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A Case for Translation from the Clinic to the Laboratory

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Abstract

Laboratory procedures have been used for decades as analogues for clinical processes with the goal of improving our understanding of psychological treatments for emotional disorders and identifying strategies to make treatments more effective. This research has often focused on translation from the laboratory to the clinic. Although this approach has notable successes, it has not been seamless. There are many recent examples of strategies that work in the laboratory that fail to lead to improved outcomes when applied clinically. One possible reason for this gap between experimental and clinical research is failure to focus on translation from the clinic to the laboratory. Here, we discuss potential benefits of translation from the clinic to the laboratory and provide examples of how this might be implemented. We first consider two well-established laboratory analogues (extinction and cognitive reappraisal), identify critical aspects of the related clinical procedures (exposure and cognitive restructuring) that are missing from these analogues, and propose variations to better capture the clinical process. Second, we discuss two clinical procedures that have more recently been brought into the laboratory (eye movement desensitization and reprocessing and imagery rescripting). We conclude by highlighting potential implications of this proposed shift in focus for translational research.

Keywords

translational; extinction; exposure; cognitive reappraisal; cognitive restructuring; imagery rescripting; EMDR; eye movement; cognitive behavioral therapy

Decades of research have focused on the goal of translating laboratory findings to the clinic in order to improve the treatment of mental health disorders (Carpenter et al., 2019; Milad & Quirk, 2012; Zilverstand et al., 2017). Although translational research has been successful in that some of the most effective treatments for emotional disorders are based on this research (e.g., exposure therapy), recent efforts to use translational research to identify methods to improve such treatments have not always been fruitful. Examples include the use of psychopharmacology to enhance extinction learning during exposure therapy (Mataix-Cols et al., 2017; Norberg et al., 2008) or pharmacological and behavioral strategies to interfere

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with memory reconsolidation (Lonergan et al., 2013; Walsh et al., 2018; Xue et al., 2012). Despite much enthusiasm about experimental studies of these strategies and the promise of better outcomes for patients (Kindt, 2014; Milad & Quirk, 2012), clinical studies of these approaches have been somewhat disheartening (Mataix-Cols et al., 2017; Steenen et al., 2016; Walsh et al., 2018), and as a result, clinical researchers have not pushed for these strategies to be disseminated to clinical practice. At the same time, there are many clinical interventions that have been disseminated widely, despite few experimental studies on and little understanding of the mechanisms of action of these interventions. For example, Eye Movement Desensitization and Reprocessing therapy (EMDR; Shapiro, 1989) is considered an evidence-based treatment for posttraumatic stress disorder (PTSD; American Psychological Association, 2017; Cusack et al., 2016; Department of Veteran Affairs & Department of Defense, 2017; International Society for Traumatic Stress Studies, 2019), despite a poor understanding of how eye movements contribute to changes in PTSD symptoms (Landin-Romero et al., 2018). As such, one may ask the question – why are we seeing this disconnect between experimental and clinical research?

The Unidirectional Problem

When discussing translational research, the focus is often unidirectional; namely translation *from* the laboratory *to* the clinic. In the current review, we argue that part of the answer to the question above may be the lack of focus on translation *from* the clinic *to* the laboratory as well. Indeed, a large number of reviews have centered around the topic of translation from the laboratory to the clinic, including successes and failures in this endeavor (e.g., Craske et al., 2018; Hofmann, 2007; Milad & Quirk, 2012; Milad et al., 2014; Zilverstand et al., 2017), whereas very few have tackled the topic of translation from the clinic to the laboratory (e.g., Carpenter et al., 2019). This lack of focus on translation from the clinic to the laboratory may contribute to experimental findings getting “lost in translation”; if laboratory analogues do not accurately model therapeutic procedures, the benefits we observe in the laboratory may not come to fruition when translated to the clinic. In other words, there are many reasons why laboratory research on various translational strategies, such as the ones mentioned above, may not lead to successful clinical trials. Here we raise the possibility that one potential reason may be that these strategies were derived from laboratory research using analogues that do not capture key nuances of therapeutic procedures. Furthermore, a failure to focus on translation from the clinic to the laboratory also leads to a lack of experimental research on, and understanding of mechanisms of action for, widely used therapeutic procedures. This may hamper researchers’ ability to optimize existing treatments or discover novel treatments.

Improving Translational Research

In this article, we suggest that focusing on translation from the clinic to the laboratory may be a means to improve translational research. However, we first need to define what successful translational research looks like. Translational research has at its core the goal of improving clinical outcomes for patients. It should result in more efficacious and effective treatments. Successful translation from the laboratory to the clinic would be evident when an intervention identified in animal models or experiments with healthy humans, results

in an intervention that improves clinical outcomes when tested in randomized controlled efficacy trials in patient populations. Ideally, this intervention also holds up to the test of effectiveness research conducted in the community with patients (for review, Nathan et al., 2000). One method of evaluating translational success is to examine whether effect sizes decrease when an intervention moves from the lab to the clinic. Although some degree of decrease is to be expected when moving from a highly controlled to a less controlled environment, the goal is to maintain a clinically-meaningful effect size and consistently observe a significant effect in patients. Given that recent translational research efforts, for example those described above, have not led to these types of outcomes (e.g., Mataix-Cols et al., 2017), we argue that it may be time to re-examine some long-standing laboratory analogues. If laboratory analogues used to test interventions align more closely with clinical practice, this may lead to improved clinical outcomes with similar effect sizes (as opposed to dramatically reduced effect sizes or non-significant effects) when interventions are tested in patient populations.

Therapeutic Procedures versus Psychotherapy

Prior to delving into examples of specific therapeutic procedures and their laboratory analogues, it is important to understand how therapeutic procedures are defined and why it is important to conduct experimental research on procedures rather than psychotherapies. *Therapeutic procedures* refer to specific therapeutic techniques that target core dimensions of psychopathology (e.g., exposure to target fear; Hayes & Hofmann, 2017, 2018). This contrasts with the term *psychotherapy*, which refers to a treatment package for a mental health disorder/s that typically includes multiple therapeutic components or procedures. Researchers and clinicians have called for a movement away from disorder-specific psychotherapies towards a transdiagnostic approach (Kozak & Cuthbert, 2016; Sauer-Zavala et al., 2017) and identifying core procedures and processes that lead to symptom change (Hayes & Hofmann, 2017, 2018; Kazantzis et al., 2018). In line with that goal, we predominantly focus on therapeutic procedures rather than psychotherapies. We only discuss psychotherapies when it is necessary in order to demonstrate the use of the therapeutic procedure.

Why Examine Therapy Procedures in the Laboratory?

There are many reasons why it is important to study therapy procedures in the laboratory. First, the laboratory allows for a more controlled environment. Variables can be more easily manipulated to examine subtle variations on procedures, leading to innovations in treatment approaches. Second, research questions can be examined in a relatively short amount of time. Rather than conducting a clinical trial, which often requires multiple years, experimental studies can be conducted relatively quickly. This not only reduces research costs, but also reduces the duration of time required to answer mechanistic questions, accelerating the research process. Third, research questions can be examined in healthy humans or non-human animals, prior to testing in patients. Laboratory procedures are often used to mimic clinical symptoms allowing researchers to then examine potential methods to reduce or eliminate symptoms. For example, threat conditioning is used to create threat responses that researchers can then aim to reduce. The ability to examine research questions

in healthy humans minimizes risk to more vulnerable patient populations, controls for confounding variables that are often present in patients (e.g., comorbidity), and allows for more rapid recruitment and assessment. Additionally, when it is too risky or challenging to examine new approaches or mechanisms in healthy humans, research in non-human animals may provide useful insights. Fourth, although the use of neuroscientific methods (e.g., neuroimaging, stimulation, psychophysiology) may not always be necessary to understand the efficacy of a strategy, these methods may help elucidate why a strategy is working (i.e., mechanisms of change). This could in turn result in the refinement or optimization of that strategy prior to translation or alternatively lead to novel approaches (e.g., drugs) to target the same mechanism.

Current Goals

Our goal in this article is to make a case for increasing the focus on translation from the clinic to the laboratory in order to improve success of translational research for emotional disorders. To accomplish this goal we take a close look at how four example therapeutic procedures are currently studied in the laboratory versus how they occur in the clinic, and we highlight means to potentially improve or exploit these laboratory analogues inspired by their clinical implementation.

We first focus on two well-established experimental analogues that aim to represent two common therapeutic procedures: (1) extinction / exposure, and (2) cognitive reappraisal / cognitive restructuring. These cognitive behavioral procedures have been used for a long time, are considered evidence-based, and are associated with a large body of clinical and experimental literature. As experimental researchers frequently use these analogues in translational research aimed at identifying strategies to enhance exposure or cognitive restructuring, our goal is to examine whether these analogues sufficiently mirror clinical practice. We start by describing the experimental analogues, followed by an explanation of how the processes engaged by these analogues typically occur in the clinic. We then discuss opportunities for improved translation. Unlike many prior reviews which focus on translation from the laboratory to the clinic (e.g., Craske et al., 2018; Kredlow et al., 2018; Milad et al., 2014), we focus on ideas for translation *from* the clinic *to* the laboratory. In other words, rather than discussing methods to enhance exposure or cognitive restructuring inspired by laboratory research, we discuss methods to improve the laboratory analogues of extinction and cognitive reappraisal inspired by clinical work. Specifically, we outline aspects of the therapeutic procedures that are missing in current experimental analogues and ways in which our experimental procedures may fail to fully capture the clinical process.

Next, we discuss two therapy procedures that are less well-known to basic experimental researchers and have only recently been brought into the laboratory: (1) eye movements as part of EMDR, and (2) imagery rescripting which is a component of various psychotherapies. Since the clinical versions of these procedures preceded the laboratory analogues, we begin by first discussing how these procedures are conducted in the clinic. Then we outline current attempts to model these procedures in the laboratory and suggest alternative laboratory models that may represent similar processes. This provides an opportunity to discuss how laboratory procedures can be developed to accurately mirror

these clinical approaches in hopes of improving translational value. This also provides an example of how clinical procedures can be used as inspiration for translational laboratory research, which may in turn lead to novel clinical interventions. We chose these two procedures in particular because we have observed a recent increase in laboratory research on these procedures, but they are far from well-studied in the laboratory. Therefore, there is ample room for discussion of future directions for translational research.

