and how to get back on track. *Behav Res Ther*. 2016;77:129–137.
105. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and commitment therapy (ACT) for chronic pain: a systematic review and meta-analyses. *Clin J Pain*. 2017;33:552–568.
106. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther*. 2016;45:5–31.
107. Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. *Ann N Y Acad Sci*. 2016;1373:114–127.
108. Pielech M, Vowles KE, Wicksell R. Acceptance and commitment therapy for pediatric chronic pain: theory and application. *Children (Basel)*. 2017;4:10.
109. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther*. 2006;44:1–25.
110. Institute for Rehabilitation Research and School for Physiotherapy Heerlen. *The Photograph Series of Daily Activities (PHODA) [computer program]*. Heerlen, The Netherlands: Institute for Rehabilitation Research and School for Physiotherapy Heerlen; 1999.
111. Simons LE, Pielech M, McAvoy S, et al. Photographs of Daily Activities-youth English: validating a targeted assessment of worry and anticipated pain. *Pain*. 2017;158:912–921.
112. den Hollander M, de Jong JR, Volders S, Goossens MEJB, Smeets RJEM, Vlaeyen JWS. Fear reduction in patients with chronic pain: a learning theory perspective. *Expert Rev Neurother*. 2010;10:1733–1745.
113. De Peuter S, Van Diest I, Vansteenwegen D, Van den Bergh O, Vlaeyen JW. Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach. *Eur J Pain (London, England)*. 2011;15:889–894.
114. Flink IK, Nicholas MK, Boersma K, Linton SJ. Reducing the threat value of chronic pain: a preliminary replicated single-case study of interoceptive exposure versus distraction in six individuals with chronic back pain. *Behav Res Ther*. 2009;47:721–728.
115. Flack F, Stahlschmidt L, Dobe M, et al. Efficacy of adding interoceptive exposure to intensive interdisciplinary treatment for adolescents with chronic pain: a randomized controlled trial. *Pain*. 2018;159:2223–2233.
116. Richardson PA, Harrison LE, Heathcote LC, et al. mHealth for pediatric chronic pain: state of the art and future directions. *Expert Rev Neurother*. 2020;20:1177–1187.
117. Eccleston C, Fisher E, Craig L, Duggan GB, Rosser BA, Keogh E. Psychological therapies (internet-delivered) for the management of chronic pain in adults. *Cochrane Database Syst Rev*. 2014;2:CD010152.
118. Hedman-Lagerlof M, Hedman-Lagerlof E, Axelsson E, et al. Internet-delivered exposure therapy for fibromyalgia: a randomized controlled trial. *Clin J Pain*. 2018;34:532–542.
119. Carl E, Stein AT, Levihn-Coon A, et al. Virtual reality exposure therapy for anxiety and related disorders: a meta-analysis of randomized controlled trials. *J Anxiety Disord*. 2019;61:27–36.
120. Matheve T, Bogaerts K, Timmermans A. Virtual reality distraction induces hypoalgesia in patients with chronic low back pain: a randomized controlled trial. *J Neuroeng Rehabil*. 2020;17:55.
121. Wiederhold BK, Gao K, Sulea C, Wiederhold MD. Virtual reality as a distraction technique in chronic pain patients. *Cyberpsychol Behav Soc Netw*. 2014;17:346–352.
122. Griffin A, Wilson L, Feinstein AB, et al. Virtual reality in pain rehabilitation for youth with chronic pain: pilot feasibility study. *JMIR Rehabil Assist Technol*. 2020;7:e22620.
123. Harvie DS, Smith RT, Moseley GL, Meulders A, Michiels B, Sterling M. Illusion-enhanced virtual reality exercise for neck pain: a replicated single case series. *Clin J Pain*. 2020;36:101–109.
124. Harvie DS, Smith RT, Hunter EV, Davis MG, Sterling M, Moseley GL. Using visuo-kinetic virtual reality to induce illusory spinal movement: the MoOVi illusion. *PeerJ*. 2017;5:e3023.
125. Schemer L, Vlaeyen JWS, Doerr JM, et al. Treatment processes during exposure and cognitive-behavioral therapy for chronic back pain: a single-case experimental design with multiple baselines. *Behav Res Ther*. 2018;108:58–67.