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Review

A systematic review of literature examining mediators and mechanisms of change in empirically supported treatments for posttraumatic stress disorder

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ABSTRACT

Despite the availability of empirically supported treatments (ESTs) for posttraumatic stress disorder (PTSD), relatively little is known regarding these treatments' mechanisms of change. This systematic review moves beyond previous reviews by summarizing the findings and reviewing the methodological quality of literature that specifically examined mediators/mechanisms of change in ESTs for PTSD. Studies were included if they were written in English, empirical, peer-reviewed, claimed to study mediators/mechanisms of a recommended PTSD treatment, measured the mediator/mechanism during or before and after treatment, and included a posttreatment PTSD or global outcome (e.g., functioning). PsycINFO and PubMed were searched on October 7, 2022. Two coders screened and coded studies. Sixty-two eligible studies were identified. The most consistent mediator/mechanism was reduction in negative posttraumatic cognitions, followed by between-session extinction and decreased depression. Only 47% of studies measured the mediator/mechanism before the outcome and measured the mediator/mechanism and outcome at least three times, and 32% also used growth curve modeling to establish temporal precedence of change in the mediator/mechanism and outcome. Many of the mediators/mechanisms examined had weak or no empirical support. Results highlight the need for improved methodological rigor in treatment mediator and mechanism research. Implications for clinical care and research are discussed. PROSPERO ID: 248088.

1. Introduction

Posttraumatic stress disorder (PTSD) is estimated to affect approximately 4% of adults worldwide at some point during their lifetime (Koenen et al., 2017), with estimates ranging between 1% and 9% depending on the country (Atwoli, Stein, Koenen, & McLaughlin, 2015). Empirically supported treatments (ESTs) for PTSD are available (e.g., American Psychological Association, 2017; Departments of Veterans Affairs and Defense (VA/DoD), 2017; International Society for Traumatic Stress Studies, 2019). PTSD treatments recommended by clinical guidelines (American Psychological Association, 2017; Department of Veterans Affairs and Department of Defense, 2017; International Society for Traumatic Stress Studies, 2019) include prolonged exposure (PE; Foa, Hembree, Rothbaum, & Rauch, 2019), cognitive processing therapy (CPT; Resick, Monson, & Chard, 2017), cognitive therapy (CT; Ehlers & Clark, 2000), cognitive behavioral therapy (CBT) for PTSD, narrative exposure therapy (NET; Schauer, Neuner, & Elbert, 2011), written exposure therapy (WET; Sloan & Marx, 2019), trauma-focused CBT (TF-CBT) for youth (Cohen, Mannarino, & Deblinger, 2006), eye movement desensitization and reprocessing (EMDR; Shapiro, 2018), interpersonal psychotherapy for trauma (IPT-T; Talbot & Gamble, 2008), brief eclectic psychotherapy (Gersons, Meewisse, & Nijdam, 2015), present centered therapy (Classen, Butler, & Spiegel, 2001), stress inoculation training (Meichenbaum, 1974), fluoxetine, paroxetine, sertraline, and venlafaxine. Randomized clinical trials of these treatment approaches report moderate to large effect sizes (e.g., Cusack et al., 2016). Overall, there have been significant advances in PTSD treatment since PTSD was first established as a diagnosis over 40 years ago (American Psychiatric

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Association, 1980).

Despite advances in PTSD treatment, relatively little is known about the therapeutic processes by which treatment procedures cause symptom reduction (i.e., treatment mechanisms). It is important to understand treatment mechanisms because if we can identify key processes that lead to therapeutic change, clinicians can focus on the procedures that target those mechanisms to maximize patient outcomes, and researchers can identify modifications to maximize the impact of those procedures. One way to understand mechanisms of therapeutic change is to examine mediators of change: variables that are statistically associated with both treatment and outcome, and that precede and predict symptom change (Kazdin, 2007; Kraemer, Wilson, Fairburn, & Agras, 2002). For example, cognitive restructuring (treatment procedure) is theorized to facilitate change in negative posttraumatic cognitions (treatment mechanism), which is thought to lead to a reduction in PTSD symptoms. Although demonstrating mediation is necessary for establishing a mechanism, it is not sufficient, given that a third variable related to the mediator and outcome may be responsible for change (Cuijpers, Reijnders, & Huibers, 2019). Rather, identifying a mediator is one step toward determining a mechanism (Kazdin, 2007; Kraemer et al., 2002).

1.1. Evidence for mediators and mechanisms of change in PTSD treatments

Multiple systematic reviews have examined mediators and mechanisms of PTSD treatments. These reviews have thoroughly presented evidence for constructs theorized to be mechanisms of change, though they have typically included studies regardless of study design or analytic approach. For example, emotional processing theory (Foa, Huppert, & Cahill, 2006), which informed the development of exposure-based trauma-focused treatments, proposes that activation of the fear network and incorporation of disconfirming information are mechanisms of change, with indicators of these mechanisms including emotional activation, fear extinction, and reductions in negative trauma-related cognitions. Cognitive theories (Beck & Dozois, 2011; Ehlers & Clark, 2000), which informed cognitive therapies for PTSD, also emphasize reductions in negative trauma-related cognitions as a mechanism of change.

There is a robust convergence of evidence for reductions in trauma-related cognitions as a mechanism of change in PTSD treatments. Change in trauma-related cognitions has been found to precede and predict reductions in PTSD symptoms across multiple trauma samples and trauma-focused treatments (Brown, Belli, Asnaani, & Foa, 2019; Brown, Zandberg, & Foa, 2019; Cooper, Clifton, & Feeny, 2017; Foa & McLean, 2016; Gallagher, 2017; Kangaslampi & Peltonen, 2022; Sripada, Rauch, & Liberzon, 2016; Wisco, Baker, & Sloan, 2016; Zalta, 2015). This potential mechanism has also been found to mediate outcome in client-centered therapy (Foa & McLean, 2016), suggesting it might not be a treatment-specific mechanism.

In line with emotional processing theory (Foa et al., 2006), numerous studies have examined emotional activation and fear habituation—recently more precisely referred to as fear extinction (Asnaani, McLean, & Foa, 2016)—as mechanisms of change in PTSD treatments. Research examining activation of fear, distress, or anxiety during sessions has produced mixed and limited support for emotional activation as a mechanism of change (Brown, Zandberg, & Foa, 2019; Cooper, Clifton, & Feeny, 2017; Foa & McLean, 2016; Sripada et al., 2016). Studies examining the contributions of fear extinction to PTSD symptom reduction have found strong evidence supporting between-session extinction as a predictor of symptom change. On the other hand, there is little support for within-session extinction as a mechanism of symptom change (Brown, Zandberg, & Foa, 2019; Cooper, Clifton, & Feeny, 2017; Foa & McLean, 2016; Sripada et al., 2016). Extinction has almost exclusively been examined during exposure-based treatments; it is unclear if it is also a mechanism of change in cognitive treatments (Sripada et al., 2016).

Some reviews have examined organization of the trauma narrative, hope, coping strategies, mindfulness and spirituality, neuroticism, inhibitory learning, attentional processes, and anxiety sensitivity as potential mechanisms of PTSD interventions, although these constructs have been more sparsely investigated. The few studies that have examined these potential mechanisms have produced mixed and weak support for their contribution to PTSD symptom change (Cooper, Clifton, & Feeny, 2017; Gallagher, 2017; Kangaslampi & Peltonen, 2022; Sripada et al., 2016; Zalta, 2015). Among these potential mechanisms, emotion regulation (Gallagher, 2017; Kangaslampi & Peltonen, 2022; Sripada et al., 2016) and hope (Gallagher, 2017) show promising evidence as mechanisms of change in PTSD.

A major limitation of these prior reviews is that they have included any studies examining associations between theorized mechanisms and outcomes, regardless of whether testing a mediator or mechanism was a study aim or whether studies instead tested correlates or predictors of outcome. Existing reviews discuss the quality of the evidence presented, and they acknowledge that correlational and predictive findings provide weaker evidence than mediational findings. Even studies reporting mediational results have methodological limitations, so Cooper, Clifton, and Feeny (2017) further reviewed each study using Kazdin's criteria (2007) criteria for testing a treatment mechanism, providing a higher-quality presentation of the quality of findings while still including studies regardless of design or analytic approach. An even stronger review of the evidence will examine only studies with a stated goal of examining mediators or mechanisms of change in PTSD treatments and will consider both the findings of those studies and the quality of the study designs and analytic approaches that produced those findings.

1.2. The study of mediators and mechanisms of change

When considering findings on mediators and mechanisms of change in treatment, it is important to assess the methodologies of the studies that generated these findings to determine the quality of the conclusions that can be drawn. The quality of a test of mediation or mechanism, and the conclusions that can be drawn about causality, are contingent upon both study design and statistical approach.