We do not aim for this to be a comprehensive overview of all therapy procedures or experimental analogues, but rather hope that these four procedures serve as examples to discuss important considerations in translation of clinical procedures from the clinic to the laboratory. It is important to note that the current experimental analogues we discuss have resulted in numerous advances in translational research, and many studies may have basic, not translational, research goals. We are not suggesting these analogues should be abandoned. Instead, we hope to inspire future research on variations of these analogues that may help bridge the gap between the clinic and the laboratory. Additionally, there are many ways to discuss translation from the clinic to the lab. Other relevant topics, such as experimental research conducted in clinical populations (Duits et al., 2015; Zilverstand et al., 2017) or translational research on the etiology of emotional disorders (Fullana et al., 2020; Jovanovic & Ressler, 2010) are discussed in prior reviews. Finally, a primary goal of ours is to discuss methodological and design features that would improve the clinical relevance of laboratory analogues, rather than the results of specific studies that have implemented these features. We conclude by discussing how improving the alignment between laboratory analogues and therapy procedures may impact future translational research and clinical outcomes.

Laboratory Analogues for Clinical Procedures

Extinction / Exposure

Extinction in the Laboratory

Procedure.: Threat extinction as a laboratory procedure has been used for decades and has resulted in a large body of research (Milad & Quirk, 2012, Dunsmoor et al., 2015). Threat extinction typically occurs following threat acquisition, which involves the pairing of a neutral stimulus (conditioned stimulus, CS; e.g., a colored shape) with an aversive outcome (unconditioned stimulus, UCS; e.g., a shock). By the end of threat acquisition, participants come to exhibit threat responses as measured by psychophysiological (e.g., increased sweating as measured by skin conductance) or subjective assessment (e.g., UCS anticipation) to the CS. In the most basic form of threat extinction, the CS that was previously associated with the UCS during acquisition, is presented repeatedly without the UCS, usually during one experimental session. Typically, extinction procedures result in a decrease in threat responses to the stimulus across CS trials as measured by psychophysiological or subjective assessment (for review, Lonsdorf et al., 2017).

Stimuli.: Extinction in the laboratory can involve various types of CSs (for review, Lonsdorf et al., 2017). Common types include simple neutral cues (e.g., colored shapes), complex fear-relevant cues (e.g., images of spiders; for review, Öhman, 2009), categories of stimuli

(e.g., different types of animals; for review, Dunsmoor & Murphy, 2015), or more complex multi-component stimuli (e.g., 3D combinations of shapes, Fribbles; Barry et al., 2014;). The UCS differs across studies, with the most common UCS being mild electric shock (for review, Lonsdorf et al., 2017), while other examples are aversive sounds and images (e.g., scream sound and fearful face; Lau et al., 2008). The most common way of inducing extinction is therefore via presentation of visual cues. However, there are other ways of inducing extinction that are clinically relevant, namely via interoception (e.g., Acheson et al., 2007) or imagination (e.g., Agren et al., 2017; Reddan et al., 2018), which will be discussed in more detail below.

Outcomes.: The outcome measures used in extinction research include psychophysiological, neurobiological, subjective, and behavioral measures of defensive responses and emotions (for review, Lonsdorf et al., 2017). Meta-analyses and reviews frequently report skin conductance to be the most commonly used psychophysiological outcome (Duits et al., 2015; Lissek et al., 2005; Lonsdorf et al., 2017). Other psychophysiological outcomes include fear potentiated startle (for review, Davis, 2006), heart rate (e.g., Wendt et al., 2015), facial muscle tension (e.g., Orr et al., 2000), and pupil dilation response (e.g., Leuchs et al., 2019). Neurobiological outcomes include fMRI (for review, Fullana et al., 2018), electroencephalography (e.g., Mueller et al., 2014), and magnetoencephalography (e.g., Moses et al., 2007). Subjective outcomes include ratings of fear/anxiety or arousal in response to the CSs (e.g., Waters & Pine, 2016), UCS anticipation (e.g., Krypotos et al., 2015), and pleasantness/liking of the CSs/UCS (for review, Hofmann et al., 2010). Studies have also employed behavioral measures of avoidance of the CS, such as time engaging in the conditioning context (e.g., Grillon et al., 2006).

Although extinction is often described as a laboratory analogue for exposure therapy (e.g., Milad et al., 2014), the laboratory extinction procedure, types of stimuli used, and the outcome measures employed are vastly different from clinical exposure procedures, as we will discuss in the next sections.

Exposure in the Clinic

Procedure.: Exposure is one of the most common and long-standing clinical procedures involved in cognitive behavioral therapy (CBT). It has been used to treat a broad range of mental health issues, including anxiety (Springer et al., 2018), traumatic stress (Cusack et al., 2016), obsessive compulsive (Öst et al., 2015), substance (Mellentin et al., 2017), and eating disorders (Butler & Heimberg, 2020). During exposure, a patient is asked to repeatedly confront stimuli that are associated with maladaptive emotional responses or behaviors until those emotional responses or behaviors diminish (for detailed explanation of exposure procedures, see Abramowitz et al., 2019; Hembree et al., 2003).

Stimuli.: There are three types of exposures conducted in the context of CBT: (1) in vivo, (2) interoceptive, and (3) imaginal exposures (Boettcher et al., 2016; Foa & McLean, 2016). In vivo exposures involve confronting real-life stimuli such as situations, places, people, or things. This often involves confronting more than one stimulus at a time. When a patient's symptoms are more strongly tied to an internal experience, in vivo exposure is typically

not sufficient (Pompoli et al., 2018). Then, interoceptive exposure (Boettcher et al., 2016) is used to expose a patient to internal physical sensations. Exercises are used to bring about internal sensations artificially (e.g., running upstairs to induce rapid heartbeat) so that the patient habituates to them and learns that the negative consequences they fear do not ensue. In other instances, a patient's symptoms may relate to memories of past events or imagined future events. In these cases, imaginal exposure is often used; patients are asked to repeatedly imagine the event occurring. For example, in the case of PTSD, patients are not only fearful of real-life stimuli related to their trauma; they are also fearful of the memory of their trauma. Because of this, exposure therapy for PTSD also involves imaginal exposure to the trauma memory (Foa et al., 2007; Resick et al., 2016).

Other Features.: Exposure typically involves a stepwise procedure meant to optimize the experience. The therapist works with the patient to design the exposure, often outlining specific goals and predictions (Abramowitz et al., 2019; Craske et al., 2014). After an exposure, the patient and clinician typically discuss what was learned and whether the patient's predictions were confirmed/disconfirmed (Abramowitz et al., 2019; Craske et al., 2014). Occasionally, if maladaptive thoughts arise during the exposure, these thoughts may be restructured (see section on Cognitive Reappraisal / Cognitive Restructuring below). Additionally, in some cases, post-exposure behaviors are monitored and changed (e.g., exposure and response prevention; Foa & Lichner, 2012).

There are also larger-scale factors involved in designing and conducting exposures. Exposures are conducted across multiple therapy sessions and also for homework (Huppert et al., 2006). Because of this, some exposures are conducted independently, whereas other exposures are conducted with the therapist by the patient's side. In addition, some exposures are conducted in the therapy room, whereas others are conducted out in public (e.g., Fang et al., 2013). Typically, at the start of therapy, the clinician works with the patient to brainstorm possible exposures based on the patient's symptoms. Next, with patient input, exposures are ranked on a hierarchy from least to most difficult (Katerelos et al., 2008). Traditionally, therapists move from engaging in less challenging exposures to engaging in more challenging exposures over time (Abramowitz et al., 2019; Jacoby et al., 2019).

Outcomes.: The most commonly used outcome measures of response to exposure therapy are clinician-assessed or self-report symptom measures. Symptom measures typically include questions about cognitive, emotional, and behavioral characteristics of a diagnosis, often mapping on to DSM 5 criteria (American Psychiatric Association, 2013). Symptom measures are often administered on a session to session basis, or at least at the start and end of treatment. Additionally, subjective units of distress are collected during exposures to measure change in distress during the exposure and as a rough guide of progress (Abramowitz, 2013; Bluett et al., 2014). Behavioral measures, such as a test of how willing a patient is to approach a feared stimulus, may also be employed, particularly in the context of clinical trials (i.e., behavioral approach test; e.g., Miloff et al., 2019).

What is Missing? Opportunities for Translation from the Clinic to the Laboratory—It is clear from our review above that many factors that are central to exposure therapy in the clinic are not sufficiently modeled in the laboratory. These represent

missed opportunities and possible explanations for why extinction findings often do not hold up when translated to the clinic. Below we will outline several discrepancies between extinction and exposure and discuss potential opportunities for translation from the clinic to the laboratory.

Our first observation is that the cues involved in extinction are far less complex than the stimuli used during exposures. With regard to in vivo exposures, which are akin to extinction to a visual CS, researchers have attempted to model the complexity of the stimuli involved in clinical exposures by using multi-component CSs, multiple CSs (e.g., deepened extinction which involves presenting trials of one CS first followed by subsequent trials of the same CS combined with a second CS, Culver et al., 2015), or categories of CSs. The use of multiple similar CSs (e.g., circles of slightly different size; Lissek et al., 2008), categories of CSs (e.g., images that belong to a category such as various animals; Dunsmoor & Murphy, 2015), and multi-component CSs (e.g., Fribbles; Barry et al., 2014) in particular has allowed for examination of processes such as generalization of fear and extinction of generalized fears. Generalization is the tendency for patients with fear-related disorders to generalize from one fear cue to another similar but not the same fear cue (e.g., a patient with specific phobia of spiders generalizing to fear other types of bugs).

Nonetheless, there is room for improvement here given that clinical exposures often involve a whole cluster of multi-component cues across various contexts. Additionally, few laboratory studies use non-visual CSs in humans (e.g., sounds, smells; Stevenson et al., 2000) despite the fact that exposures often involve approaching multi-sensory cues. More advanced multi-component CSs that incorporate fear relevant stimuli and multiple senses, may be a useful means to model complex exposures that are often employed in the clinic. Virtual reality technology has allowed researchers to explore extinction in multiple virtual reality contexts (e.g., Dunsmoor et al., 2014), mirroring clinical procedures of conducting exposures across various settings. Virtual reality could also be used to expand the complexity of CSs and present multi-component multi-sensory CSs across various contexts. Furthermore, sometimes exposures only involve non-visual cues. For example, this is the case when conducting exposures with blind individuals or individuals whose anxiety is provoked by certain sounds (e.g., Frank & McKay, 2019). Therefore, additional laboratory research in humans using non-visual CSs alone would also be informative.

