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Great expectations: inhibitory learning and change processes in exposure therapy for PTSD

Kooistra, M.J.

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Chapter 1



General introduction



Introduction

It is estimated that 81.5% of the people in the Netherlands experience at least one potentially traumatic event during their lifetime, such as a serious traffic accident, physical violence or sexual assault (Hoeboer et al., 2025). Following such events, some people develop a posttraumatic stress disorder (PTSD). In the Netherlands, the estimated lifetime prevalence of PTSD is 11.1% (Hoeboer et al., 2025). Individuals with PTSD experience several symptoms associated with the traumatic event(s), including: 1) recurring intrusions, 2) persistent avoidance of thoughts, feelings or stimuli, 3) negative changes in cognitions and mood, and 4) changes in arousal and reactivity (American Psychiatric Association, 2022). See the vignette for a more detailed illustration of how these symptoms may manifest.

Multiple factors further increase the risk of developing PTSD, such as an interpersonal nature of the traumatic events (e.g., sexual assault), being female, and childhood adversity (Hoeboer et al., 2025; Kessler et al., 2017). Left untreated, PTSD can persist for many years, with delayed onset also possible (Kessler et al., 2017; Koenen et al., 2017). PTSD is a debilitating disorder, associated with substantial costs to the individual and society (Magruder et al., 2017; Warth et al., 2020). Moreover, PTSD has a high rate of comorbidity with other disorders, such as anxiety disorders and major depressive disorder (Hyland et al., 2021; Pietrzak et al., 2011; Walter et al., 2018). These findings highlight the need for effective treatments for PTSD.

Prolonged Exposure

Effective treatments for PTSD exist, with Prolonged Exposure (PE) being one of the first-choice treatments in multiple international guidelines (American Psychological Association, 2017; Federatie Medisch Specialisten, 2025; Hamblen et al., 2019; National Institute for Health and Care Excellence, 2018). PE includes several critical components (Foa et al., 2019). First, it includes psychoeducation about common reactions to trauma, PTSD symptoms and the treatment rationale. Second, PE includes repeated confrontations with objectively safe, trauma-related stimuli, situations, or people that the patient avoids (i.e., in vivo exposure). For example, after experiencing an assault, a patient might practice spending time around unfamiliar individuals who resemble the assailant's appearance or visit the location where the attack occurred. Third, PE includes repeatedly revisiting the traumatic memory (i.e., imaginal exposure), followed by emotional processing. During imaginal exposure, a patient is asked to recount the traumatic event out loud, with their eyes closed, in as much detail as possible. During the processing afterwards, the experience of recounting the event is discussed and the therapist provides support, psycho-education and explores erroneous thoughts that the patient might have

about themselves, other people and/or the world. Between sessions, patients are instructed to repeat in-vivo exposure exercises and listen to recordings of their imaginal exposure sessions on a daily basis.

Vignette

Charlotte is a 30-year-old woman who was sexually assaulted four years ago. Since then, she has experienced intrusion symptoms daily. She frequently re-experiences aspects of the event, often seeing the perpetrator's vividly face in her mind. She also has nightmares of being trapped and unable to escape. Charlotte tries to distract herself from thoughts of the assault by keeping herself busy, often by working extra hours or scrolling on her phone. Since the event, Charlotte avoids being alone with men she does not know well. She takes extra precautions when going out, such as planning her routes carefully or only meeting friends in familiar places. She finds it difficult to trust others, especially men, and often questions their intentions. She no longer goes jogging in the park, something she used to enjoy. She also avoids discussing the assault, fearing that people will not understand or will blame her. Charlotte is afraid that she will be harmed again and believes that she must always be on guard as the world is a dangerous place. She struggles with negative thoughts about herself, such as 'I am weak' and 'I should have done more to stop it'. Charlotte experiences arousal symptoms, including irritability, difficulty sleeping, and an exaggerated startle response, especially when someone unexpectedly appears behind her. Her symptoms have significantly impacted her daily life, making ordinary activities, such as commuting and socializing, feel exhausting and overwhelming. Charlotte's relationship with her partner has become strained, partly due to her withdrawal and her struggles with intimacy.