1.2.1. Study design considerations

To establish a mediator of PTSD treatment, there are study design conditions that must be met. 1) The design must be longitudinal and able to show that treatment causally influences change in the mediator, followed by change in the mediator causally influencing change in the outcome. 2) Temporally, the mediator must be some change that happens during treatment. A construct measured only at pretreatment or posttreatment cannot be examined to determine mediation of therapeutic change (Kazdin, 2007; Kraemer et al., 2002). 3) Researchers must measure hypothesized mediator and outcome variables frequently enough to establish temporal sequencing, and ideally such that the reverse direction of effects can be ruled out (i.e., that change in the proposed outcome did not precede and predict change in the proposed mediator). To demonstrate this sequencing, at least three measurement points are needed (Kraemer et al., 2002; Preacher, 2015). Two time points (e.g., pretreatment and posttreatment) cannot demonstrate whether change in the mediator preceded change in the outcome. Moreover, three assessments only allow testing of linear change, and symptom reduction is not always linear (Hayes, Laurenceau, Feldman, Strauss, & Cardaciotto, 2007). The greater the measurement frequency, the better researchers can determine temporal sequencing (Kazdin, 2007) and the timing and shape of change (Hayes et al., 2007).

Additional study design factors can clarify which specific processes serve as mechanisms for different treatments. To demonstrate specificity, a study must measure multiple potential mediators and show that only one mediated outcome (Kazdin, 2007). Additionally, a stronger study design involves manipulating the mechanism to show causality

(Kazdin, 2007; Kline, 2015). A study might further demonstrate a dose-response relationship such that a higher level of the proposed mechanism leads to greater symptom improvement (Kazdin, 2007); this relationship may be linear, or there may be an on-off effect or a non-linear relationship between a mechanism and an outcome (Kazdin, 2007).

1.2.2. Statistical considerations

A common statistical approach for mediation was proposed by Baron and Kenny (1986). In this approach, associations are examined among an independent variable (e.g., treatment condition), a proposed mediator (e.g., change in negative cognitions from pretreatment to posttreatment), and an outcome (e.g., change in PTSD symptoms from pretreatment to posttreatment), and then a Sobel test is performed to test whether criteria for partial or full statistical mediation are met. The Baron and Kenny (1986) model was designed to be cross-sectional and does not extend to longitudinal study designs (Cole & Maxwell, 2003; Kline, 2015). Holmbeck (2002) also proposed a test of mediation that includes an indirect effect, similarly using treatment condition as the independent variable and symptom outcome as the dependent variable. Holmbeck's approach also does not model change over time.

Although data collected at different waves of a longitudinal study design can be entered into Baron and Kenny (1986) or Holmbeck (2002) models, these models are still cross-sectional. Even in the presence of a significant Sobel test or indirect effect, they do not model temporal sequencing (Kazdin, 2007; Kline, 2015). In fact, results from a cross-sectional mediational model are statistically indistinguishable from a correlational model (Cole & Maxwell, 2003; Kline, 2015). Therefore, they cannot rule out the alternative hypothesis that change in the proposed outcome preceded and caused change in the proposed mediator. Further, entering longitudinal data into a cross-sectional model when temporal mediation is present can yield results that are statistically biased and misleading (Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011), and this approach has been found to produce inferior results compared to mediation analyses that model change over time (Mitchell & Maxwell, 2013).

Longitudinal mediation analyses that account for measurement of the mediator before the outcome across multiple measurement points are required to examine mediational effects over time. Such analyses include cross-lagged panel models (CLPM; Cole & Maxwell, 2003; Kline, 2015; Maxwell & Cole, 2007; Maxwell et al., 2011; Preacher, 2015) and lagged mediation or regression analyses. A CLPM is a longitudinal model that includes autoregressive effects, meaning it includes all measurements of the independent, mediator, and outcome variables over time, with the level of each variable at a given time point regressed on level of each variable at the previous time point. Because this model covaries for prior levels of each variable, it demonstrates the sequence of relationships among variables over time (Maxwell & Cole, 2007), which is necessary for demonstrating mediation. Lagged analyses involve using measurements of a variable at each time point to predict levels of another variable at a follow-up time point, also helping determine temporal sequencing of the mediator and outcome variables. However, lagged analyses constrain the time lag between each time point and the following time point to be the same, even if it was not (e.g., pretreatment to mid-treatment, mid-treatment to posttreatment, posttreatment to follow-up). Additionally, CLPM and lagged models do not model absolute change in a variable over time, but rather the level of a variable at one time point accounting for variance in the level of that variable at a previous time point (Schlueter, Davidov, & Schmidt, 2007). Despite their limitations, CLPM and lagged models are preferable to cross-sectional mediational analyses (Selig & Preacher, 2009).

Growth curve models can further distinguish intraindividual change from interindividual change (Gallagher et al., 2013; Kenny, Korchmaros, & Bolger, 2003; Selig & Preacher, 2009). Growth curve models include longitudinal multilevel models (e.g., multilevel CLPMs, multilevel lagged regression, and multilevel latent change score [LCS] models, also known as latent difference score [LDS] models), as well as latent growth curve (LGC) models (Curran, Obeidat, & Losardo, 2010). Growth curve models are most appropriate for testing mediation, given that mediation is a process occurring within individuals (Gallagher et al., 2013; Kenny et al., 2003; Selig & Preacher, 2009). Other types of models only examine change at the between-person level, aggregating across participants. LGC models have the added benefit of accounting for the effect of the time lag between measurements (Preacher, 2015; Selig & Preacher, 2009). Models that include LCS can also estimate error-free change scores across multiple time intervals and can model whether change in a mediator variable at one interval predicts subsequent change in an outcome variable at the next interval (Gallagher et al., 2013; Selig & Preacher, 2009). Larger structural equation models can also be estimated that include both LGC and LCS modeling (e.g., Gallagher et al., 2013). Of note, LCS models that include change-to-change paths can be used to examine processes of change in psychotherapy as well other questions related to temporal sequences of change processes. Importantly, because these models are not specifically mediation models, studies utilizing these models may not use the terms "mediation" or "mechanism" (e.g., Dillon et al., 2020; Ehlers, Wiedemann, Murray, Beierl, & Clark, 2021; King et al., 2006). Together, accounting for temporal precedence of the mediator before the outcome, employing study designs with three or more measurement points, and analyzing data using growth curve models will move the field toward better understanding mediators and ultimately mechanisms of change in PTSD treatments.

1.3. Current study

The objective of the current study is to systematically review literature that examines mediators and mechanisms of ESTs for PTSD, including reviewing the findings and commenting on the appropriateness of the methodologies for testing mediation. Prior reviews have included studies that examined associations between theorized mechanisms and treatment outcomes regardless of whether they tested mediation, prediction, or correlation. The current study builds on prior reviews by examining only empirical studies explicitly claiming to study mediators or mechanisms of symptom change in PTSD treatments. This scope allows for the review of findings specifically when mediators and mechanisms are examined, rather than predictors or correlates of symptom change. Reviewing both the findings of these studies and the quality of the methodologies of these studies allows for the clarification of which findings come from studies that used more stringent approaches to testing mediators and mechanisms.

2. Method

2.1. Transparency and openness

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). A protocol for this systematic review was preregistered (CRD42021248088) and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=248088. This study was declared not human subjects research by the institutional review board at VA Boston Healthcare System.

2.2. Eligibility criteria

To be included in the current systematic review, studies had to meet the following criteria: 1) written in English, 2) empirical investigations, 3) published peer-reviewed, 4) claimed to examine mediators or mechanisms of PTSD treatment and included a variation on one of these words in the title and/or abstract, 5) examined at least one treatment for PTSD determined to have empirical support and recommended in treatment guidelines published by APA, ISTSS or VA/DoD, 6) the proposed mediator or mechanism was measured at least one time during the

course of treatment or at both pretreatment and posttreatment, and 7) the outcome was posttreatment PTSD symptoms or change in symptoms from pretreatment to posttreatment, or a more global measure such as quality of life or functioning. Studies were included regardless of participant characteristics, comparison condition(s), or study design. Studies needed to be published and peer-reviewed because the peer review process impacts whether authors use words like mediator or mechanism to describe their approaches.

2.3. Information sources and search strategy

The search was conducted using PsycINFO and PubMed databases (last search was on October 7, 2022). Search terms for PsycINFO were as follows: (ab(posttraumatic stress disorder or PTSD) OR ti(posttraumatic stress disorder or PTSD)) AND (ab(therapy or treatment) OR ti(therapy or treatment)) AND (ab(mediat* or mechanism*) OR ti(mediat* or mechanism*)). Search terms for PubMed were as follows: (posttraumatic stress disorder[Title/Abstract] OR PTSD[Title/Abstract]) AND (therapy [Title/ Abstract] OR treatment[Title/Abstract]) AND (mediat*[Title/ Abstract] OR mechanism*[Title/Abstract]).

2.4. Selection process and data collection process

Four study team members screened studies, and three study team members coded studies. First, the first author used database output to remove duplicate studies, and when additional information was indexed, to remove studies written in languages other than English and study types that were not empirical and peer-reviewed (e.g., reviews, letters to the editor). Two coders then independently screened the title and abstract of each remaining study for eligibility for full study coding based on the inclusion criteria for the systematic review. Next, two coders independently reviewed the full text of each paper to determine eligibility for inclusion in the systematic review and to code paper characteristics. Throughout screening and coding, each coder was paired with all other coders, and weekly meetings were held to resolve discrepancies among the team of coders.