Our second observation is that there is a poverty of laboratory research on interoceptive and imaginal extinction. As described above, interoceptive and imaginal exposure are two of the three types of exposures used in CBT. Interoceptive exposure involves exposure to bodily sensations and imaginal exposure involves exposure to memories or imagined future events. To date, few studies have attempted to model these procedures in the laboratory. To provide a rough estimate, 72 articles result from a PubMed title/abstract search on “interoceptive extinction” (conducted on December 9th, 2020). Further, we were only able to identify two studies to date on imaginal extinction that conditioned participants in the laboratory then asked them to imagine the CS during extinction (rather than viewing the CS); one from a PubMed title/abstract search on “imaginal extinction” conducted on December 9th, 2020 (Agren et al., 2017) and one from discussion with researchers in the field (Reddan et al., 2018), albiet there is a larger literature on imaginal/instructed acquisition of conditioned

threat (Dadds et al., 1997) and imaginal extinction of naturally acquired CS-US associations (e.g., Redd et al., 1993). This stands in contrast to the over 33,000 articles on extinction alone (PubMed title/abstract search on "extinction" conducted on December 9th, 2020). As few studies have used these procedures, their validity is yet to be established, an issue that has been raised more broadly for extinction (for review, Craske et al., 2018; Scheveneels et al., 2016).

Research in this area is particularly valuable given that the use of interoceptive and imaginal exposure is common across many disorders (Boettcher et al., 2016; Foa & McLean, 2016). For example, although interoceptive exposure was initially conceived as a treatment for panic, it is also applied in the treatment of PTSD, social anxiety, specific phobia, irritable bowel syndrome, and chronic pain (Boettcher et al., 2016). In contrast, in the laboratory, interoceptive extinction has predominantly been used to research panic (Acheson et al., 2007; Benke et al., 2018; Pappens et al., 2014) and pain (De Peuterl et al., 2011; Zaman et al., 2016). Additionally, imaginal exposure is one of the most prominent interventions used in the treatment of PTSD. In the case of prolonged exposure therapy, imaginal exposure comprises approximately half of the in-session time whereas in vivo exposures are only assigned for homework (Foa et al., 2007). Furthermore, imaginal exposure is frequently used in the treatment of OCD if, for example, a patient has obsessions about future horrific events for which it is not practical or safe to design an in vivo exposure (Gillihan et al., 2012). Imaginal exposure is also occasionally used to treat other anxiety disorders (Koerner & Fracalanza, 2012). The strong focus on visual CSs relative to interoceptive and imaginal CSs may result in research on extinction potentially being more successful when translated to the treatment of simple phobias, as these disorders are readily treated with in vivo exposures and do not typically require imaginal or interoceptive exposure as do more complex fear-related disorders (Kaczkurkin & Foa, 2015; Wolitzky-Taylor et al., 2008). For example, in the case of d-cycloserine research, translation to specific phobias proved to be more promising than translation to more complex disorders, such as PTSD (Rosenfield et al., 2019).

Our third observation is that extinction as a model for exposure fails to take into account that some of the benefits of exposure may come from habituation to the UCS. Clinical researchers have argued that the decrease in emotional responses during exposure is thought to occur because of two processes: (1) inhibitory learning (e.g., learning that a situation is safe, that a stimulus will not lead to a negative consequence; Craske et al., 2014; Rauch & Foa, 2006) and (2) habituation (i.e., diminished physiological or emotional responses to a frequently repeated stimulus; Gallagher & Resick, 2012; Rauch & Foa, 2006). This is particularly clear when comparing imaginal exposure and imaginal extinction. A prominent characteristic of imaginal exposure is that the patient imagines the "CS" and "UCS." According to a habituation model, the previously neutral cues associated with the trauma event (e.g., the location, the time of day, etc.) are conceptualized as the CSs and actual negative consequences of the trauma are conceptualized as the UCSs (e.g., pain, injury, etc.). Patients are asked to imagine the full traumatic event, not just the neutral cues related to the event, and thus, some habituation to the UCS occurs. The imaginal extinction procedures used by Agren et al. (2017) and Reddan et al. (2018) in the laboratory fail to mirror the clinical procedure in that they do not have participants imagine the UCS. Expanding their model to incorporate the UCS may be helpful for translational research

on methods to enhance imaginal exposure. This issue applies more broadly, although likely to a lesser degree, in that in vivo and interoceptive exposure cues have often acquired a negative valence and are at times experienced as aversive. Thus, some of the benefit from exposure involves getting used to the cues and the anxiety that results from them (i.e., habituation), rather than learning that the cues are safe (i.e., extinction learning). Laboratory models using fear-relevant stimuli begin to capture this aspect of exposure, however, very few extinction studies have examined habituation to a UCS directly (e.g., Haesen & Vervliet, 2015). Outside of the threat conditioning literature, there is considerable laboratory research demonstrating habituation to repeatedly presented emotional stimuli (e.g., Wright et al., 2001; Averill et al., 1972). However, it would still be beneficial to incorporate a habituation to the UCS procedure within the extinction laboratory procedure. For example, in conducting translational research on a method to enhance imaginal exposure, using a variation on extinction that includes habituation to the UCS in the laboratory may improve translational success.

Our fourth observation is that laboratory models of extinction primarily involve a single session, whereas exposure therapy involves multiple exposure sessions conducted sequentially. Despite increasing complexity of CSs used in the laboratory, extinction in the laboratory typically still focuses on one or two stimuli during a discrete experimental session. As exposure in the clinic occurs to many complex stimuli over multiple therapy sessions spanning longer stretches of time, questions emerge about the most effective order in which to engage in exposures (Jacoby et al., 2019). For example, should clinician follow the traditional guidance and start with easier items on a patient's hierarchy and move towards more challenging items over time or is a different approach preferable? Taking laboratory models beyond single session paradigms, may help answer this and other questions. This could potentially involve acquisition to multi-component cues and extinction to single cues across multiple experimental sessions and/or days. For example, research in rodents has demonstrated that a compound conditioned fear memory (tone + light CS were associated with shock UCS during acquisition) can be disrupted using sequential rounds of retrieval-extinction, only if the stronger compound component is retrieved and extinguished first (Jones et al., 2013). Further research along these lines in humans, could provide useful information about the order in which therapists should assign exposures.

Our fifth observation is that extinction is experiment driven, whereas exposure is therapist and patient driven. Exposures begin with the therapist explaining what is going to occur and instructing the patient to stay engaged with the stimuli and avoid safety behaviors (i.e., subtle avoidance behaviors; Blakey & Abramowitz, 2016). Although some forms of instructed extinction have been explored in the laboratory (i.e., telling participants that the CS will not be followed by the UCS; Hugdahl & Öhman, 1977), this is rare. More often, participants are simply instructed to pay attention to the relationship between the CS and UCS and then procedures ensue. Additionally, patients are active participants throughout exposures; at the start they often verbalize their goals and predictions, throughout they report their subjective units of distress, and at the end they report what they have learned. This participation is thought to be important for inhibitory learning (Craske et al., 2014). Although expectancy, arousal, or contingency ratings are often used during or after extinction as outcomes (for review, Lonsdorf et al., 2017), the impact of using

these ratings on the success of extinction or to guide decision-making has not been explored to our knowledge. Furthermore, at any point in the process of exposure, the patient and therapist may engage in discussing and challenging the patient's thoughts (e.g., cognitive restructuring; see section on Cognitive Reappraisal / Cognitive Restructuring below). The combination of extinction and cognitive reappraisal / cognitive restructuring has not been examined in the laboratory (Hofmann, 2008). Such research may be helpful to address questions as to whether cognitive restructuring before or during exposure is counter-productive, as has been suggested by some clinical researchers (Craske et al., 2014). These differences between extinction and exposure likely lead to different levels of uncertainty and prediction error, variables that we know impact learning (for review, Li & McNally, 2014). Although there are many non-extinction specific reasons supporting therapist guidance and patient involvement in therapy (Joosten et al., 2008), laboratory research in this area (see Duits et al., 2017; Hollandt et al., 2020 for examples) may help clinicians understand how these factors may impact the extinction process and how to optimize patient/therapist involvement in exposures.

Finally, our last observation is the striking difference in outcomes used in extinction versus exposure research. While extinction research predominantly uses psychophysiological outcomes, exposure research predominantly uses measures of symptom change. This is problematic and may explain part of the challenge in translation. It is understandable that changes on psychophysiological measures in the laboratory may not translate into changes in subjective measures in the clinic, given that laboratory studies often find discrepant results for subjective and psychophysiological outcomes within the same study (e.g., Hollandt et al., 2020; Lonsdorf et al., 2019; White & Graham, 2016) and across psychophysiological outcomes (e.g., Leuchs et al., 2019; Sevenster et al., 2012). Furthermore, exposure therapy that has a positive impact on subjective symptoms, does not always lead to corresponding changes in psychophysiological measures. Some studies have found decreases in psychophysiological responses to fear-related stimuli from pre to post exposure therapy (e.g., Côté & Bouchard, 2005; Davis et al., 2006) while others have not (e.g., Diemer et al., 2014; Kircanski et al., 2012), and there is also evidence that this may vary by psychophysiological outcome (e.g., Maples-Keller et al., 2019). For this reason, some have argued that objective measures of psychophysiological arousal are at best, indirect indicators of emotion (LeDoux & Hofmann, 2018; LeDoux & Pine, 2016; also see Fanselow & Pennington, 2017). As such, increased use of subjective ratings and behavioral measures of avoidance in extinction studies (for discussion, Boddez et al., 2013) may improve predictive validity and lead to more fruitful translation.

Cognitive Reappraisal / Cognitive Restructuring

Cognitive Restructuring in the Laboratory

Procedure (Cognitive Reappraisal).: Cognitive restructuring and components of cognitive restructuring have been examined in the laboratory. The majority of studies have used *cognitive reappraisal* procedures (for review, Uusberg et al., 2019). Cognitive reappraisal is an emotion regulation strategy that involves changing one's thoughts about a stimulus in order to change the affective impact of the stimulus. Research on cognitive reappraisal in the laboratory has grown tremendously in the past two decades, with recent meta-analyses

(Buhle et al., 2014; Kohn et al., 2014; Lee & Xue, 2018) identifying over 40 laboratory-based neuroimaging studies of cognitive reappraisal conducted since the first neuroimaging study in 2001 (Beauregard et al., 2001), and a PubMed search revealing over 800 studies on cognitive reappraisal in general (PubMed title/abstract search on "cognitive reappraisal" conducted on December 9th, 2020).