Effectiveness of PE

Multiple meta-analyses have shown that PE is an effective treatment that reduces PTSD symptoms, with these effects being relatively well maintained over time (Mavranouzouli et al., 2020; McLean et al., 2022). It has been shown to be superior to waitlist, 'treatment as usual', and non-trauma focused treatment. On the longer term, PE also appears more effective than medication (particularly, antidepressants) (Lee et al., 2016; McLean et al., 2022). Besides reducing PTSD symptoms, PE has also been associated with improved quality of life (Kaur et al., 2024), increased perceived social support (Bourassa et al., 2020), and reductions in comorbid symptoms, such

as depressive and psychotic symptoms (Bont et al., 2016; Brown et al., 2018). PE is typically delivered in 8–15 weekly sessions, each lasting 90 minutes (Foa et al., 2019). Recently, there is growing interest in alternative delivery formats that may accelerate recovery and improve efficiency. For instance, intensive formats of PE (i.e., multiple sessions within one week) have been shown to be effective. Compared to weekly delivery, they are associated with a faster recovery and lower dropout rates (Levinson et al., 2022; McLean & Foa, 2024).

Despite PE's well-established efficacy and effectiveness, not all patients benefit sufficiently. A systematic review showed that after treatment for PTSD (including PE), 31% of patients still reported clinical symptom levels, and 59% reported subthreshold symptom levels (Larsen et al., 2019). Predicting who will benefit from treatment in advance is challenging (Barawi et al., 2020). Individuals with more severe symptoms or comorbidities often report higher symptom severity after treatment, but show a comparable rate of improvement (Barawi et al., 2020; Kline et al., 2021; van Minnen et al., 2015). Additionally, PE drop-out rates are generally high. While approximately 16–18% of patients drop out of psychological treatments for PTSD overall, estimates for PE range from 22% to 29% (Imel et al., 2013; Lewis et al., 2020; Varker et al., 2021). Although dropout occurs across all PTSD treatments, recent meta-analyses suggest that slightly more patients drop out from psychological treatments that are trauma-focused, including PE, than non-trauma-focused treatments (Hoppen et al., 2023; Lewis et al., 2020). Given that trauma-focused treatments also demonstrate the strongest efficacy, understanding and addressing the causes of dropout in these treatments remains a critical priority.

In summary, PE and related trauma-focused treatments are quite effective but there is ample room for improvement. Optimizing treatment effectiveness may be dependent on a better understanding of its mechanisms of change.

Studying change mechanisms

Identifying the mechanisms that drive symptom reduction could help refine interventions by ensuring that treatment targets the most critical change processes and by strengthening the therapeutic elements that facilitate these processes (Kazdin, 2007, 2009). Kazdin (2007, 2009) describes several recommendations for research on treatment mechanisms. First and foremost, using theory as a guide to understand the critical processes and how they drive change is essential. Second, to establish a treatment mechanism, several criteria must be met, and empirical research should be designed to rigorously test these criteria. These criteria include: 1) a strong association between the intervention, proposed mechanism and outcome; 2) specificity of this association, showing that the proposed mechanism is uniquely responsible for change; 3) consistency, demonstrating an observed result

repeatedly across studies, samples and conditions; 4) experimental manipulation, where direct manipulation of the proposed mechanism impacts the outcome; and 5) a timeline showing that change in the mechanism precedes the change in the outcome.

Theories of exposure therapy for PTSD

Multiple theories aim to explain the maintenance and recovery of PTSD, but two are particularly relevant for understanding how exposure therapy for PTSD is presumed to work. These two are the Emotional Processing Theory (EPT) and the Inhibitory Learning and Retrieval (ILR) model.