2.5. Data Items

Papers were coded for characteristics relating to their methods and results. Coding categories included: treatment(s) examined, method of assignment to treatment conditions, sample characteristics, mediator (s)/mechanism(s) measured, outcome(s) measured, measures and types of measures used (e.g., self-report, clinical interview), whether interviewers were masked to treatment condition if applicable, time points of measurement, whether analyses examined change or level in the mediator and outcome, whether multilevel models were used, whether latent growth curve models were used, and significant and nonsignificant results. Papers were coded as examining change in the mediator or mechanism and outcome if their analyses included difference scores or autoregressive effects. Papers were also coded for some of Kazdin's criteria (2007) recommendations for measuring mediation, including whether the mediator or mechanism was measured before the outcome, whether the mediator or mechanism and outcome were measured at each session, whether the reverse direction of temporal precedence was tested and if so whether it was found, whether multiple mediators or mechanisms were measured and if so whether there were differential findings, whether effects were compared across treatments, and whether the proposed mechanism was manipulated.

3. Results

3.1. Study selection

PsycINFO and PubMed searches identified 3840 papers (2913 papers after removing duplicates). After removing papers that were indexed as written in a language other than English, an article type other than a peer-reviewed journal article (e.g., unpublished dissertation, book chapter), or whose title indicated the paper was a review or meta-analysis, 2140 papers remained to be screened. After screening the title and abstract of each paper for preliminary eligibility, 105 papers were identified for full-text coding. After coding, 62 studies published between 2006 and 2022 met all inclusion criteria for the present review. Fig. 1 presents a flow diagram of the screening and coding process.

3.2. Study characteristics

Table 1 presents characteristics of each study included in the current review, including the treatment(s) examined, sample characteristics, significant mediators/mechanisms of treatment outcome, non-significant mediators/mechanisms of treatment outcome, whether the mediator(s)/mechanism(s) were measured before the outcome, whether the mediator(s)/mechanism(s) and outcome were both measured at least three times, whether the analysis captured change in rather than level of the mediator/mechanism and outcome, whether the analysis used was multilevel or modeled latent growth, and whether the reverse direction of effects was tested and if so what was found. Appendix Table A1 presents frequencies of each of these study characteristics aggregating across the 62 studies. The two most frequently studied treatments were PE (21 studies; 33.9%) and CPT (12 studies; 19.4%). All other characteristics coded are presented in the appendix. Table A2 presents additional characteristics related to each study's mediator(s)/mechanism(s), and Table A3 presents additional characteristics related to each study's outcome(s). Tables A4 and A5 present frequencies of characteristics related to the mediator(s)/mechanism(s) and outcomes(s), respectively, including the measures and types of measures used, whether interviewers were masked to treatment condition if applicable, whether multiple mediators/mechanisms were examined, the time points of measurement, whether the mediator(s)/mechanism(s) and outcome(s) were measured at each session, and whether the mediator (s)/mechanism(s) were compared across treatments.

Most studies utilized adult samples (47; 75.8%). Thirteen (21.0%) studies focused on veteran participants, 3 (4.8%) focused on active duty military participants, and three (4.8%) studies included a sample of active duty and veteran participants. Thirteen (21.0%) studies included female samples, and one (1.6%) included a male sample. Twenty-seven (43.5%) studies included samples based on trauma type. Eleven (17.7%) studies focused on specific comorbid diagnoses or conditions. Most studies (59; 95.2%) were conducted in outpatient settings, and most (57; 91.9%) examined treatment delivered in an individual format. Among the 36 (58.1%) studies examining more than one treatment, 35 described random assignment to treatment condition; one paper (Hinton, Hofmann, Pitman, Pollack, & Barlow, 2008) did not describe assignment to treatment condition in one of the samples used.[1] Although all studies included in this review indicated in their title or abstract that their purpose was to examine mediators or mechanisms of PTSD treatment, 25 (40.3%) only mentioned mediators or mechanisms of change in the abstract or title and introduction and/or discussion sections, without claiming in their method or results section to analyze mediation or test a putative mechanism. Additional details are presented in Table A1.

3.3. Study methodology

Just over half of studies included in this review (33; 53.2%) measured the mediator before the outcome, 36 (58.1%) measured both the mediator and the outcome at three or more time points, and 29 (46.8%) studies conducted analyses that both accounted for the mediator occurring before the outcome and included three or more

[1] The authors of this study did not respond to attempts to clarify their study procedure.

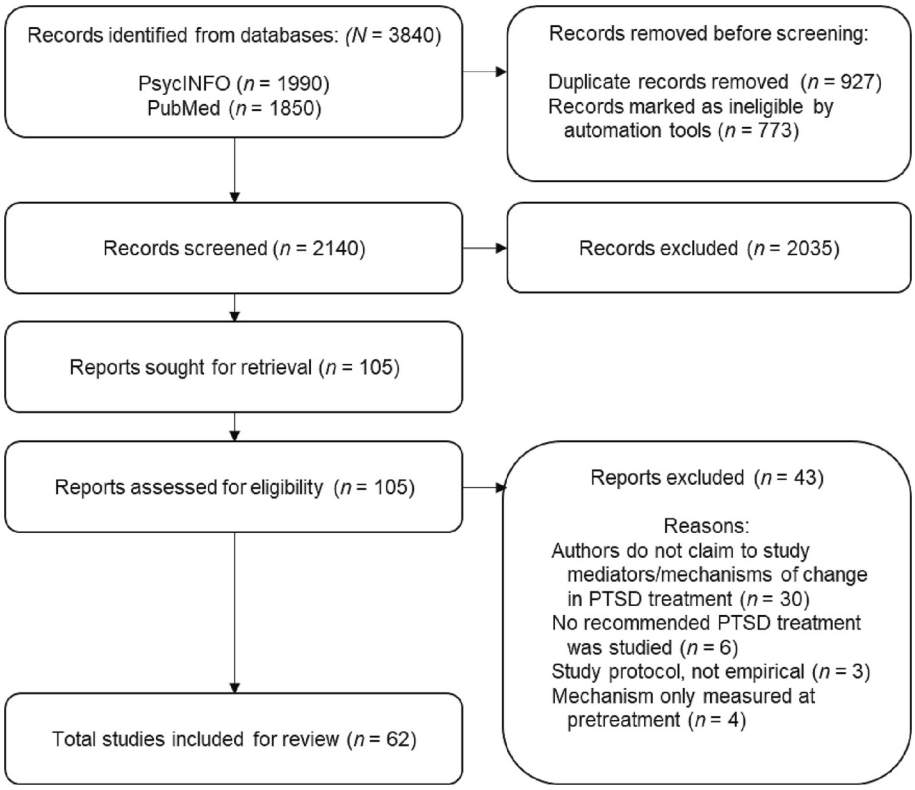

Fig. 1. Flow diagram of study identification, screening, coding, and inclusion.

assessment points. Twenty-five (40.3%) studies tested the reverse direction of effects (i.e., change in PTSD mediating change in the proposed mediator), and of those, 11 found the reverse direction to be significant for at least one mediator tested. Fifty-one (82.3%) studies tested change in the mediator or mechanism and outcome rather than the level of the mediator or mechanism and outcome over time, and 29 (46.8%) used a growth curve model to examine mediation at the within-person level. Twenty studies (32.3%) met all of the following criteria: measured the mediator before the outcome, measured the mediator and outcome at three or more time points, and used growth curve models that tested change in the mediator and outcome and examined mediation at the within-person level. Only one study (1.6%) manipulated the proposed mechanism.

3.4. Study results

Significant and nonsignificant mediator findings are presented for the 62 studies together. Percentages are given for the number of studies out of all 62 studies included, and for mediators or mechanisms that were examined in more than one study, percentages are also given for the number of tests finding that construct significant out of the number of tests in which it was examined. The most frequently-studied mediator/mechanism of PTSD symptom change was change in negative posttraumatic cognitions. Out of 19 tests of this construct across 17 studies, 14 had significant results (22.6% of all studies included, 73.7% of tests of this construct). Studies with significant findings included five studies examining change in PTSD in PE for adults (Cooper, Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2017; McLean, Su, & Foa, 2015; Rauch et al., 2015; Wells et al., 2022; Zalta et al., 2014), one study examining change in PTSD, global social adjustment, interpersonal problems, quality of life, and health-related quality of life in dialectical behavior therapy with prolonged exposure (DBT PE) (Harned, Wilks, Schmidt, & Coyle, 2018), one study examining change in PTSD in PE for youth (McLean, Yeh, Rosenfield, & Foa, 2015), two studies examining change in PTSD in CPT for adults (Gobin et al., 2018; Peck, Coffey, McGuire, Voluse, & Connolly, 2018), two studies examining change in PTSD in CT for PTSD (Kleim et al., 2013; Meiser-Stedman et al., 2017), two studies examining change in PTSD in CBT for PTSD (Mueser et al., 2008; Smith et al., 2007), and one study examining change in PTSD in TF-CBT for youth (Pfeiffer, Sachser, de Haan, Tutus, & Goldbeck, 2017). Five tests of negative posttraumatic cognitions as a mediator or mechanism of change (8.1% of all studies, 26.3% of tests of this construct) found this relationship to be non-significant in at least one analysis, including predicting global social adjustment in a study of DBT PE (Harned et al., 2018), predicting PTSD change in PE (Åkerblom, Perrin, Fischer, & McCracken, 2022), predicting PTSD change in CPT and WET (Lee et al., 2021), predicting PTSD change in NET (Kangaslampi & Peltonen, 2020), and predicting PTSD change in sertraline (Cooper, Zoellner, et al., 2017). Of note, two studies examining negative posttraumatic cognitions had significant findings in one or more analyses and nonsignificant findings in another: Harned et al. (2018) found negative posttraumatic cognitions to mediate change in PTSD, global social adjustment, interpersonal problems, quality of life, and health-related quality of life, but not global social adjustment, and Cooper, Zoellner, et al. (2017) found negative posttraumatic cognitions to mediate PTSD change in PE but not sertraline. One study found the reverse direction of effects also significant (i.e., change in PTSD preceding and predicting change in negative posttraumatic cognitions; McLean, Su, & Foa, 2015), though five studies found the reverse direction nonsignificant (Cooper, Zoellner, et al., 2017; Kleim et al., 2013; Lee et al., 2021; McLean, Yeh, et al., 2015; Zalta et al., 2014).