In the laboratory, cognitive reappraisal procedures typically involve presenting a participant with a negatively-valenced stimulus (e.g., image, video, or autobiographical memory) and asking the participant to adjust the way they are thinking about the stimulus (i.e., reappraise the stimulus). Prior to the reappraisal task, participants typically complete a training session with the experimenter during which the experimenter explains the task, teaches them potential methods to reappraise stimuli, and has the participant practice. The reappraisal instructions and strategies used by participants vary across studies (for review, McRae et al., 2012). These include instructing participants to: (1) change their interpretation of what is occurring in the picture or video (i.e., situational reinterpretation; e.g., Ochsner et al., 2004; Willroth & Hilimire, 2016); (2) imagine that the stimulus is not real or that they are a detached observer (i.e., distancing; e.g., Domes et al., 2010; Eippert et al., 2007; for review, Powers & LaBar, 2019); and (3) think about the stimulus in a more positive way (e.g., Shiota & Levenson, 2009). Some studies present all of these strategies and others as possible ways to reappraise and let participants choose which strategy to use (i.e., unrestricted reappraisal; e.g., Harenski & Hamann, 2006; Kanske et al., 2011). During the reappraisal task itself, the experimenter is not involved. The participant is typically presented with multiple trials of images either preceded by the word "reappraise" or the control instructions (often "immerse" or "look"). Occasionally, information about the type of reappraisal used will be collected after the fact (e.g., McCrae et al., 2012) and participants are excluded for non-compliance with the reappraisal instructions (e.g., Nook et al., 2020).

Outcomes (Cognitive Reappraisal).: Typical outcomes include subjective feelings (e.g., McRae et al., 2012), psychophysiological outcomes (e.g., skin conductance; Eippert et al., 2007), and blood-oxygen-level-dependent imaging (BOLD) response patterns (Buhle et al., 2014; Kohn et al., 2014; Lee & Xue, 2018).

Procedure (Threat Conditioning Cognitive Restructuring).: Other researchers have attempted to model cognitive restructuring in the laboratory in the context of threat conditioning. Shurick and colleagues (2012) had participants undergo threat acquisition in which stimuli (i.e., images of snakes and spiders) were associated with a shock. After acquisition, participants completed a cognitive restructuring task. During this task, participants were first taught about the relationship between thoughts and emotions through the use of cartoons taken directly from a CBT protocol (Kendall & Hedtke, 2006). Next, the experimenter worked with participants to elicit automatic thoughts about the conditioned stimuli and the shock, challenge these thoughts using Socratic questioning, and identify alternative thoughts. This procedure has been used across a few studies (Kroes et al., 2019; Raio et al., 2013; Shurick et al., 2012), but is much less commonly used than the cognitive reappraisal procedure described above.

Outcomes (Threat Conditioning Cognitive Restructuring).: Typical outcomes included subjective and physiological threat responses when the conditioned stimuli were represented.

Cognitive Restructuring in the Clinic

Procedure.: Cognitive restructuring is a common CBT procedure used to identify and challenge maladaptive thoughts with the goal of regulating emotions (Beck, 2011; Beck & Dozois, 2011). It has been used in the treatment of almost all mental health conditions and there is particularly strong evidence for its efficacy in the treatment of anxiety and depression (for review, Clark, 2013; Kazantzis et al., 2018). Cognitive restructuring is initially a collaborative process between the therapist and the patient. Once the patient has learned how to engage in cognitive restructuring, it becomes a skill that the patient can use on their own to regulate their emotions.

The first step of cognitive restructuring, identifying automatic thoughts and corresponding emotions, involves the patient collecting data on their own internal experiences (Beck, 2011; McManus et al., 2012). Automatic thoughts are defined as unfiltered thoughts that come to mind. To help identify automatic thoughts, the patient is often asked to keep a record of their thoughts (i.e., thought record), focusing on thoughts that arise when they experience a negative emotion or an emotion-ridden situation. Through this process, the patient learns that their thoughts influence their emotions and vice versa and starts to recognize patterns in their thinking (e.g., Beck, 2011). The therapist also provides psychoeducation on the relationship between thoughts and emotions.

The second step of cognitive restructuring, determining whether automatic thoughts are maladaptive or represent problematic patterns of thinking, typically involves education on common problematic patterns of thinking and identifying patterns in the patient's thought records. Beck outlines many common problematic patterns of thinking (a.k.a., cognitive distortions; Beck, 2011; 2016). These patterns are presented to the patient, often with accompanying examples. With practice, the patient can label the problematic patterns of thinking they tend to use in the moment as they experience automatic thoughts.

The third step of cognitive restructuring involves challenging automatic thoughts through Socratic questioning (for review, Carey & Mullan, 2004; Clark & Egan, 2015) and encouraging flexibility of thinking. This step typically involves a significant amount of collaboration with the therapist. Socratic questioning is a conversational technique used to examine and question the logic behind an automatic thought. Rather than simply telling the patient why an automatic thought is untrue, illogical, or unhelpful, or telling the patient what they should think, through a series of questions, the therapist guides the patient to examine and question their own automatic thoughts. Inherent in this process is encouraging flexibility of thinking. Often automatic thoughts consist of one interpretation of an event or experience. Socratic questioning is used to help the patient realize that multiple interpretations exist and that their first automatic interpretation may not necessarily be true. Other strategies are also used to encourage flexibility of thinking; for example, a patient may be asked to generate multiple interpretations of what is occurring in an ambiguous picture (Barlow et al., 2017).

The fourth step of cognitive restructuring is generating more realistic/helpful alternative thoughts to replace unrealistic/unhelpful automatic thoughts (for review, Beck, 2011). After the process of Socratic questioning, the patient is asked to generate new ways of thinking (i.e., alternative thoughts/rational responses) about the situations that originally led to their automatic thoughts. The alternative thought is meant to be a more realistic/helpful interpretation of the situation, not an overly positive interpretation of the situation. This alternative thought is then rehearsed and used in similar situations moving forward.

Outcomes.: As with exposure, the most commonly used outcome measures of response to cognitive restructuring are clinician-assessed or self-report symptom measures.

What is Missing? Opportunities for Translation from the Clinic to the Laboratory—There are advantages and disadvantages of the current laboratory procedures as methods for studying cognitive restructuring. Prior to delving into these, it is important to note that these laboratory procedures were not necessarily constructed as a means to study the clinical procedure of cognitive restructuring. Nonetheless, they have been used in this manner and thus a discussion of opportunities for translation from the clinic to the laboratory is warranted.

Our first observation is that only some of the types of reappraisal used in the laboratory are commonly used in cognitive restructuring in the clinic. As described above, laboratory studies of cognitive reappraisal have examined many different reappraisal strategies (e.g., situational reinterpretation, distancing strategies, thinking positively, etc.; for review, McRae et al., 2012). However, some reappraisal strategies are more similar to cognitive restructuring as it occurs in the clinic than others. For example, reappraisal using situational reinterpretation is akin to patients changing their interpretation of a situation they experienced during clinical cognitive restructuring. In contrast, reappraisal using distancing is not akin to clinical cognitive restructuring; patients are not typically asked to imagine that a situation they experienced is not real or pretend they are a detached observer of the situation. This process is more similar to a different clinical technique called cognitive defusion, commonly employed in Acceptance and Commitment Therapy (Deacon et al., 2011; Forman et al., 2012; Larsson et al., 2016). When using cognitive defusion patients are asked to refrain from trying to change their thoughts and instead attempt to change their relationship to their thoughts. For example, a cognitive defusion exercise may involve reading an automatic thought over and over again until it feels “not real.” These techniques are similar in that they attempt to achieve “distance” between the stimulus and the individual; however, an important caveat is that in the case of cognitive defusion the stimulus is a thought that may or may not be about a situation and in distancing the stimulus is a situation/image. The third common cognitive reappraisal strategy of thinking more positively is also dissimilar from clinical cognitive restructuring in that patients are typically asked to think more realistically, which may or may not equate to more positive thinking (Beck & Dozois, 2011). The threat conditioning cognitive restructuring procedure (Kroes et al., 2019; Raio et al., 2013; Shurick et al., 2012) described above, is more in line with clinical cognitive restructuring in that participants are asked to interpret the stimuli in a less negative way. Distancing from the stimulus is not presented as an option, although it

is possible that participants still could spontaneously decide to use such a strategy. To aid translation of findings from laboratory studies of cognitive reappraisal to clinical studies of cognitive restructuring researchers should avoid suggesting multiple reappraisal strategies to one group of participants and continue to focus on the specific reappraisal strategies (e.g., situational reinterpretation) that are most similar to clinical cognitive restructuring.

Our second observation is that the cognitive reappraisal laboratory procedure does not fully capture the multi-step interpersonal process of cognitive restructuring as it occurs in the clinic. Although many studies seem to employ a brief training session, this appears to be a more didactic rather than a Socratic process. Participants are given direct instructions about how to reappraise stimuli, rather than learning through a back and forth discussion with the experimenter. The Socratic process is much more dynamic and is thought by many cognitive therapists to be key to change (for discussion, Braun et al., 2015; Carey & Mullan, 2004; Clark & Egan, 2015; Kazantzis et al., 2014). Therefore, while an advantage of the cognitive reappraisal laboratory procedure is that it is relatively easy to implement with minimal interaction from an experimenter and therefore less prone to experimenter bias, this can also be considered a weakness. Additional research on interpersonal cognitive reappraisal (Zaki & Williams, 2013) or experimenter-assisted versus non-assisted cognitive reappraisal would be beneficial.

Furthermore, as described above, after cognitive reappraisal training, the participant is asked to switch between reappraising and the control behavior (“look” or “immerse”) across many trials. Switching between reappraising and not reappraising is less of a focus in clinical cognitive restructuring. Cognitive restructuring may involve initial awareness and recognition of automatic thoughts (which could be similar to attending to a stimulus), however, once restructuring has occurred and an alternative thought is identified, patients are encouraged to implement this new thinking pattern consistently. Additional laboratory research using between group designs where participants are only instructed to either reappraise or engage in a control behavior consistently (e.g., Denny et al., 2015; Wolgast et al., 2011) and studies examining the effects of practicing cognitive reappraisal over time (e.g., Denny et al., 2015; for review, Denny, 2020) would be beneficial.

The threat conditioning cognitive restructuring procedure described above (Shurick et al., 2012) more closely mirrors the process of cognitive restructuring as it occurs in the clinic. This includes experimenter facilitated elicitation of automatic thoughts, Socratic questioning, reappraisal, and generating alternative thoughts. Additionally, the participant is instructed to apply what they have learned from the cognitive restructuring throughout the full period that they are re-exposed to the stimuli. Some challenges with this laboratory procedure, however, are that it requires extensive training of the experimenter and there may be variability in how experimenters deliver the cognitive restructuring and how participants implement the cognitive restructuring. Albeit, this is also true of clinical cognitive restructuring. Additionally, unlike the cognitive reappraisal procedure, the threat conditioning cognitive restructuring procedure is restricted to the domain of threat responses. As cognitive restructuring is used in the clinic to target more negative emotions than just fear or anxiety, results from research using threat conditioning cognitive restructuring may not generalize widely.