Emotional processing theory

EPT was first introduced as a framework for understanding the development and maintenance of anxiety-related disorders, including PTSD (Foa & Kozak, 1986). Inspired by the bio-informational theory of fear (Lang, 1979), EPT posits that fear is represented in memory as a cognitive structure. This structure includes representations of the fear stimuli (e.g., a knife), the fear responses (e.g., increased heart rate and muscle tension, running away), and their meaning (e.g., danger). Activation of one element generalizes to activate other elements in the structure. EPT makes a distinction between pathological and non-pathological structures. The fear structure is non-pathological if it becomes activated in the face of actual danger (e.g., a slashing movement with a knife) and elicits an appropriate response (e.g., moving away). The fear structure is considered pathological when it contains inaccurate associations that do not reflect reality, and when the structure becomes activated through stimuli or responses that are wrongfully viewed as dangerous (e.g., 'someone cutting food with a knife means danger') and elicits a maladaptive response (e.g., 'freezing'). Moreover, EPT posits that in PTSD, the structure also includes representations of someone's own reactions during and after the traumatic event and a meaning of self-incompetence. For example, freezing during the event may be interpreted as weakness. Two core dysfunctional cognitions are thought to underly PTSD (Rauch & Foa, 2006): negative cognitions about the self (e.g., 'I am weak'), and the world (e.g., 'the world is a dangerous place').

According to EPT, emotional processing is key to reducing symptoms, either via natural recovery or therapeutically. Emotional processing involves integrating corrective, realistic information into the fear structure, altering its pathological components. To do this, two conditions have to be met: a) the fear structure needs to be activated, and b) new information that is incompatible with the pathological elements must be presented and integrated. Repeatedly activating the fear structure (e.g., by talking about the traumatic event or confronting trauma-

reminders) in the absence of feared outcomes allows for recovery. Emotional processing is not directly observable; however, distress reduction¹ (in and over sessions) and change in posttraumatic cognitions may be indicators of effective processing. Although distress reduction was considered essential for corrective learning, empirical findings linking distress reduction to symptom improvement have been mixed (Cooper, Clifton, et al., 2017; Craske et al., 2008). Nevertheless, many current therapeutic procedures in PE are influenced by the assumption that distress reduction across repeated exposures indicates successful emotional processing, as reflected in session length, repetition of exposure exercises, the use of breathing exercises, and the use of exposure hierarchies. Throughout the PE treatment manual, therapists are instructed to monitor distress levels, to encourage their patients to continue exposure until their distress levels have decreased, and to move to more challenging exercises when distress levels during less challenging exercises have diminished.

Regarding changes in posttraumatic cognitions, EPT suggests that cognitions do not need to be explicitly addressed during exposure in order for them to change (Foa & McLean, 2016). For instance, someone who believes the world is completely dangerous may revise this belief after repeated in vivo exposures, like jogging alone in the park and experiencing that nothing bad happens, even if this belief was never directly addressed in therapy. A review of empirical studies shows that PE is related to decreases in posttraumatic cognitions and that this is related to PTSD symptom reduction (Brown, Belli, et al., 2019). These studies most often use the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999) to measure posttraumatic cognitions about the self, world and self-blame. Findings on whether changes in posttraumatic cognitions temporally precede symptom reductions are, however, mixed (Brown, Belli, et al., 2019) and require further investigation.

Inhibitory learning and retrieval model

The premise of EPT that distress reduction is necessary for successful treatment has been questioned due to the inconsistent empirical findings (Craske et al.,

1 In EPT, this is often referred to as habituation, which involves a decrease in response to a stimulus after repeated exposure. Distress reduction, measured via subjective units of distress (SUDs), is commonly used to operationalize habituation. There is unclarity about what distress reduction precisely captures; it may reflect more than just the non-associative process of habituation. Throughout this dissertation, we therefore use 'distress reduction' to remain close to what is actually measured.

2008). The inhibitory learning and retrieval (ILR²) model of extinction offers a new perspective on the workings of exposure therapy, proposing refinements to the way it is conducted to enhance treatment efficacy (see Table 1 for an overview of these proposed refinements to exposure). This perspective has become increasingly influential in exposure therapy for anxiety and related disorders, including PTSD (Craske et al., 2008, 2014, 2022). The ILR model is based on classical conditioning paradigms, which posit that fear is acquired by the association of a conditioned stimulus (CS) with an inherently aversive, unconditioned stimulus (US), leading to a conditioned fear response (CR). In the context of PTSD, a trauma reminder (CS, e.g., knife) becomes associated with the traumatic experience (US, e.g., assault), triggering a fear response (CR). Repeated presentations of the CS in the absence of the US will lead to a reduction of the acquired fear response, a process called extinction³. Extinction is used in exposure therapy, where a patient is repeatedly exposed to innocuous but fear-provoking stimuli, in the absence of aversive outcomes. According to the ILR model, the original fear-excitatory associations (CS-US) are not fully erased or altered during extinction. Instead, a new, competing association is formed – one in which the CS no longer predicts danger (CS-noUS). This means the original fear excitatory association (CS-US) and the new inhibitory association (CS-noUS) coexist. Because the CS-US association is not erased, fear may return, also after apparent extinction. This would explain the return of fear that is sometimes seen after successful exposure therapy. Following the ILR model, exposure therapy should focus on developing new ***inhibitory associations*** that compete with initial fear-based associations and enhancing their retrievability to reduce the likelihood of fear returning. The effectiveness of exposure therapy thus depends on the strength and accessibility of the inhibitory associations.