Nine analyses across seven studies examined fear habituation or extinction as a mediator or mechanism of PTSD symptom change. Given variation in the terminology these studies used, we use the term extinction for ease of interpretation (Asnaani et al., 2016). Given variation in how extinction is operationalized, the measure each study used is described. Between-session extinction was found to mediate PTSD change in six tests (9.1% of all studies, 66.7% of tests of this construct). A

Table 1
Characteristics of each study included in the present review.

Study	Treatment(s) Examined	Sample	Analysis Used to Test Mediation	Significant Mediator(s) or Mechanism(s)	Nonsignificant Mediator(s) or Mechanism(s)	Mediator/ Mechanism Before Outcome	Mediator/ Mechanism & Outcome Measured ≥3 Times	Analysis of Change, Multilevel, Latent Growth	Reverse Direction Tested
Lee, Taylor, & Drummond, 2006	EMDR	Adults	Partial correlations	Distancing	Reliving	No	No	No, No, No	No
Smith et al., 2007	CBT for PTSD; Waitlist	Youth ages 8–18; single incident events	Baron & Kenny mediation, Indirect effect mediation	Negative posttraumatic cognitions	None	No	Yes	Yes, No, No	No
Kindt, Buck, Arntz, & Soeter, 2007	CBT for PTSD	Adults	Regression	Conceptual processing	Perceptual processing	Yes	Yes	Yes, No, No	No
Mueser et al., 2008	CBT for PTSD; TAU	Adults; comorbid SMI	Baron & Kenny mediation	Negative posttraumatic cognitions	None	No	Yes	Yes, Yes, No	No
Hinton et al., 2008	CBT for PTSD and orthostatic panic attacks; Waitlist	Adults; Cambodian refugees with PTSD and comorbid orthostatic panic attacks	Baron & Kenny mediation	Orthostatic panic	None	No	No	Yes, No, No	No
Hinton et al., 2009	CBT for PTSD and orthostatic panic attacks; Waitlist	Adults; Cambodian refugees with PTSD and comorbid orthostatic panic attacks	Baron & Kenny mediation	Orthostatic panic; Emotion regulation	None	No	No	Yes, No, No	No
Aderka et al., 2011	PE for youth	Youth ages 8–18	Lagged analysis	Depression	None	Yes	Yes	Yes, Yes, No	Yes; stronger
Gilman, Schumm, & Chard, 2012	CPT (individual + group)	Veterans	CLPM	Hope	None	Yes	Yes	No, No, No	Yes; N.S.
Liverant et al., 2012	CPT-C; CPT-A; Written Account	Adult women	Lagged analysis	None	Depression	Yes	Yes	Yes, Yes, No	Yes; N.S.
Gallagher & Resick, 2012	PE; CPT	Adult women; sexual assault	Indirect effect mediation	Between-session extinction; Hopelessness	None	No	No	Yes, No, No	No
Kleim et al., 2013	Cognitive therapy for PTSD	Adults	LGCM, CLPM	Negative posttraumatic cognitions	None	Yes	Yes	Yes, No, Yes	Yes; N.S.
Aderka et al., 2013	PE; PE with cognitive restructuring	Adult women; physical or sexual assault	Lagged analysis	Depression (both treatments)	None	Yes	Yes	Yes, Yes, No	Yes; stronger
Zalta et al., 2014	PE; Waitlist	Adult women; physical or sexual assault	Lagged analysis	Negative posttraumatic cognitions	None	Yes	Yes	Yes, Yes, No	Yes; N.S.
Bluett et al., 2014*	PE	Adults	ANOVA	Between-session extinction predicting posttreatment PTSD	Between-session extinction predicting loss of PTSD diagnosis	No	No	Yes, No, No	No
Holt et al., 2014	TF-CBT; TAU	Youth ages 10–18 and their caregivers	Indirect effect mediation	None	Parental emotional reactions; Parental depression	Yes	Yes	Yes, Yes, No	No
Rauch et al., 2015*	PE; Present-centered therapy	Veterans	Regression	Cortisol awakening response (PE); Script-driven cortisol response (PE); Negative posttraumatic cognitions (both)	Cortisol awakening response (present-centered therapy)	No	Yes	Yes, No, No	No
Sripada & Rauch, 2015*	PE	Veterans	Correlations	Between-session extinction; within-session extinction predicting PTSD	Within-session extinction predicting PTSD change and responder status among intent-to-treat	No	Yes	Yes, Yes, No	No

(*continued on next page*)

Table 1 (*continued*)

Study	Treatment(s) Examined	Sample	Analysis Used to Test Mediation	Significant Mediator(s) or Mechanism(s)	Nonsignificant Mediator(s) or Mechanism(s)	Mediator/ Mechanism Before Outcome	Mediator/ Mechanism & Outcome Measured ≥3 Times	Analysis of Change, Multilevel, Latent Growth	Reverse Direction Tested
				change among completers	sample and responder status in completer sample				
McLean, Yeh, et al., 2015	PE for adolescents; Client-centered therapy	Adolescent girls ages 13–18; sexual assault	Lagged analysis	Negative posttraumatic cognitions (both treatments)	None	Yes	Yes	Yes, Yes, No	Yes; N.S.
McLean, Su, & Foa, 2015	PE (+ Naltrexone or placebo); Supportive counseling (+ Naltrexone or placebo)	Adults; comorbid alcohol use disorder	Lagged analysis	Negative posttraumatic cognitions (both PE conditions)	None	Yes	Yes	Yes, Yes, No	Yes; significant
Schumm et al., 2015	CPT (individual + group)	Veterans; residential	CLPM	Self-blame; Negative beliefs about the self	Negative beliefs about the world	Yes	Yes	Yes, No, No	Yes; N.S.
Wisco et al., 2016	Written exposure therapy	Adults; motor vehicle accident	Multilevel regression	Between-session distress extinction; Emotion activation	Between-session heart rate extinction; Within-session extinction	No	No	Yes, Yes, No	No
Sharma-Patel & Brown, 2016	TF-CBT	Youth ages 4–17	Indirect effect mediation	None	Emotion regulation; Self-blame	No	Yes	No, No, No	No
Cisler et al., 2016	TF-CBT	Adolescent girls ages 11–16; physical or sexual assault	Regression	Network assortativity	Network modularity; Global efficiency	No	No	Yes, No, No	No
Cisler, Sigel, et al., 2016	TF-CBT	Adolescent girls ages 11–16, physical or sexual assault	Regression	Emotion regulation	Amygdala-insula functional connectivity while re-appraising	No	No	Yes, No, No	No
Kumpula et al., 2017	PE	Adults	Lagged analysis	Negative beliefs about the self; Negative beliefs about the world	Self-blame	Yes	Yes	Yes, Yes, No	Yes; significant for negative beliefs about the world
Badour et al., 2017	COPE	Veterans; comorbid substance use disorder	Growth models: Slope of mediators predicting slope of outcome	Between-session extinction; Between-session craving reductions	Within-session extinction	Yes	Yes	Yes, Yes, No	No
Meiser-Stedman et al., 2017	Cognitive therapy for PTSD; Waitlist	Youth ages 8–17; single incident events	Indirect effect mediation	Negative posttraumatic cognitions; Trauma memory quality; Rumination; Safety-seeking behaviors	None	No	Yes	Yes, No, No	No
de Kleine, Hendriks, Becker, Broekman, & van Minnen, 2017	Intensive exposure therapy	Adults; interpersonal victimization	Correlations	None	Harm expectancy	No	No	Yes, No, No	No
McLean et al., 2017	PE for adolescents; Client-centered therapy	Adolescent girls ages 13–18; sexual assault	Lagged analysis	Depression (PE)	None	Yes	Yes	Yes, Yes, No	Yes; stronger

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Table 1 (*continued*)