Our third observation is that current laboratory models of cognitive restructuring are predominantly focused on the end of the restructuring process (i.e., reappraisal). While some have argued that reappraisal is the most crucial aspect of the cognitive restructuring intervention (Braun et al., 2015), it has been questioned whether the act of identifying and labeling automatic thoughts alone may be helpful for changing emotions (Longmore & Worrell, 2007). The early stages of cognitive restructuring (psychoeducation and eliciting automatic thoughts) are missing from the cognitive reappraisal laboratory procedure. Participants in these studies typically reappraise photos or videos that have previously been rated as negative in emotional valence (e.g., IAPS pictures). Automatic thoughts are not elicited before participants are asked to reappraise. Because of this, it is unclear whether participants' responses to such stimuli warrant reappraisal and what the impact of appraisal alone would be. Additionally, data from the training session is not typically captured or examined. The threat conditioning cognitive restructuring procedure (Shurick et al., 2012) more clearly mirrors all four steps of clinical cognitive restructuring; however, it is still not possible to isolate the impact of each step on emotion. When participants are re-exposed to the conditioned stimuli, they are told to use what they have learned from the cognitive restructuring task and particularly focus on using alternative thoughts, however, data is not collected as to what participants end up using. More systematic collection of data throughout the initial training sessions of laboratory procedures and gathering information from participants about what tactics they employ during procedures, may help improve the clinical relevance of this area of research.

Our fourth observation is that current laboratory procedures typically do not use personally relevant stimuli, save for a few exceptions (e.g., Holland & Kensinger, 2013; Kross et al., 2009), whereas this is all that is restructured in clinical settings. It is likely much easier to reappraise another person's circumstances than one's own. As a result of not being personally relevant, participants' initial appraisals of negative images or videos may vary. Researchers have improved the clinical relevance of this approach by examining the reappraisal of negative autobiographical memories (e.g., Holland & Kensinger, 2013; Kross et al., 2009). Additionally, the threat conditioning cognitive restructuring procedure addresses this issue by first having participants undergo threat conditioning, increasing the likelihood that a negative appraisal is present. That being said, threat conditioning does not always result in negative appraisals or cognitive awareness of negative appraisals (for review, Lonsdorf et al., 2017). However, the use of negative images as the CSs may enhance the effect (Shurick et al., 2012). Another approach is the conditioning of negative emotions using negative personally-relevant images combined with cognitive reappraisal. For example, Olatunji and colleagues (2017) had participants high in contamination fear go through a disgust conditioning procedure. In the disgust conditioning procedure, neutral food items (CS) were paired with videos of individuals vomiting (UCS). Next, participants underwent cognitive reappraisal of their learned disgust. This approach may be one method to ensure that the typical stimuli used during the cognitive reappraisal procedure (e.g., IAPS pictures) take on a personal relevance and elicit negative automatic thoughts for participants. Additionally, as done in the Olatunji and colleagues (2017) study to elicit disgust, varying the type of UCS used in the conditioning cognitive restructuring procedure may allow for examination of restructuring of emotions beyond fear/anxiety in the laboratory.

Our final observation is that relative to the extinction literature, the outcomes used in laboratory studies of cognitive reappraisal and restructuring more closely mirror the outcomes used in clinical studies of cognitive restructuring. The primary focus on subjective feelings over psychophysiological or biological outcomes may aid translation.

Therapeutic Procedures Translated from the Clinic to the Lab

In the last decade, basic researchers have turned their attention to therapeutic procedures that are distinct from exposure and cognitive restructuring. Two examples are eye movements, which is a procedure used in EMDR (Shapiro, 1989), and imagery rescripting, which is a procedure used in various imagery rescripting-based therapies. Although there is clinical evidence for the efficacy of these less traditional therapeutic procedures (Cusack et al., 2016; Morina et al., 2017), the mechanisms behind these procedures that lead to a reduction in symptoms are far less studied and known. In the case of EMDR, experimental studies in the laboratory have crucially contributed to the understanding of the mechanism behind EMDR and have challenged original clinical hypotheses (for example see: van den Hout and Engelhard, 2012).

Given that clinical use of these procedures preceded laboratory research and the fact that these clinical procedures may be less well-known to experimental researchers, in the following two sections we will first describe the clinical procedures and then describe the recent attempts to model them in the laboratory. Although this structure is a departure from our prior sections, it is important to first understand what led to the generation of the laboratory procedures. Finally, as we have done in the prior sections, we will highlight what is missing and opportunities to enhance translation between the clinic and the laboratory. This will include discussion of additional laboratory procedures which were not specifically modeled off of EMDR or imagery rescripting but may capture similar core processes.

EMDR / Eye Movements

EMDR / Eye Movements in the Clinic

Procedure.: Eye movements are a core procedure involved in EMDR, which is an effective treatment for PTSD and part of mental health care guidelines in many countries (American Psychological Association, 2017; Cusack et al., 2016; Department of Veteran Affairs & Department of Defense, 2017; International Society for Traumatic Stress Studies, 2019). EMDR is also used to treat other mental health conditions (for review, Cuijpers et al., 2020) such as mood disorders, anxiety disorders, substance use disorders, and chronic pain, although there is less evidence to support these uses.

In order to understand the use of eye movements as a therapeutic procedure, it is important to understand how it fits into EMDR therapy. According to the guidelines written on EMDR (de Jongh & ten Broeke, 2012; Shapiro, 2017), the patient and therapist first work together to understand the patient's history and identify treatment targets (e.g., past memories). Next, the therapist prepares the patient by offering a treatment rationale and introducing procedures. One of the key procedures is left-right (bilateral) stimulation, such as eye movements, tones, or tapping. For example, to administer bilateral eye movement

stimulation, the therapist uses their hand or an automated light to direct the patient to move their eyes left and right. After these procedures are introduced, the patient is asked to make a visual representation of their trauma memory in their mind, briefly narrate the trauma memory, and identify the most disturbing image/part of their memory. Then, the therapist elicits negative thoughts or beliefs the patient has with regards to the most disturbing image from their memory and preferred (positive) thoughts or beliefs the patient would like to have. The patient is asked to make subjective ratings of the emotions and distress they feel in relation to the image. Finally, the patient is asked to bring the most disturbing image to mind and the therapist simultaneously administers bilateral stimulation. Ratings of emotion and distress are then collected again, and these last two steps are repeated until the image feels emotionally neutral. Finally, the patient is asked to return to the positive thoughts or beliefs they identified previously and think about them in relation to the image.

Outcomes.: As with exposure and cognitive restructuring, the most commonly used outcome measures of response to EMDR are clinician-assessed or self-report symptom measures.

Unique Component.: The component of EMDR that is different from any other psychotherapy is the bilateral stimulation, with the most common form being bilateral eye movements. The laboratory studies on EMDR, which we will discuss in the next section, therefore mainly focus on this part of the EMDR procedure.

EMDR / Eye Movements in the Laboratory

Procedure.: Eye movements as a procedure to impact emotion have been examined in the laboratory for the past few decades. We systematically searched through the literature (PubMed title/abstract search on “EMDR,” or “eye movement desensitization and reprocessing,” or “EMD-R” on December 12, 2020 resulted in 638 articles) for articles on EMDR / eye movements and encountered around 41 experimental studies involving healthy volunteers. Therefore, this is still a relatively small area of experimental research compared to extinction or cognitive reappraisal.

Stimuli.: Laboratory models of EMDR have mainly investigated whether combining recall of an emotional (non-traumatic) memory with bilateral eye movements attenuates a range of emotional responses when the memory is recalled at a later time. The control condition in these studies typically involves recalling the emotional memory without making the bilateral eye movements. The type of memory targeted in these studies varies. The majority of studies have asked participants to recall negatively valenced autobiographical memories while making bilateral eye movements (e.g., Engelhard et al., 2010; Gunter & Bodner, 2008; Schubert et al., 2011; for less common application to positive memories see Engelhard et al., 2010). In other studies, participants are first exposed to negatively valanced images (e.g., Andrade et al., 1997; van den Hout et al., 2013) or movie clips (e.g., van Schie et al., 2019), after which they are asked to recall these stimuli while making bilateral eye movements. Lastly, some studies first condition threat-related memories using fear conditioning and then bilateral eye movements are incorporated during extinction learning (de Voogd et al., 2018b) or following recall of the conditioned stimuli (Leer & Engelhard, 2020).

Other Features.: The way in which the bilateral eye movements are implemented also varies across studies. In earlier studies, the experimenter moved their hand horizontally in front of participants' eyes mimicking how bilateral eye movements are often implemented in the clinic (e.g., van den Hout et al., 2001). More recent studies have implemented eye movements by having a dot on a computer screen direct participants' eyes at a fixed pace (de Voogd et al., 2018b; Nieuwenhuis et al., 2013; van den Hout et al., 2013). Although the majority of studies have used horizontal (bilateral) eye movements, as has been implemented in the clinic, some have also examined the effectiveness of making vertical eye movements (e.g., Gunter & Bodner, 2008), while others have compared bilateral eye movements to other bilateral stimulation tasks such as finger tapping (Andrade et al., 1997), tones (van den Hout et al., 2011), and tactile stimulation (Nieuwenhuis et al., 2013), or playing the computer game Tetris (Engelhard et al., 2010).

Outcomes.: The outcome measures used in EMDR laboratory research to evaluate the success of the intervention mostly include measuring subjective reports of how emotional the participant feels and the vividness of the memory when the it is recalled again at a later time (e.g., Engelhard et al., 2010; Gunter & Bodner, 2008). However, some researchers have also measured psychophysiological responses to these recalled stimuli (de Voogd et al., 2018b; Dibbets et al., 2018; Engelhard et al., 2010) or intrusions, as indicated by mental images or verbal thoughts of an aversive movie clip. Intrusions were assessed via a diary that participants took home (e.g., van Schie et al., 2019). There is also an example where memory accuracy was measured using an item recognition memory paradigm (Nieuwenhuis et al., 2013) and UCS expectancy ratings were measured in a threat conditioning paradigm (Dibbets et al., 2018). Finally, one study examined BOLD responses while executing eye movements (de Voogd et al., 2018b).