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- 2 The Inhibitory Learning and Retrieval model of extinction was first introduced as the Inhibitory Learning model of extinction (Craske et al., 2008, 2014) and is often referred to as Inhibitory Learning Theory (ILT) in earlier work, including some of our own. The model's name was later revised to include retrieval processes (Craske et al., 2022).
 - 3 In earlier work, the terms extinction and habituation have occasionally been used interchangeably. However, extinction refers to an associative process characterized by a decrease in conditioned responding, whereas habituation is a non-associative process involving a reduction in responsiveness following repeated stimulus exposure.

Table 1. Strategies to enhance inhibitory learning (reproduced from Craske et al., 2014)

Strategy	Description
Expectancy violation	Design exposures to violate specific expectations
Deepened extinction	Present two cues during the same exposure after conducting initial extinction with at least one of them
Reinforced extinction	Occasionally present the US during exposures
Variability	Vary stimuli and contexts
Remove safety behaviors	Decrease the use of safety signals and behaviors
Attentional focus	Maintain attention on the target CS during exposure
Affect labeling	Encourage the clients to describe their emotional experience during exposure
Mental reinstatement/ retrieval cues	Use a cue present during extinction or imaginably reinstate previous successful exposures

Although there is overlap between EPT and the ILR model (see, for instance, Cooper et al., 2017), they highlight different mechanism variables. Craske et al. (2008, 2014) propose moving away from focusing on distress levels during exposure, suggesting instead a focus on expectancies to strengthen inhibitory learning. More specifically, in the context of PTSD, a patient needs to learn and remember that confrontation with trauma-related stimuli (CS) does not lead to their expected negative outcomes (e.g., 'I will be attacked', or 'I will go crazy'). Expectancy violation and expectancy changes are thus proposed to indicate successful learning. The focus should be on tolerating distress (i.e., 'I can handle it') to allow new learning, rather than attempting to reduce it. The retrievability of the inhibitory learning is enhanced by conducting exposure in a variety of contexts and with different stimuli. Table 2 provides an overview of EPT and ILR-informed exposure characteristics.

Although the ILR principles are based on a well-established empirically supported model (Craske et al., 2008, 2014; Pittig et al., 2016), studies testing these principles in clinical practice, especially in patients with PTSD, are lacking (Jacoby & Abramowitz, 2016; Weisman & Rodebaugh, 2018). At the start of this dissertation, maximizing expectancy violation and incorporating variability were proposed as the primary guiding principles to enhance exposure efficacy (Weisman & Rodebaugh, 2018).

Table 2. Characteristics of EPT and ILR-based exposure

	EPT exposure	ILR exposure
Rationale	Emotional processing	Inhibitory learning and retrieval
View on distress	Reduction (distress diminishes over time)	Tolerance (distress can be experienced and withstood)
Change indices	1) WS distress reduction 2) BS distress reduction 3) Posttraumatic cognitions	1) Threat expectancies
Structure of exposure	Gradual, focus on repetition	Variable, focus on maximizing expectancy violation

Note. WS = within session; BS = between session.

Violating expectancies

Threat expectancies are beliefs about the likelihood that confronting a feared stimulus will lead to a negative outcome (e.g., “If I go out in the dark, I will be attacked”). New learning is thought to occur when there is a discrepancy between expectation and reality (Rescorla & Wagner, 1972). In other words, stronger expectancy violations lead to greater inhibitory learning. Following the ILR model, exposure should thus focus on maximally violating expectancies (Craske et al., 2014, 2022). Expectancies are distinct from posttraumatic cognitions emphasized in EPT, as expectancies refer to specific, concrete expectations formulated in an ‘if-then’ statement, whereas posttraumatic cognitions are more general beliefs about the self, others, and the world.