Study	Treatment(s) Examined	Sample	Analysis Used to Test Mediation	Significant Mediator(s) or Mechanism(s)	Nonsignificant Mediator(s) or Mechanism(s)	Mediator/ Mechanism Before Outcome	Mediator/ Mechanism & Outcome Measured ≥3 Times	Analysis of Change, Multilevel, Latent Growth	Reverse Direction Tested
Cooper, Zoellner, et al., 2017	PE; Sertraline	Adults	Lagged analysis	Negative posttraumatic cognitions (PE)	Negative posttraumatic cognitions (sertraline)	Yes	Yes	Yes, Yes, No	Yes; N.S.
Pfeiffer et al., 2017	TF-CBT; Waitlist	Youth ages 7–17	Indirect effect mediation	Negative posttraumatic cognitions	None	Yes	No	No, No, No	No
Gobin et al., 2018	CPT (in-person and telehealth)	Adult women	Indirect effect mediation	Negative posttraumatic cognitions	Treatment expectancy	No	No	No, No, No	No
Harned et al., 2018*‡	DBT PE; DBT (DBT individual + group; PE individual)	Adult women; comorbid BPD and recent suicidal behavior or NSSI	Lagged analysis	Negative posttraumatic cognitions predicting all outcomes except global social adjustment; PTSD symptoms	Negative posttraumatic cognitions predicting global social adjustment	Yes	Yes	Yes, Yes, No	No
Holliday et al., 2018	CPT	Veterans; military sexual trauma	CLPM	Self-blame	Negative beliefs about the self; Negative beliefs about the world	Yes	Yes	Yes, Yes, No	Yes; N.S.
Norr et al., 2018	PE; Virtual reality exposure; Waitlist	Active duty; deployment-related trauma	CLPM	Suicidal ideation	Depression	Yes	Yes	No, No, No	Yes; N.S.
Peck et al., 2018	CPT (individual + group)	Veterans; comorbid substance use disorder	Indirect effect mediation	Negative posttraumatic cognitions	None	No	No	Yes, No, No	No
Peskin et al., 2019	Virtual reality exposure (+ D-Cycloserine or placebo)	Adults; World Trade Center trauma	Lagged analysis	Depression	None	Yes	Yes	Yes, Yes, No	Yes; significant
Holder et al., 2019	CPT	Veterans; military sexual trauma	CLPM	Depression	Hyperarousal; *Re*-experiencing; Avoidance	Yes	Yes	Yes, Yes, No	Yes; N.S.
Tutus, Goldbeck, Pfeiffer, Sachser, & Plener, 2019*	TF-CBT; Waitlist	Youth ages 6–17 and their caregivers	Indirect effect mediation	Parental negative posttraumatic cognitions mediating caregiver report of PTSD	Parental negative posttraumatic cognitions mediating child report of PTSD	No	No	No, No, No	No
McLean et al., 2019*	PE; Present-centered therapy	Active duty post-deployment	Lagged analysis	Negative beliefs about the self; Negative beliefs about the world; Emotion regulation –catastrophizing	Self-blame; Emotion regulation – positive refocusing, acceptance, blames others	Yes	Yes	Yes, No, No	No
Littleton & Grills, 2019	CBT for PTSD; Psychosocial self-help	Adult women; rape survivors	Correlations	Self-blame; Negative beliefs about the self; Negative beliefs about the world (CBT)	Coping strategies	No	No	Yes, No, No	No
Kangaslampi & Peltonen, 2020	Narrative exposure therapy; TAU	Youth ages 7–17	Indirect effect mediation	None	Negative posttraumatic cognitions; Trauma memory quality	No	No	Yes, No, No	No
Harlé, Spadoni, Norman, & Simmons, 2020	PE	Veterans; combat-related trauma	Correlations	Inhibitory control	None	No	No	Yes, Yes, No	No
Bourassa et al., 2020	PE with and without virtual	Active duty; deployment-related trauma	CLPM	Social support	None	Yes	No	No, No, No	Yes; N.S.

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Study	Treatment(s) Examined	Sample	Analysis Used to Test Mediation	Significant Mediator(s) or Mechanism(s)	Nonsignificant Mediator(s) or Mechanism(s)	Mediator/ Mechanism Before Outcome	Mediator/ Mechanism & Outcome Measured ≥3 Times	Analysis of Change, Multilevel, Latent Growth	Reverse Direction Tested
	reality; Waitlist								
Cox et al., 2020	PE	Veterans	Lagged analysis	Shifts in meaning/ perspective	Emotion activation	Yes	Yes	No, No, No	Yes; significant for shifts in meaning/ perspective
McGuire, Frankfurt, Anderson, & Connolly, 2020	CPT (individual + group)	Veterans; comorbid substance use disorder; residential	Indirect effect mediation	Trauma-cued sadness	Trauma-cued disgust, shame, anger, guilt	No	No	Yes, No, No	No
Rauch et al., 2020	PE + placebo; PE + Sertraline; Sertraline + enhanced medication management	Active duty and veterans; combat-related trauma	Correlations	None	Cortisol awakening response	No	Yes	Yes, Yes, No	No
König et al., 2021	CPT for youth; Waitlist	Adolescents and young adults ages 14–21	Correlations	Accommodated beliefs	Overaccommodated beliefs; Assimilated beliefs	No	No	Yes, No, No	No
Fonzo et al., 2021	PE; Waitlist	Adults	Linear mixed model	Amygdala-frontal connectivity and insula-parietal connectivity	Amygdala and insula connectivity with other regions	No	No	Yes, Yes, No	No
Lee et al., 2021	CPT; WET	Adults	Latent parallel growth curve model	None	Negative post-traumatic cognitions; Between-session change in post-session emotional arousal and valence	Yes	Yes	Yes, No, Yes	Yes; N.S.
Allard et al., 2021‡	PE; PE + placebo; PE + Sertraline; Sertraline + enhanced medication management	Active duty and veterans; combat-related trauma	Regression	Guilt cognitions (PTSD outcome)	Guilt cognitions (functioning outcome)	Yes	No	Yes, Yes, No	Yes; significant for PTSD, N.S. for functioning
Vuper, Philippi, & Bruce, 2021	CPT	Adult women; interpersonal violence	Correlations	None	Resting-state functional connectivity in default mode network [DMN], central executive network [CEN], and salience network [SN]	No	No	Yes, No, No	No
Wells et al., 2022	PE; Relaxation therapy	Older adult men combat veterans; military-related PTSD	Indirect effect mediation	Negative posttraumatic cognitions	None	Yes	Yes	Yes, Yes, No	No
Schumm et al., 2022	Trauma-focused CBT for PTSD	Adults	Linear mixed models examining lagged associations	None	Rumination	Yes	Yes	Yes, Yes, No	Yes; significant
Hoeboer et al., 2022	PE; intensive PE	Adults; childhood physical or sexual abuse	Dynamic panel models	Within-session extinction	Between-session extinction	Yes	Yes	Yes, No, No	Yes; N.S.
Maples-Keller et al., 2022	PE	Active duty and veterans	ANOVA	Extinction learning and retention	Fear acquisition	No	No	Yes, No, No	No
Zoellner et al., 2022	Brief imaginal exposure and processing	Adults	Growth curve modeling	Between-session extinction (peak and post-exposure distress)	Between-session reduction in pre-exposure distress	No	No	Yes, Yes, No	No

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Table 1 (*continued*)

Study	Treatment(s) Examined	Sample	Analysis Used to Test Mediation	Significant Mediator(s) or Mechanism(s)	Nonsignificant Mediator(s) or Mechanism(s)	Mediator/ Mechanism Before Outcome	Mediator/ Mechanism & Outcome Measured ≥3 Times	Analysis of Change, Multilevel, Latent Growth	Reverse Direction Tested
	(modified PE)								
Glanton Holzhauer, Duberstein, Ward, & Talbot, 2022	IPT-T; TAU	Adult women; childhood sexual abuse; comorbid depression	Indirect effect mediation	Social functioning	None	Yes	Yes	No, No, No	Yes; N.S.
Shenk et al., 2022	TF-CBT for youth, Animal-assisted therapy	Youth ages 6–17; interpersonal violence	Multilevel regression	RSA variability, RSA change	RSA intercepts and slopes	No	No	Yes, Yes, No	No
Saraiya et al., 2022	COPE; Relapse Prevention	Veterans; comorbid substance use disorder	Lagged analysis	Guilt	Anger	Yes	Yes	Yes, Yes, No	Yes; significant for anger, N.S. for guilt
Åkerblom et al., 2022	PE with CBT for chronic pain	Adults; comorbid chronic pain; inpatient for pain rehabilitation	Graphical inspection, randomization tests for single-case experimental designs	None	Pain-related acceptance, anxiety/ depression (one measure), negative posttraumatic cognitions	Yes	Yes	Yes, No, No	Yes; significant
Susanty et al., 2022	EMDR; EMDR without eye movements	Adults	Group differences in slopes of change	None	Eye movements	Yes	No	No, Yes, No	No

Note. Several studies tested fear habituation or extinction as a mediator of PTSD symptom change; given variation in the terminology these studies used, we use the term extinction for ease of interpretation. EMDR = eye movement desensitization and reprocessing, CBT = cognitive behavioral therapy, PTSD = posttraumatic stress disorder, TAU = treatment as usual, SMI = severe mental illness, PE = prolonged exposure, CPT = cognitive processing therapy, CPT-C = cognitive processing therapy – cognitive (without written accounts), CLPM = cross-lagged panel model, N.S. = not significant, CPT-A = cognitive processing therapy with written accounts, TF-CBT = trauma-focused cognitive behavioral therapy, COPE = concurrent treatment of PTSD and substance use disorders using prolonged exposure, DBT = dialectical behavior therapy, IPT-T = interpersonal psychotherapy—trauma, BPD = borderline personality disorder, NSSI = nonsuicidal self-injury, RSA = respiratory sinus arrythmia.