What is Missing? Opportunities for Translation from the Clinic to the Laboratory—Although a large variety of stimulus types and outcome measures are employed in laboratory studies of EMDR, most studies use autobiographical memories as the stimulus and subjective feelings about these memories as the outcome. This aligns closely with the clinical EMDR procedure, which was less the case in the previous sections on extinction / exposure and cognitive reappraisal / cognitive restructuring. As such, in this section, we will focus less on suggestions for how to improve the laboratory analogue and more on future directions for basic research on the mechanisms of EMDR, since this is an area where we believe laboratory research can contribute substantially.

A first important question to answer, is whether eye movements are essential for EMDR treatment? Historically, there has been a debate as to whether the eye movements in EMDR play a critical role in the therapeutic outcome above other processes such as exposure (i.e., by recalling traumatic memories) or changing negative thoughts or beliefs which are part of EMDR as well (Devilly, 2002; Lee & Cuijpers, 2013; Rogers & Silver, 2002). Clinical trials suggest that EMDR is as effective as exposure-based treatments for PTSD (Bisson et al., 2013; Cusack et al., 2016), but this does not address the question of whether the effectiveness of EMDR is due to exposure alone because the amount of the exposure in EMDR may differ from the amount of exposure in exposure-based treatments for PTSD.

Insight into this question can be obtained by examining extinction in the laboratory to determine if there is an additional benefit in the rate and persistence of extinction learning if eye movements are incorporated. De Voogd and colleagues (2018b) had participants engaged in threat extinction with or without bilateral eye movements and found that the group that engaged in eye movements demonstrated reduced return of threat responses (i.e., more persistent extinction) and stronger amygdala deactivation during extinction. This initial research may suggest an added benefit of eye movements. Given the longstanding debate as to whether EMDR's efficacy is simply due to extinction / exposure, additional laboratory research along these lines would be beneficial.

The second question that laboratory research can help answer, is *why* eye movements would have an added value in reducing symptoms? Research shows that combining recall of an emotional (non-traumatic) memory with another cognitively demanding task, instead of bilateral eye movements, also attenuates a range of emotional responses when the memory is recalled at a later time. A few studies have addressed this directly in a design similar to the EMDR / eye movement laboratory experiments. In one example, participants were instructed to recall a specific stressful event they had witnessed in the news (i.e., an attempted attack on the Dutch royal family involving a car driving into a crowd) in combination with executing a mental arithmetic task. Researcher found that participants reported to feel less emotional and rated the memory as less vivid when they recalled the event at a later time point (Engelhard et al., 2011). Another experiment directly compared a bilateral eye movement condition with a condition during which participants played a game of Tetris (Engelhard et al., 2010). These two conditions both reduced reported emotionality of the recalled memory compared to when memories were recalled without an additional task, however, the two conditions did not differ significantly from each other. However, not all interventions are as effective as eye movements. For example, bilateral stimulation using tones, which are used in the clinic, in combination with memory recall was examined in a laboratory study of PTSD patients (van den Hout et al., 2012). This study showed that bilateral stimulation with tones was less effective than eye movements, if at all effective, in reducing subjective reports of how emotional the participants felt and the vividness of the memory when it was recalled again at a later time. Furthermore, converging evidence indicates that only cognitively demanding tasks compared to tasks that are not or less cognitively demanding are successful in reducing emotional responses (e.g., de Voogd & Phelps, 2020; Onderdonk & van den Hout, 2016). Therefore, the effectiveness of the eye movements in EMDR may not be specific to the eye movements per se and the working mechanism might be related to the cognitively demanding nature of the task.

Interestingly, cognitive demand has been proposed as a therapeutic intervention in a number of different studies in which researchers did not directly address EMDR therapy but have reported findings consist with the EMDR laboratory studies. For example, in a series of studies, participants played a game of Tetris, however, they did so 10 minutes after watching a negatively valenced movie clip (Holmes et al., 2009) or 10 minutes after recalling the negatively valenced movie clip they had previously watched (James et al., 2015). It was found that playing Tetris reduced visual intrusions of the movie clips assessed after the participants left the lab using a diary that they took home (Holmes et al., 2009; James et al., 2015). Other studies have examined the emotion regulation technique distraction (Kanske et

al., 2011; McRae et al., 2010; van Dillen & Koole, 2007; for review, Webb et al., 2012). Distraction often explicitly involves executing a cognitively demanding task such as keeping a 6-letter string in working memory (McRae et al., 2010) or solving equations (Kanske et al., 2011). Distraction performed after viewing negatively valenced images impacted amygdala BOLD responses and reduced negative affect (Kanske et al., 2011; McRae et al., 2010).

A crucial difference between the experiments with Tetris and distraction and the EMDR / eye movement laboratory experiments is that in EMDR participants are asked to keep the memory in mind while they make bilateral eye movements (e.g., van Schie et al., 2019; van Veen et al., 2020) and the eye movements are executed immediately after memory recall without a time delay (e.g., Engelhard et al., 2010; Gunter & Bodner, 2008; Schubert et al., 2011; van den Hout et al., 2013; van Schie et al., 2019). In contrast, in the studies involving Tetris or distraction, there is no direct instruction to keep the movie clips or negative images in mind while participants are distracted. If executing a cognitively demanding task following exposure to a negative stimulus or memory also reduces intrusive mental images and negative affect, one might wonder if keeping the memory in mind while making the eye movements is essential? And further, what is the most effective timing of eye movements (or another cognitively demanding task) and memory recall in reducing negative affect? Studies directly comparing memory recall with eye movements while holding the memory in mind versus not holding the memory in mind are needed to help answer this question.

One final question is, what is it about cognitive demand that could explain these findings? It is possible that eye movements (de Voogd et al., 2018b), playing the computer game Tetris (Price et al., 2013), distraction techniques (Kanske et al., 2011; McRae et al., 2010), or any other cognitively demanding task (e.g., tasks that tax working memory; de Voogd et al., 2018a) may impact the overlapping neural pathways that play a role in reducing negative affect. Namely, all these tasks recruit regions of the central-executive control network which includes regions such as the dorsal lateral prefrontal cortex (dlPFC), but crucially also reduce amygdala reactivity (de Voogd et al., 2018a). Down-regulation of the amygdala via top-down control of the dlPFC is considered one of the hallmarks of cognitive regulation of emotion (for review, Buhle et al., 2014), but it may also underlie the effectiveness in reducing the range of emotional responses of all the techniques mentioned here. A possible explanation as to why this occurs is that cognitively demanding tasks potentially shift resources away from brain networks involved in threat-related processes, such as the amygdala, to brain networks involved in executive control (de Voogd et al., 2018a). Via this reorganization, cognitive demand could reduce conscious subjective feelings or negative affect during the threatening event and when the event is recalled later in time. Explicitly linking EMDR treatment to other cognitively demanding emotion regulation techniques may lead to a better understanding of EMDR and provide a potential path for optimizing its efficacy.

Imagery Rescripting / Imagery Rescripting

Imagery Rescripting in the Clinic

Procedure.: Imagery rescripting is a therapeutic procedure that is distinct from exposure, cognitive restructuring, and EMDR. Although imagery rescripting has a long clinical

history (for review, Arntz, 2012), it has only recently been integrated into some CBTs and empirically tested in clinical trials (Morina et al., 2017). Imagery rescripting has predominantly been used in the treatment of PTSD but has also been proposed as a possible treatment for anxiety, eating, obsessive compulsive, personality, and depressive disorders, and nightmares (Morina et al., 2017; Arntz, 2012). Although there is some research to support its efficacy, imagery rescripting is still a rather new procedure and because of this, it is not yet recommended in clinical practice guidelines for the treatment of PTSD or anxiety (American Psychological Association, 2017; Department of Veteran Affairs & Department of Defense, 2017; International Society for Traumatic Stress Studies, 2019; Katzman et al., 2014).

Imagery rescripting procedures vary somewhat depending on the diagnosis and protocol (Arntz & Weertman, 1999; Hackmann, 2011; Wild & Clark, 2011) but generally include the following components. First, the therapist works with the patient to choose an autobiographical memory to target in treatment. Typically, this is a memory that is vivid and distressing for the patient. Next, it is common, although not necessary, for the therapist to ask the patient to relive the memory, describing and imagining it vividly. During this exercise, the therapist may ask some probing questions to elicit more details of the memory and subjective units of distress are typically collected throughout. The process of reliving is similar to imaginal exposure described previously. After reliving the memory, rescripting of the memory begins. The therapist asks the patient to interfere in their memory narrative and change it based on how they would want the event or experience to end. The therapist and patient work together to identify any reactions the patient wished they had had or actions the patient wished they had taken at the time of a traumatic or unpleasant event. The patient is given freedom to come up with any type of alterative ending (realistic or fantastical) to their memory as long as they are able to imagine it vividly. The point at which rescripting is initiated varies; in some cases, it is done right before the patient gets to a point of their memory that is particularly distressing for them and in other cases, the full memory is relived and then the patient goes back and rescripts the most distressing part. The process of rescripting is repeated until the patient forms an imagined script of the event that is satisfying and less distressing than the original memory.

Outcomes.: As with the other clinical procedures we have discussed, the most commonly used outcome measures of response to imagery rescripting are clinician-assessed or self-report symptom measures.

Unique Component.: Although imagery rescripting-based treatments may involve other procedures, such as exposure or cognitive restructuring, their unique component is the rescripting procedure: the instruction to change the aversive outcome of an autobiographical memory to a different ending with a new preferred story line. The laboratory studies on imagery rescripting, which we will discuss in the next section, therefore mainly focus on this part of the imagery rescripting procedure.

Imagery Rescripting in the Laboratory

Procedure.: Imagery rescripting is a rather new focus of laboratory research. We only encountered around 16 laboratory studies of imagery rescripting conducted in healthy participants (from 134 articles identified through a PubMed title/abstract search on "rescripting"conducted on December 12, 2020). Laboratory studies on imagery rescripting have mainly investigated the effects of imagery rescripting on memory for (non-traumatic) emotional stimuli.