Expectancy violation during exposure

Emerging studies are investigating whether there is an association between expectancies and symptom improvement during exposure, as is one of the requirements for establishing a mechanism of change (Kazdin, 2009). A large study in a sample of mixed anxiety disorders showed that the extent to which threat expectancies change is associated with symptom improvement (Pittig et al., 2022). In patients with PTSD, threat expectancies (e.g., ‘If I do the exposure, I will go crazy’) have been found to decrease over the course of treatment (de Kleine et al., 2017), although these changes in expectancies were not associated with reductions in PTSD symptoms. This study used a standardized measure to assess expectancies, which may not have captured the threat expectancies most relevant to individual patients throughout treatment. Further research is needed to clarify the relationship

between threat expectancies and symptom improvement, and particularly which expectancies must be violated for change to occur.

Manipulating expectancy violation

Another way of examining whether expectancy violation drives symptom reduction, is by *promoting* (i.e., manipulating) expectancy violation through therapeutic procedures and assessing whether it affects outcomes. Designing exposure as a hypothesis-testing mini-experiment, thereby emphasizing expectancies and their non-occurrence, may promote expectancy violation, which in turn is thought to strengthen inhibitory learning and enhance treatment effects (Craske et al., 2014, 2022). Support for the idea that expectancy violation enhances exposure outcomes is often drawn from two pre-clinical studies. One study found that administering one trial of expectancy-disconfirming exposure every two days was equally effective compared to daily repeated trials of non-disconfirming exposure, which was interpreted as evidence that expectancy violation enhanced treatment effects (Baker et al., 2010). Another study showed that exposure that continued until expected aversive outcomes dropped below a credibility of 5% was more effective than exposure focused on distress reduction for individuals with elevated anxiety sensitivity (Deacon et al., 2013). It is still unclear whether emphasizing expectancies and their non-occurrence will enhance exposure outcomes for PTSD.

Incorporating variability

Incorporating variability, across both contexts and stimuli, is presumed to enhance the generalization and retrievability of the inhibitory associations, thereby optimizing treatment efficacy (Craske et al., 2014, 2022). This is based on research on (non-emotional) learning which suggests that variability enhances memory retrievability and promotes generalization (Bjork & Bjork, 1992, 2006). Variability is presumed to offset context renewal (i.e., the return of fear in a different context after previous successful extinction). In the context of exposure therapy, context variability refers to varying the situations or environments in which exposure occurs (e.g., in different rooms, places, or varying times a day). Variability might also refer to varying distress levels during exposure which serve as an internal context (e.g., conducting exposures while being relatively calm vs. highly distressed). Stimulus variability refers to varying the specific features of the feared stimulus during exposure (e.g., in vivo exposure to different men in various social settings).

Variability during exposure

Only a small number of studies have assessed the association between variability during exposure and symptom improvement. Some empirical evidence suggests

that more variable in-session distress levels during exposure is associated with better treatment outcomes in adults with public speaking anxiety and contamination anxiety (Culver et al., 2012; Kircanski et al., 2012). Whether more variable levels of distress precede symptom improvement is still unknown and has not yet been investigated in samples of patients with PTSD.

Manipulating variability

Several laboratory and pre-clinical studies have shown that exposure in varying contexts (i.e., context variability) results in less return of fear than exposure in a single context, both in spider-fearful and healthy participants (Bandarian-Balooch et al., 2015; Dunsmoor et al., 2014; Shiban et al., 2015). Similarly, using multiple stimuli during exposure (i.e., stimulus variability) has been linked to reduced return of fear in spider-fearful individuals (Shiban et al., 2015). However, the order of stimulus presentation, gradual versus variable, has not been found to affect exposure outcomes in adults with obsessional thoughts, although this study may have been underpowered (Jacoby et al., 2019). Again, it remains unclear whether increasing variability (either in contexts or stimuli) as a therapeutic strategy optimizes exposure outcomes for PTSD.