* The same construct was found to be both a significant mediator of outcome and a nonsignificant mediator of outcome depending on the treatment condition, the way the mediator was measured, or the way the outcome was measured. These differences are noted in the significant mediator(s) and nonsignificant mediator(s) columns.

‡ Outcomes included measures of functioning and/or quality of life in addition to PTSD symptoms.

significant relationship was found in four studies of PE, including measuring between-session extinction as between-session reductions in self-reported subjective units of distress (SUDS; Bluett, Zoellner, & Feeny, 2014; Gallagher & Resick, 2012; Sripada & Rauch, 2015) and as reductions in self-reported distress during exposure assessed via the self-assessment manikin (Wisco et al., 2016). A significant relationship was also found in a study of concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE), measuring extinction as reduction in SUDS (Badour et al., 2017), and a study of brief imaginal exposure and processing, a modification of PE, measuring extinction as reduction in SUDS (Zoellner et al., 2022). One of these studies also found a significant relationship in CPT, measuring extinction as reduction in SUDS (Gallagher & Resick, 2012). Three tests (4.8% of all studies, 33.3% of tests of this construct) found that between-session extinction was unrelated to outcome, including in two studies previously listed that found between-session extinction not to mediate outcome in a different analysis. Bluett et al. (2014) found that self-reported between-session extinction (reduction in SUDS) predicted PTSD symptom change but not loss of PTSD diagnosis in PE, and Wisco et al. (2016) found that in WET, between-session reductions in self-reported distress during exposure on the self-assessment manikin, but not between-session extinction measured via heart rate, mediated PTSD symptom change. One study (Hoeboer et al., 2022) found that between-session extinction (reduction in SUDS) did not mediate change in PTSD symptoms in PE.

Emotional activation and within-session extinction are also posited by emotional processing theory to be indicators of emotional processing in exposure therapies for PTSD. Of the two studies examining emotional activation, one (1.6% of all studies, 50.0% of tests of this construct) found emotional activation, measured as heart rate during exposure, to mediate PTSD change in WET (Wisco et al., 2016), whereas one other study (1.6% of all studies, 50.0% of tests of this construct) found emotional activation, assessed via therapist report of observed patient activation, not to mediate outcome in PE (Cox et al., 2020). Of the five tests across four studies examining within-session extinction, two tests (3.2% of all studies, 40.0% of tests of this construct) found within-session extinction to mediate PTSD symptom change in PE, both assessed as reduction in SUDS (Hoeboer et al., 2022; Sripada & Rauch, 2015), although Sripada and Rauch (2015) only found this effect among PE treatment completers. Three tests (4.8% of all studies, 60.0% of tests of this construct) found this relationship not to be significant, including in the intent-to-treat sample in Sripada & Rauch's study of PE (Sripada and Rauch, 2015), in a study of COPE (assessed as reduction in SUDS; Badour et al., 2017), and in a study of WET (assessed as within-session reduction in heart rate; Wisco et al., 2016). Taken together, there is little evidence for emotional activation or within-session extinction as mediators or mechanisms of PTSD symptom change.

Depression was examined in seven tests across seven studies and found to mediate PTSD outcome in five of those (8.1% of all studies,

71.4% of tests of this construct). Studies with significant findings included one study of PE and PE + cognitive restructuring (Aderka, Gillihan, McLean, & Foa, 2013), two studies of PE for youth (Aderka, Foa, Applebaum, Shafran, & Gilboa-Schechtman, 2011; McLean, Su, Carpenter, & Foa, 2017), one study of CPT (Holder, Holliday, Wiblin, & Surís, 2019), and one study of virtual reality exposure with and without d-cycloserine (Peskin et al., 2019). Two other studies (3.2% of all studies, 28.6% of tests of this construct) found depression not to mediate change in PTSD, including one study of PE + virtual reality (Norr, Smolenski, & Reger, 2018) and one study of CPT (Liverant, Suvak, Pineles, & Resick, 2012). Of note, four out of the five studies finding depression to mediate PTSD change found the reverse direction of effects to also be significant (PTSD mediating change in depression; Aderka et al., 2011; Aderka et al., 2013; McLean et al., 2017; Peskin et al., 2019), and in three cases, the reverse direction of effects was stronger (Aderka et al., 2011; Aderka et al., 2013; McLean et al., 2017).

Some studies examined specific types of negative cognitions. Negative beliefs about the self mediated outcome in four studies (6.5% of all studies, 80.0% of tests of this construct), including two studies of PE (Kumpula et al., 2017; McLean et al., 2019), one study of CPT (Schumm, Dickstein, Walter, Owens, & Chard, 2015), and one study of CBT for PTSD (Littleton & Grills, 2019), but did not mediate outcome in one study of CPT (1.6% of all studies, 20.0% of tests of this construct; Holliday, Holder, & Surís, 2018). Negative beliefs about the world mediated outcome in three studies (4.8% of all studies, 60.0% of tests of this construct), including two studies of PE (Kumpula et al., 2017; McLean et al., 2019) and one study of CBT for PTSD (Littleton & Grills, 2019). Negative beliefs about the world did not mediate outcome in two studies of CPT (3.2% of all studies, 40.0% of tests of this construct; Holliday et al., 2018; Schumm et al., 2015). Self-blame mediated outcome in three studies (4.8% of all studies, 50.0% of tests of this construct), including two studies of CPT (Holliday et al., 2018; Schumm et al., 2015) and one study of CBT for PTSD (Littleton & Grills, 2019), but did not mediate outcome in three other studies (4.8% of all studies, 50.0% of tests of this construct), including two studies of PE (Kumpula et al., 2017; McLean et al., 2019) and one study of TF-CBT for youth (Sharma-Patel & Brown, 2016). Guilt cognitions were found to mediate change in PTSD but not functioning in one (1.6%) study of PE and sertraline (Allard et al., 2021).

Emotion regulation was examined in four studies; McLean et al. (2019) examined four emotion regulation subscales separately, so seven tests are considered. Emotion regulation was found to mediate PTSD symptom improvement in three tests across three studies (4.8% of all studies, 42.9% of tests of this construct), including the catastrophizing subscale in a study of PE (McLean et al., 2019) and broad emotion regulation in TF-CBT for youth (Cisler, Sigel, et al., 2016) and CBT for PTSD and orthostatic panic attacks (Hinton, Hofmann, Pollack, & Otto, 2009). Emotion regulation was not found to be a significant mediator of symptom change in four tests across two studies (3.2% of all studies, 57.1% of tests of this construct), including the positive refocusing, acceptance, and blames others subscales in a study of PE (McLean et al., 2019) and broad emotion regulation in a study of TF-CBT for youth (Sharma-Patel & Brown, 2016). If only tests of emotion regulation broadly are considered, rather than subscales, this mediator was found to be significant in two out of three tests (66.7%; Cisler, Sigel, et al., 2016; Hinton et al., 2009) and not significant in one test (33.3%; Sharma-Patel & Brown, 2016).

Orthostatic panic was also found to mediate PTSD change in two (3.2%) papers specifically examining a combined treatment for PTSD and orthostatic panic (Hinton et al., 2008; Hinton et al., 2009), although these papers drew from the same sample of participants. Mediators for which one study or no studies found significant results are presented in Table A1.

3.5. Findings from studies with the highest-quality tests of mediation

The findings of the 20 (32.3%) studies with the most stringent approaches to testing mediation are highlighted. These studies measured the mediator temporally before the outcome, measured the mediator and outcome at three or more time points, and used growth curve models that tested change in the mediator and outcome and examined mediation at the within-person level. This combination of characteristics allowed these studies to establish temporal precedence of change in the mediator predicting subsequent change in the outcome within individuals. Eight of the 20 studies included 11 tests of change in negative posttraumatic cognitions; seven out of those 11 tests (63.6%) found significant results, and three out of those 11 (27.3%) found nonsignificant results. Zalta et al. (2014) found negative posttraumatic cognitions to mediate outcome in PE, and they found the reverse direction of effects nonsignificant (n.s.). McLean, Yeh, et al. (2015) found negative posttraumatic cognitions to mediate outcome in both PE for youth and client-centered therapy (reverse direction n.s.). McLean, Su, and Foa (2015) found negative posttraumatic cognitions to mediate outcome in PE + naltrexone and PE + placebo for adults with PTSD and comorbid alcohol use disorder (reverse direction also significant). Cooper, Zoellner, et al. (2017) found negative posttraumatic cognitions to mediate outcome in PE (reverse direction n.s.). Wells et al. (2022) found negative posttraumatic cognitions to mediate outcome in PE. Harned et al. (2018) found negative posttraumatic cognitions to mediate PTSD, global functioning, interpersonal problems, quality of life, and health-related quality of life, and PTSD symptoms to mediate all quality of life and functioning outcomes in DBT PE for adult women with comorbid BPD and recent suicidal behavior or nonsuicidal self injury (reverse direction not tested). Kleim et al. (2013) found negative posttraumatic cognitions to mediate outcome in CT for PTSD (reverse direction n.s.). However, Cooper, Zoellner, et al. (2017) also found negative posttraumatic cognitions not to mediate change in sertraline (reverse direction also n.s.), Harned et al. (2018) also found negative posttraumatic cognitions not to mediate change in global social adjustment in DBT PE (reverse direction not tested), and Lee et al. (2021) found negative posttraumatic cognitions not to mediate PTSD symptom change in CPT or WET (reverse direction also n.s.).