Stimuli.: The material being rescripted in laboratory studies of imagery rescripting is typically film clips or autobiographical memories. In studies using film clips, participants first watched a film clip in which an aversive event occurred (Dibbets & Arntz, 2016; Hagenaars & Arntz, 2012; Siegesleitner et al., 2019). Then, participants were asked to recall the film clip, but change the ending of the aversive event. For example, they were asked to imagine something that they wished had happened instead. Subsequently, participants were asked to recall and experience this new version of the event, by focusing on the sensory details, instead of the original event. In other experiments, participants performed a novel threat conditioning paradigm where the UCS is also a negatively valanced film clip (e.g., Dibbets et al., 2012; Landkroon et al., 2019). In these cases, in the imagery rescripting condition, participants were also asked to change the ending of this film clip. The other common method to examine imagery rescripting in the laboratory is to have participants recall negative autobiographical memories and change the way the event unfolded (e.g., Çili et al., 2017; Slofstra et al., 2016). For example, in these studies, participants were instructed to (1) think of helpful things they could have said to themselves at the time of the event, and imagine saying those things to themselves, or (2) imagine another person coming to help them. The main aim of imagery rescripting experiments is to change the narrative of what happened (e.g., in their own lives or in the movie clip) and imagine this newly modified narrative to reduce subjective feelings of distress or intrusive thoughts or images of the event in the future. Imagery rescripting in these studies was instructed via text that was presented on a computer screen or directed by clinical psychologists (e.g., Çili et al., 2017) or by a computer (e.g., Dibbets et al., 2012; Hagenaars & Arntz, 2012). Additionally, even though the rescripting instructions were the same for each participant, participants were often given freedom to change the negative event in any manner they liked.

Other Features.: The imagery rescripting experiments conducted to date have often involved multiple control conditions across studies or within a given study. This includes active control conditions such as reexperiencing the negative event without rescripting which is similar to extinction / exposure (e.g., Hagenaars & Arntz, 2012), recalling and reexperiencing a different positive event (e.g., Hagenaars & Arntz, 2012), or recalling the negative event in combination with attentional breathing (Slofstra et al., 2016). Other studies have included passive control conditions, for example merely recalling but not reexperiencing the negative event (Rijkeboer et al., 2020).

Outcomes.: The outcome measures used in laboratory studies of imagery rescripting mostly include subjective ratings of distress when thinking about the movie clip or memory (e.g., Dibbets et al., 2012) and intrusive thoughts or images related to the movie clip or memory

that occur in the following week reported by participants via a diary (Hagenaars & Arntz, 2012). Some studies (Hagenaars & Arntz, 2012) have also used clinical PTSD measures (e.g., Posttraumatic Cognitions Inventory) as an outcome. Individual studies have reported that imagery rescripting yielded success in changing the mentioned outcome measures, however, no systematic reviews or meta-analyses have been conducted on laboratory rescripting studies to date. Therefore, more research is needed to determine the efficacy of imagery rescripting as a laboratory intervention as well as determine the consistency of the findings.

What is Missing? Opportunities for Translation from the Clinic to the Laboratory—A clear mechanistic explanation for *how* imagery rescripting reduces symptoms remains to be determined. As with the eye movements / EMDR research, the procedures and outcomes used in laboratory studies of imagery rescripting closely mirror those used in the clinic. Some even involve clinical psychologists and include instructions that are almost precisely what patients are instructed to do when imagery rescripting is used clinically (e.g., Slofstra et al., 2016). Given the similarity of the laboratory and clinical procedures, we mainly focus on opportunities for translation that are related to understanding the mechanism behind imagery rescripting.

One important feature of imagery rescripting for trauma memories that differs from most laboratory studies of memory is that it aims to change the subjective feelings associated with a memory, and not necessarily the accuracy of the memory. Most laboratory studies of memory focus on the accuracy of the memory content, not the subjective feelings evoked (Phelps & Hofmann, 2019). Nevertheless, there are a few hypotheses about how imagery rescripting might effectively reduce the negative subjective feelings associated with traumatic memories that could be further investigated in laboratory studies.

One hypothesis is that imagery rescripting changes the valence of the outcome (which some refer to as the UCS) of the event that is being rescripted by making it less negative. Imagery rescripting explicitly instructs patients to change the narrative of the memory by replacing the negative outcome of the traumatic event with a more favorable one. Although this has been suggested to be akin to UCS devaluation (Arntz & Weertman, 1999), it is also similar to counterconditioning in which an aversive UCS is replaced with an appetitive UCS. Counterconditioning, much like extinction learning, is hypothesized to result in a new CS-appetitive UCS memory that competes for expression with the old CS-aversive UCS memory. Because of this, expression of the original threat association in counterconditioning is susceptible to relapse (e.g., Bouton & Peck, 1992; Brooks et al., 1995). Given this, one avenue to test this hypothesis in the laboratory is to examine if the passage of time (spontaneous recovery) or exposure to the negative outcome UCS prior to retrieval (reinstatement) results in the recovery of negative affective responses to the memory.

A second hypothesis is that imagery rescripting induces competition during retrieval. This relates to the notion that both emotions and behaviors are under the control of multiple memory representations that compete for retrieval (Brewin, 2006). By adding new contextual information, via imagery rescripting, new memory representations are formed that outweigh the old representations, in this case the negative outcome of the traumatic

event (Brewin et al., 2010). It is proposed that imagery rescripting may lead to alternative, more positive memories which are more accessible than the negative memories. However, a retrieval competition account would predict that even though a new memory can be retrieved, the old memory is still intact. If this is the case, one might expect, much like in counterconditioning, that the original memory is still accessible and may be expressed under certain conditions.

In contrast to this account, a third hypothesis would be that imagery rescripting might change the original representation of the memory via memory updating or altering reconsolidation. Studies of memory reconsolidation suggest that memories may be malleable after retrieval or reactivation. One proposed adaptive function of these windows of memory lability during reconsolidation is that old memories can be updated with new, relevant information available at the time of retrieval (Phelps & Hofmann, 2019). This line of research relates to early studies on false memories which demonstrated that post-event information often becomes incorporated into a memory and alters the recollection of that memory (Loftus, 1996). More recent experiments have shown that episodic memory reactivation followed by new learning reliably leads to intrusions of the newly learned information into the original memory (for review, Scully et al., 2017). In a classic example of this work, Hupbach and colleagues (2007) had participants learn a list of objects. Two days later, they learned a second list of objects. Prior to learning the second list, half of the participants were reminded of the first session learning experience (i.e., memory reactivation group) and half were not (i.e., no-reactivation group). When asked to recall the list from the first session a couple days later, participants in the memory reactivation group misattributed items from the second session to the first session more often than participants in the no-reactivation group. By introducing new information after recalling a memory, imagery rescripting could potentially update the autobiographical memory with new information about the valence of the event, similar to these episodic memory updating studies. If this is the case, then unlike the retrieval competition hypothesis and counterconditioning, the original memory would be permanently modified and no longer exist in its original form.

Determining if the original memory is intact, but less accessible, or modified would be difficult in laboratory studies that assess only behavioral data. However, using brain imaging techniques, such a representational similarity analysis (Kriegeskorte et al., 2008) or pattern classifiers (Gershman et al., 2013), it may be possible to investigate this question. Specifically, these techniques have been used to capture memory traces in the brain and investigate how they are activated or altered under different conditions (Chadwick et al., 2010; Polyn et al., 2005; Ritchey et al., 2013; Staresina et al., 2012; Wimber et al., 2015). If imagery rescripting results in updating the original memory with new information, then evidence from brain imaging should find more alterations in the BOLD pattern representing the original memory at later retrieval, or BOLD evidence of intrusions of the new rescripted memory, relative to memories that have not been rescripted.

Another benefit of laboratory studies of imagery rescripting is that it is possible to more thoroughly investigate which aspects of the memory are altered. As mentioned earlier, one fundamental difference between studies of imagery rescripting and most laboratory studies of episodic memory, is that laboratory studies are generally concerned with assessing

if the memory accurately reflects the details of the original event, whereas studies of imagery rescripting are concerned with changes in the subjective feelings evoked by the memory. However, it is possible that both memory accuracy and subjective feelings, or other qualities evoked by the memory, are altered. Using laboratory analogues of imagery rescripting one could investigate to what extent this technique alters a range of mnemonic factors, including, but not limited to, memory accuracy for details of the original event, confidence in memory accuracy, vividness of the memory, the subjective feelings evoked by the memory, or the sense of agency evoked by the memory, which has also been linked to more adaptive responding to threats (Moscarello & Hartley, 2017). Studies of this type would provide insight into the psychological qualities of the rescripted memory that underlie the therapeutic benefit.

In conclusion, there are far fewer laboratory studies investigating imagery rescripting than any of the other procedures we have described. To fully understand how imagery rescripting can reduce symptoms of mental health disorders more laboratory research is needed. In particular, research examining the impact of imagery rescripting on the qualities of the episodic memory in combination with brain imaging techniques could be beneficial for our understanding of the mechanisms behind imagery rescripting.

Conclusions

The goal of this article was to make a case for increased focus on translation from the clinic to the laboratory in order to improve translational outcomes, and to provide examples of ways this might be implemented. To achieve this goal we first described two key therapeutic procedures involved in treating emotional disorders as they are implemented in the clinic and studied in the laboratory, identified shortcomings of our current laboratory analogues, and discuss opportunities for improving translation from the clinic to the laboratory. We then presented two examples of clinical procedures that have recently been brought into the laboratory for further study and discussed how laboratory investigations of these procedures might inform our understanding of mechanisms of action.

The well-established laboratory analogues for the cognitive behavioral clinical procedures of exposure and cognitive restructuring have been used for decades across countless of studies and have historically resulted in advances in translational and clinical research. However, there still seems to be a disconnect between laboratory and clinical research. Despite much effort on both ends, more recent laboratory studies of these processes have not always resulted in seamless successful clinical translation. As is evident from juxtaposing the laboratory procedures and their clinical counterparts, there are many ways in which our laboratory analogues fall short, which may help explain the translational gap. Rather than being discouraged, we view these shortcomings as opportunities for our laboratory analogues to grow and evolve and innovative research to occur. Historically, a the focus of extinction and cognitive reappraisal research has been on using simple analogues to examine basic mechanisms. This research is valuable, however additional translational research using more nuanced analogues may be necessary for optimizing treatment innovations. We outlined potential ways to modify laboratory procedures to address clinical aspects of

exposure and cognitive restructuring that are missing or misrepresented in hopes that this may provide a roadmap forward and improve future translational research.

Nonetheless, there are benefits and costs to consider regarding the possible modifications to laboratory studies. We believe that one potential benefit is a body of translational research that is more attuned to clinical questions and further bridges the gap between experimental and clinical research. This is particularly important for translational researchers who aim to identify strategies to enhance the clinical procedures of exposure or cognitive restructuring by studying extinction or cognitive reappraisal in the laboratory. The costs of some of the modifications we suggest may include the potential need for larger sample sizes or increased variability/noise. For example, although switching to the use of a between-subject design for cognitive reappraisal studies would more closely mirror how patients reappraise during cognitive restructuring, this would require a larger sample size and inevitably result in more between participant variability. However, some of the changes we suggest may reduce variability/noise and not necessitate larger sample sizes. For example, studies that restrict participants to the use of one reappraisal strategy would likely reduce variability, and early research on imaginal extinction suggests that it results in similar outcomes to in vivo extinction without necessitating a larger sample size (Agren et al., 2018).