Examining ILR principles in PTSD

In conclusion, further research is needed to determine whether principles from the ILR model enhance exposure therapy. Some proposed ILR-strategies have been tested in pre-clinical samples (e.g., samples with elevated levels of symptoms), but not yet in samples of patients with PTSD. Moreover, the exploration of a comprehensive PTSD treatment protocol that integrates multiple of these strategies is warranted. Below, we illustrate a suggested application of ILR-based exposure using Charlotte's case vignette.

Aims and outline of the dissertation

The aims of this dissertation are to 1) further understand the underlying mechanisms of action of exposure therapy for PTSD, and 2) to assess whether we can enhance the efficacy of exposure for PTSD by manipulating treatment elements proposed to promote inhibitory learning. In this dissertation, data from a large treatment study were analyzed, and additional studies were conducted, comprising studies with both experimental and observational designs.

Chapter 2 investigates whether changes in posttraumatic cognitions temporally precede changes in PTSD symptoms during PE in patients with DSM-5 defined PTSD following childhood abuse, using data from the IMPACT study. The IMPACT study is a randomized controlled trial (RCT) comparing the effectiveness of different PE

treatment deliveries in 149 patients with PTSD. Given the emphasis on cognitive shifts in both EPT and ILR models, further investigation is needed to clarify their role in symptom improvement. **Chapter 3** investigates whether in-session distress variability precedes PTSD symptom improvement, also using data from the IMPACT study. **Chapter 4** assesses whether explicitly focusing on expectancy violation leads to better exposure outcomes in patients with PTSD, using data from the OPENup RCT study. In this study, 60 patients with PTSD received one session of exposure therapy followed by a one-week follow-up assessment. Patients were randomized to either exposure with an explicit focus on expectancy violation or exposure where expectancies were not explicitly addressed. **Chapter 5** presents results of a single case experimental design, OPENup SCED, where we evaluated the applicability and effects of a comprehensive, ILR adapted exposure therapy in patients with PTSD. The study consists of two single case experimental design studies where 19 patients with PTSD were tracked daily over the course of treatment and three-month follow-up. Patients either received ILR-based exposure or EPT-based exposure. When conducting our experimental studies, we discovered that, despite growing interest, no validated measure existed for assessing concrete negative expectancies. **Chapter 6** assesses the psychometric properties of a measure we developed, called 'Threat Appraisal in PTSD Scale' (TAPS), that aims to assess concerns for concrete trauma-related negative outcomes. We collected data from 309 non-clinical participants and 125 patients with PTSD. **Chapter 7** contains a summary and discussion of the main findings in this dissertation, the strengths and limitations, clinical implications and recommendations for future research.

A suggested application of ILR-based exposure in Charlotte's case

Charlotte follows exposure treatment for her PTSD symptoms based on ILR principles. In her first session, after having received psycho-education on PTSD and exposure therapy, Charlotte and her therapist identified her greatest fears when faced with trauma reminders. Charlotte was most afraid that someone would assault her again ('If I go jogging by myself, I will be assaulted again', 90% credibility). She also mentioned that she feared she would be unable to tolerate the distress she feels when thinking about the event ('If I think about the event, I will go crazy', which she further specified as being 'unable to hold a conversation and stand on her feet', 80% credibility). Exposure exercises (in vivo and imaginal) were designed as hypothesis testing experiments aimed to challenge these expectations. Charlotte and her therapist paid specific attention to elements that affect the likelihood of the feared outcome (i.e., safety signals). During exposure, she optimally tested her feared outcome by removing these safety signals or adding elements that increased the likelihood of the feared outcome. The exposure exercises followed a somewhat random order, i.e., they did not follow a gradual approach from least to most distressing. This would also allow Charlotte's distress levels to show a more variable pattern. Situations where Charlotte felt the feared outcomes were most likely to happen were prioritized (e.g., 'going jogging by myself without my phone') to maximize expectancy violation. Exposure was continued or repeated until the credibility of Charlotte's expectancies went down. After each exercise, her therapist asked Charlotte whether her feared outcome occurred and what she learned from this. Charlotte was instructed to practice her exposure exercises in different places and situations (e.g., at home, at varying times of the days). Charlotte's therapist also switched treatment rooms throughout the treatment and their appointments varied over the week.