Two of the 20 studies examined specific types of negative cognitions. Kumpula et al. (2017) found that negative beliefs about the self and world mediated outcome in PE, while self-blame did not, and the reverse direction of effects was also significant for negative beliefs about the world. Conversely, Holliday et al. (2018) found that self-blame mediated outcome in CPT for veterans who had experienced military sexual trauma (reverse direction n.s.), while negative beliefs about the self and world did not; each of these types of cognitions was significant in one study (50.0%) but not the other (50.0%). One study (Schumm et al., 2022) examined rumination, a cognitive process involving becoming stuck in negative thinking, and found that it did not mediate PTSD change in trauma-focused CBT for adults.

Three studies examined different emotion-related constructs as mediators or mechanisms of PTSD symptom change. Badour et al. (2017) found between-session extinction and between-session reduction in substance cravings to mediate PTSD outcome in COPE for veterans with PTSD and comorbid substance use disorder (reverse direction not tested). Lee et al. (2021) found post-session emotional arousal and valence not to mediate change in CPT and WET (reverse direction also n.s.). Saraiya et al. (2022) found change in guilt, but not anger, to mediate PTSD outcome in COPE for veterans with PTSD and comorbid substance use disorder (reverse direction significant for anger, n.s. for guilt).

Six of the 20 studies examined change in depression as a mediator of change in PTSD; five tests (83.3%) had significant findings and one (1.7%) did not. Aderka and colleagues found depression to mediate change in PTSD in PE for youth (Aderka et al., 2011), as well as PE with and without cognitive restructuring for adults (Aderka et al., 2013), though in both studies the reverse direction of effects was stronger.

McLean et al. (2017) found depression to mediate change in PE for adolescent girls, although the reverse direction was again more robust. Peskin et al. (2019) found depression to mediate change in virtual reality exposure with and without d-cycloserine for adults with trauma related to the World Trade Center attacks (reverse direction also significant), and Holder et al. (2019) found depression to mediate outcome in CPT for veterans with military sexual trauma (reverse direction n.s.). Liverant et al. (2012) found depression not to mediate outcome in CPT. Finally, one of the 20 studies examined a mediators not conceptually related to those examined by the other studies. Holt, Jensen, and Wentzel-Larsen (2014) found that parental emotional reactions and parental depression did not mediate youth PTSD outcome in TF-CBT for youth.

4. Discussion

Of the mediators and mechanisms of symptom change examined in the 62 studies included in this review, the most frequently and consistently found mediator of PTSD improvement was reductions in negative posttraumatic cognitions, followed by between-session extinction and decreased depression. The pattern of findings in this review, which only included studies with the stated goal of examining mediators or mechanisms of change, is consistent with previous reviews of theorized mechanisms of change that examined predictors and correlates of outcome as well as mediators (e.g., Asnaani et al., 2016; Brown, Belli, et al., 2019; Cooper, Clifton, & Feeny, 2017; Craske et al., 2008; Kangaslampi & Peltonen, 2022; Sripada et al., 2016; Zalta, 2015). The current review's findings provide stronger support for the identified constructs as mediators or mechanisms of therapeutic change in PTSD treatments by examining studies that specifically aimed to test these questions. Additionally, many of the mediators and mechanisms examined in the present review had weak or no empirical support.

The finding that change in negative posttraumatic cognitions consistently emerged as a mediator of PTSD symptom change during treatment provides support for cognitive theory as an explanatory framework for mechanisms of change in PTSD treatment. Cognitive change was found to mediate PTSD improvement in both treatments founded in cognitive theory (e.g., CPT, CT) as well as treatments founded in emotional processing theory (e.g., PE). Studies that did not find negative posttraumatic cognitions to mediate or relate to change in outcome had some differences when compared to the studies finding significant effects. Studies with significant findings included all studies examining PTSD outcome in PE and variations in an outpatient setting, CT, TF-CBT for youth, and CBT for PTSD, as well as two out of three studies of CPT. Tests with nonsignificant findings examined different treatments (NET in Kangaslampi & Peltonen, 2020; sertraline in Cooper, Zoellner, et al., 2017), samples (patients receiving PE in the context of inpatient pain rehabilitation in Åkerblom et al., 2022), and outcomes (global social adjustment in Harned et al., 2018). That said, Lee et al. (2021) conducted a statistically stringent test of mediation in an outpatient sample receiving CPT and WET and found negative posttraumatic cognitions not to mediate change in PTSD. Additionally, few studies examined functioning as a treatment outcome (Allard et al., 2021; Harned et al., 2018); mechanisms of change in functioning may be different than mechanisms of change in PTSD symptoms.

Cognitive change has been a significant focus of researchers examining mediators of PTSD treatments and has been studied more than other constructs, but the most frequently-examined or frequently-found mediator may not necessarily be the most important mediator. Potentially important mediators may have received little study to date. Additionally, while 73.7% of tests of negative posttraumatic cognitions had significant results, 66.7% of tests of between-session extinction had significant results, suggesting that between-session extinction may be a similarly or only slightly less consistent mediator or mechanism of change. Unlike between-session extinction, however, change in negative posttraumatic cognitions was found to mediate change in multiple of the highest-quality examinations, and it was also found to mediate change across PTSD treatments. These findings suggest clinicians providing PTSD treatments should continue to focus on procedures that facilitate patients' cognitive change, e.g., Socratic dialogue in CPT and CT, and using the processing part of PE and spending time in sessions of other treatments working to facilitate cognitive change.

Evidence for between-session extinction as a mediator of PTSD symptom improvement was fairly consistent across studies examining this construct, providing support to emotional processing (Foa et al., 2006) as a putative mechanism of change. Less consistent with emotional processing theory, support was weaker for emotional activation and within-session extinction as mechanisms of change in ESTs for PTSD. Importantly, between-session extinction was only tested in in exposure-based treatments (PE, COPE, brief imaginal exposure and processing, and WET), raising the empirical question as to whether reductions in emotional distress mediate change in other therapies like CPT. Comparing tests finding between-session extinction significant vs. nonsignificant, some differences can be noted. All but one of the tests of self-reported distress mediating or predicting change in PTSD across exposure-based treatments had significant results. One of the nonsignificant tests included a more stringent outcome criterion (i.e., loss of PTSD diagnosis as opposed to PTSD change in Bluett et al., 2014), and another test used a physiological measure (heart rate in Wisco et al., 2016). That said, Hoeboer et al. (2022) conducted a statistically stringent test of change in SUDS in PE and found null results. Overall, this pattern of findings suggests that clinicians providing exposure-based treatments should continue to attend to patients' reductions in self-reported distress and aim to help patients tolerate their distress so it can ultimately decrease. At the same time, more and better-quality research is needed on this putative mechanism, including in non-exposure treatments. Future research might also clarify the roles of inhibitory learning vs. extinction learning (Craske et al., 2008; Lee et al., 2021), as well as the roles of self-reported distress vs. physiological markers of distress, in the treatment process.

Of note, only one study examined trauma-related cognitions and emotions together in the same study (Lee et al., 2021), although they were not examined in the same model, and this study did not identify significant mediators of change. As such, it is unclear whether these factors independently lead to symptom change, nor is it clear whether there is a temporal or potentially reciprocal relationship between change in trauma-related cognitions and emotions. Despite the difficulty of conducting such complex analyses with adequate power, future research should examine these mediators together in the same model to elucidate whether multiple mechanisms are at play in the same treatments.

Multiple of the studies reviewed found that improvement in depression mediated PTSD improvement. These findings are notable because none of the PTSD treatments examined were theoretically designed to reduce PTSD symptoms by reducing symptoms of depression. However, almost all of these studies also found that PTSD symptoms significantly mediated depression symptoms, and of those, most found that relationship to be stronger. This pattern of findings calls into question change in depression as a true mediator or mechanism of change in PTSD symptoms and suggests depression symptoms may instead change concurrently or reciprocally with PTSD symptoms. This explanation would seem plausible given the high overlap in depression and PTSD symptoms (e.g., anhedonia, negative beliefs about the self, negative emotions such as guilt or shame, difficulty sleeping, difficulty concentrating), which confounds examinations of depression as a mediator of change in PTSD. Future studies could take a symptom-level approach, including symptoms of both PTSD and depression, to examine which symptoms change earlier and may predict later change in other symptoms.