The eye movement procedure from EMDR and imagery rescripting have only recently been translated to laboratory paradigms. Laboratory research on these procedures is beginning to provide insight into the mechanisms behind the clinical benefits of eye movements in EMDR, and future laboratory research has the potential to do the same for imagery rescripting. This is an important step along the road to improving the related clinical interventions. Additionally, the translation of these procedures from the clinic to the laboratory allows for easy comparison of these procedures to other potentially related processes that have predominantly been examined in the laboratory (e.g., episodic memory updating). Future laboratory studies directly comparing these procedures to the potentially related processes we mention above may provide insight into further ways to enhance existing clinical interventions or develop novel interventions.

More generally, research on these procedures is relatively sparse compared to extinction and cognitive reappraisal and there is room for novel investigations along various lines. Similar to the extensive research on strategies to enhance extinction (Craske et al., 2018), one line of research would be to use these clinically-relevant laboratory analogues to conduct studies aimed at identifying methods to enhance imagery rescripting and eye movement-based interventions in the laboratory, and then translating this work to the clinic. Given that the laboratory analogues for imagery rescripting and EMDR more closely mirror the related clinical procedures, it is possible that research on augmentation strategies in the laboratory would lead to better results than what has been observed with laboratory studies aimed at enhancing extinction (e.g., Mataix-Cols et al., 2017).

Ultimately, we argue that harmonizing methodologies between clinical and laboratory studies of exposure and cognitive restructuring (see Haaker et al., 2019 for a similar approach regarding rodent-to-human translation), and further laboratory research on the under-studied clinical procedures of eye movements and rescripting, will improve

translational research. This hypothesis, however, remains to be tested. Many of the more clinically-informed versions of extinction and cognitive reappraisal described or proposed here have yet to be used to examine potential augmentation strategies. This could, however, be easily done. If we take d-cycloserine as an example, although initial laboratory studies of d-cycloserine to enhance extinction learning were promising (Norberg et al., 2008), clinical studies using d-cycloserine to enhance imaginal exposure, in particular, have been mostly unsuccessful (Mataix-Cols et al., 2017). Although there are many possible reasons why d-cycloserine to enhance imaginal exposure, which is often conducted in PTSD patients, has been less successful (see Otto et al., 2016 for discussion), one explanation could be that laboratory research on d-cycloserine has always used the traditional laboratory analogue of extinction that involves visual, rather than imaginal, cues. If this research were done using a laboratory analogue that more closely represented imaginal exposure (i.e., extinction to imaginal cues), it is possible that laboratory research would be more informative and translation more successful. This is just one example in which a methodological change with regard to a laboratory analogue may help inform translational research. Nonetheless, much research still needs to be conducted to test the variations we propose in the laboratory and then use these modified analogues to study potential augmentation strategies. Similarly, understanding the mechanisms of change underlying eye movements and rescripting may lead to novel clinical interventions, but we are currently far from realizing this goal.

It is also important to note that we have only focused on four procedures that are used clinically. There are other clinical procedures that may benefit from further study in the laboratory. Such procedures could be identified from examining clinical efficacy literature. For example, one clinical procedure which is starting to be studied in the laboratory, but we did not discuss here, is mindfulness (for review, Tang & Leve, 2016). In addition, another potential ground for identifying clinical procedures that may benefit from laboratory study is to examine clinical work as it is conducted in more “real-world” settings through the lens of effectiveness research. Furthermore, there are likely other laboratory analogues that would benefit from critique relative to their associated clinical procedures. For example, we did not critique laboratory analogues of operant conditioning despite their relevance to clinical techniques such as contingency management used in substance abuse treatment (for review, Silverman et al., 2019). Although far from exhaustive, we hope that the current examples provide some insight into factors to consider regarding other translational research from the clinic to the laboratory.

Another important point to consider is that improving translational research may also be facilitated by increasing crosstalk between basic scientists and clinical scientist. Basic research and clinical research often operate from different (physical) locations. Despite funding organizations and journals encouraging basic researchers to discuss the clinical implications of their work, these basic researchers have typically not conducted clinical work. Therefore, basic scientists may not be fully aware of precisely how therapeutic procedures are implemented in the clinic, and how they differ from laboratory analogues. Similarly, clinical researchers are often expected to discuss basic mechanisms and may only have a sparse understanding of the laboratory procedures and related research outcomes. Given this, we hope the descriptive information provided here regarding these

four laboratory analogues and clinical procedures facilitates increased understanding and crosstalk between basic and clinical scientists.

In sum, there is great benefit to be gained from both clinical and experimental research. However, there has been a long-standing disconnect between these fields, in part due to insufficient laboratory analogues. Given the strong historical focus on translation from the laboratory to the clinic, our laboratory analogues have remained unquestioned. Focusing on translation from the clinic to the laboratory in the manner described in this review may help bring experimental and clinical researchers together, improve our laboratory analogues, and allow for more successful future translational research.

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Table 1.

Characteristics of Extinction / Exposure and Opportunities for Translation

In the Laboratory (Extinction)	In the Clinic (Exposure)
• Typically, simple single cues	• Multi-component multi-sensory cues
• Typically, one or two contexts	• Typically, multiple contexts
• Typically, 2D visual cues	• 2D and 3D visual but also interoceptive and imaginal cues
• Habituation to UCS rarely studied	• Some benefits thought to come from habituation to aversive stimuli
• Typically, a single session	• Typically, multiple sessions
• Experiment driven	• Therapist and patient driven
• Rarely studied in conjunction with cognitive reappraisal	• Often occurs in conjunction with cognitive restructuring
• Predominantly psychophysiological outcomes	• Predominantly subjective outcomes

Opportunities for translation from the clinic to the laboratory:

- More research on extinction to multi-component and multi-sensory cues
- Extinction to multiple stimuli or parts of multi-component stimuli across multiple experimental sessions/days to examine potential order effects
- Additional research on interoceptive and imaginal extinction
- Habituation to UCSs and imaginal extinction involving CS and UCS
- Impact of various experimenter instructions before, during, or after extinction on learning (e.g., instruction not to engage in safety behaviors)
- Impact of participant involvement before, during, or after extinction on learning (e.g., goal setting)
- Impact of varying extinction duration based on participant report of subjective distress
- Influence of cognitive reappraisal before, during, or after extinction on learning
- Additional research using subjective and behavioral outcomes

Table 2.

Characteristics of Cognitive Reappraisal / Cognitive Restructuring and Opportunities for Translation

In the Laboratory (Cognitive Reappraisal)	**In the Clinic (Cognitive Restructuring)**
• Multiple reappraisal strategies (e.g., situational reinterpretation, distancing, thinking positively) • Reappraisal content is not necessarily realistic (e.g., distancing) • Focus on generating alternative thoughts • Initially didactic then independent process • Participant often asked to switch between reappraising and not reappraising • Typically, non-personally relevant images/videos reappraised • Typical outcomes include ratings of subjective feelings, psychophysiology, and BOLD response patterns	• Predominantly involves situational reinterpretation • Focus on identifying realistic alternative thoughts • Multi-step process of eliciting automatic thoughts, questioning automatic thoughts, and generating alternative thoughts • Interpersonal Socratic process • Patient instructed to consistently engage in restructuring • Personally-relevant situations restructured • Predominantly subjective outcomes

Opportunities for translational from the clinic to the laboratory:

Additional laboratory research on:

- Single reappraisal strategies, particularly situational reinterpretation
- Different forms of situational reinterpretation
- Use of personally-relevant stimuli
- The steps of cognitive restructuring beyond reappraisal (i.e., identifying initial appraisals, questioning initial appraisals, rehearsing reappraisals, using reappraisals in new related situations)
- Interpersonal reappraisal and experimenter-assisted versus non-assisted reappraisal
- Between group designs where participants are instructed to either reappraise or not
- Potential costs of switching between reappraising and control behavior
- Threat conditioning cognitive restructuring, particularly using negatively valenced stimuli or personally-relevant stimuli

Table 3.

Characteristics of Eye Movements / EMDR and Additional Mechanistic Questions

In the Laboratory (Eye Movements)	In the Clinic (EMDR)
• Typically, negative autobiographical memories targeted. Some have experimentally induced negative memories.	• Traumatic or other distressing negative autobiographical memories targeted.
• Typically, bilateral (horizontal) eye movements. Vertical eye movements, bilateral finger tapping, tones, and tactile stimulation, and other visuospatial tasks have also been examined.	• Most common form of bilateral stimulation is (horizontal) eye movements. Bilateral tones, tapping, and tactile stimulation also used.
• Directed by experimenter or a computer	• Directed by a therapist with their hand or a light
• Delivered while keeping negative memory in mind	• Eye movements delivered while keeping negative memory in mind
• Rarely studied in conjunction with extinction	• Eye movements delivered in conjunction with recollection of the negative memory, which may constitute exposure
• Predominantly subjective outcomes. Occasionally, psychophysiology or intrusive thoughts.	• Predominantly subjective outcomes (often including intrusive thoughts).

Additional mechanistic questions:

- If eye movements add value, why?
- Are there other procedures that tap into the same mechanism more effectively (e.g., any cognitively demanding tasks, distraction)?
- If so, what is the best approach to timing (e.g., is it more effective to administer the cognitively demanding task concurrently or after memory reactivation)?
- How do eye movements or cognitively demanding tasks influence the brain systems involved in cognitive control and emotion?

Table 4.

Characteristics of Imagery Rescripting / Imagery Rescripting and Additional Mechanistic Questions

In the Laboratory (Imagery Rescripting)	**In the Clinic (Imagery Rescripting)**
• Typically, autobiographical memories or film clips targeted	• Traumatic or other distressing negative autobiographical memories targeted
• Beginning of the memory/film is often recalled before the most distressing part is rescripted	• Memory is often relived (partially or fully) before the most distressing part is rescripted
• Participant comes up with an alternative ending (realistic or fantastical) and imagines it vividly	• Patient comes up with an alternative ending (realistic or fantastical) and imagine it vividly
• Directed by an experimenter (sometimes a therapist) or computer	• Directed by a therapist
• Predominantly subjective outcomes or intrusive thoughts. Clinical PTSD measures have also been used.	• Predominantly subjective outcomes (often including intrusive thoughts).

Additional mechanistic questions:

- What is the underlying mechanism of imagery rescripting (e.g., counterconditioning, retrieval competition, memory reactivation-induced updating)?
- Does imagery rescripting result in false memories?
- Does imagery rescripting change the original memory trace as it is stored in the brain?