Summarizing the quality of the mediation analyses, under half of the studies included in this review conducted analyses that accounted for the mediator occurring before the outcome and included three or more assessment points, which are required for tests of longitudinal

mediation. A more stringent approach to testing mediation would include these two design and analytic techniques, modeling change in the mediator and outcome rather than the level of the mediator and outcome over time, and using a growth curve model to examine mediation at the within-person level. This combination of criteria allows a study to establish temporal precedence of change in the mediator predicting and predicting subsequent change in the outcome within individuals. Under a third of studies met all of these criteria. The pattern of findings in these studies was generally similar to the findings in the overall samples of studies reviewed: negative posttraumatic cognitions was generally supported as a putative mechanism, and depression had more limited support. Only one of these studies examined between-session extinction, and that study did find it to significantly mediate change in PTSD symptoms, but additional high-quality studies are needed to support this as a mechanism. It is promising that cross-sectional mediation models analyzing change in the mediator and outcome from pretreatment to posttreatment seem to be moving out of favor, while growth curve models testing change in the mediator and outcome across multiple time points are becoming more common. More studies should use growth curve models that account for temporal precedence and include multiple assessment points, test multiple mediators, examine treatment specificity of mediators, and test the reverse direction of effects. Taken together, the studies reviewed here and particularly the studies with the highest-quality tests of mediation provide good-quality evidence for today's standards, although there is a need for improved methodological rigor in tests of treatment mediators and mechanisms going forward.

4.1. Obstacles to studying mediators and mechanisms of therapeutic change

There are numerous obstacles to high-quality investigations of mediators and mechanisms of therapeutic change, including obstacles related to study design, measurement, analysis, and conceptualization. Related to study design, to test mediational or mechanistic questions, researchers need many assessments of the proposed mediator and outcome among a large enough sample to adequately power complex analyses, decreasing feasibility and increasing participant burden. Assessing multiple mediators in the same study, while valuable for establishing a mediator's specificity, further increases participant burden. Similarly, assessing mediators across treatments can establish treatment specificity of a mediator, but this study design requires considerably more resources and raises study costs. While using archived data from completed trials has historically been the most feasible way to test mechanistic questions in light of grant funding priorities, it was previously not the norm to collect assessments beyond pretreatment and posttreatment, making this approach difficult. Even if one research study has a design that facilitates the examination of mediators or mechanisms, it takes more than one high-quality study to establish a mechanism (e.g., a mechanism cannot be manipulated in the same study that examines whether a proposed mechanism mediates symptom change; Kazdin, 2007).

An additional set of obstacles to studying mediators and mechanisms of change pertains to measurement. First, it is necessary to measure purported *indicators* of proposed mechanisms of change. For example, emotional processing is a proposed mechanism of PE, which involves activation of the fear network and incorporation of disconfirming information, yet emotional processing is a hypothetical construct (Foa et al., 2006). Fear activation and extinction are suggested as measurable indicators that emotional processing has occurred (Foa et al., 2006). More generally, it is difficult if not impossible to measure internal processes that may be mechanisms of change on the necessary time scale. Self-report measures rely on participants to accurately report small changes in nuanced processes over time. Weekly self-reports of negative cognitions cannot capture the range and variability of thoughts patients have throughout a week, nor how those thoughts are associated with other PTSD symptoms day to day or moment to moment. Psychophysiological measures can capture processes on a finer time scale, but they cannot capture the extent to which newly learned associations inhibit old associations in a moment when a trauma-related stimulus is present, as posited by inhibitory learning theory (Craske et al., 2008).

There are also obstacles to researchers' gaining the statistical expertise required to test mediation well. Mediation is best tested using complex statistical models that require specialized knowledge not taught in most psychology graduate programs. Few people have the level of statistical expertise to conduct rigorous mediation analyses. Further, modeling approaches are advancing rapidly, and it can be difficult for researchers to stay up to date on the latest approaches.

A conceptual issue when studying mechanisms of PTSD treatment is overlap between proposed mechanisms of change and DSM-5 symptoms of PTSD (American Psychiatric Association, 2013). Change in negative cognitions is inherently part of change in PTSD, including symptom D2 Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world and D3 Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others. Between-session extinction can reflect change in symptoms B4 Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s) or B5 Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). McLean et al. (2019) attempted to circumvent this problem by running an additional model using a PTSD symptom measure with the reexperiencing symptoms omitted. While a creative solution to this problem, taking such an approach renders the outcome a construct that is distinct from PTSD. Additionally, if a study were to include multiple proposed mediators (e.g., cognitions and emotions), as Kazdin (2007) and others recommend, this would not be a feasible solution. Additional approaches could be to examine mediators of change in PTSD symptom clusters or in functioning or quality of life.

Another conceptual issue is that certain processes that mediate treatment outcome may not change in a linear way (Alpert, Hayes, Yasinski, Webb, & Deblinger, 2021; Kazdin, 2007; Robison-Andrew et al., 2014). The most modern mediational analyses examine whether change in the mediator between two time points predicts change in the outcome between two subsequent time points, which does not examine whether an increase then decrease in a mediator (e.g., activation and then extinction of negative emotions across exposures) may account for an overall decrease in symptoms over the course of treatment.

Further, multiple mediators may be relevant in the same treatment concurrently or sequentially, and it may be unrealistic to expect specificity of one proposed mediator over another (Kazdin, 2007). Different procedures within the same treatment (e.g., exposure vs. processing) may also affect symptoms via different mechanisms. The connections between procedures and mechanisms may not always be intuitive, given that PE was designed to attenuate PTSD via fear activation and extinction, yet change in negative cognitions has been a significant mediator in multiple studies. Dismantling studies can add to understanding of the link between treatment procedures and mechanisms (Lee et al., 2021).

It may also be the case that multiple mediators have additive or cascading effects. Network approaches suggest symptoms function together such that change in one (e.g., cognitions) drives change in another (e.g., emotions) and vice versa (e.g., Borsboom, Epskamp, Kievit, Cramer, & Schmittmann, 2011). These relationships are not possible to parse apart when only one mediator is measured. Even if multiple mediators were assessed, network analyses require a dense measurement schedule that is not feasible in most psychotherapy studies. Mediators may also have interactive effects. For example, Ready et al. (2015) found an interaction such that the presence of accommodated beliefs attenuated the relationship between overaccommodated beliefs and poor symptom outcome in TF-CBT. These issues present a disconnect between complex mechanistic theories and the analytic tools currently available to test these theories.

Adding complexity, mechanisms of change and relationships among processes may vary from person to person (Kazdin, 2007). For example, change in cognitions may be the key ingredient for one person, while change in emotional responses may be the key ingredient for another person. We may have to manipulate interventions in different ways to enhance outcomes for different people. Moderated mediation can help answer these questions, but the full complexity of variation that might exist among people will be difficult to capture using existing statistical approaches.

4.2. Limitations and future directions

The current systematic review has important limitations. First, this review included studies that examined both mediators and mechanisms of treatment outcome, without differentiating between the two. Limiting the review to studies that used these words allowed examination of findings beyond predictors of outcome, yet mediators and mechanisms are not the same, and studies tended to use only one of these words. Some studies that used the term mechanism used analyses that provided an even less stringent test of a mechanism than mediation. Because of the inclusion criteria, this review included studies that claimed to study mediators or mechanisms of PTSD treatment, but then used correlations, ANOVAs, or regression analyses to test the research questions. On the other hand, this review did not include studies that examined mediators or mechanisms but did not use these words in the title or abstract. For example, some authors have used growth curve models to examine temporal precedence of treatment processes and outcomes across multiple time points, but they did not use the word mediation or mechanism to describe their study (e.g., Dillon et al., 2020; Ehlers et al., 2021). To be conservative, authors may have not have used the word mediation when examining temporal sequencing of change in treatment processes and outcomes. The wording used in peer-reviewed papers may be impacted by authors' choices or by reviewers' recommendations. When papers did not use terms related to mediation or mechanism in the title or abstract, they were excluded from this review.

This review may also be impacted by reporting bias. Examinations with null results may not have been submitted to journals or published. Results also focus on the constructs that have been studied most often. Researchers may be more likely to examine constructs that have received the most attention (e.g., negative posttraumatic cognitions), while other potentially important processes may receive less focus. Finally, this review is limited in its ability to draw conclusions about the quality of analyses and findings, as there are no agreed-upon criteria for tests of mediation, and statistical approaches to testing mediation are developing quickly. It is likely that in the years after the publication of this review, better approaches to testing mediation will become available and more mainstream, such that findings these authors consider to be of higher quality are no longer the highest-quality findings.

There are many ways the field can move forward to answer questions of mechanisms of change in PTSD treatments. First, researchers should move beyond examining predictors of outcome. Prediction is a step toward identifying key treatment ingredients, but it is not sufficient to demonstrate a mechanism of change. Researchers should incorporate repeated measurement of multiple potential mechanisms as a standard part of study design and include dense enough data collection such that they can apply up-to-date statistical approaches after the study ends. Growth curve models should be used that incorporate at least three time points and account for temporal sequencing of change in the mediator and outcome. Researchers should continue to test the reverse direction of proposed effects.

Systemic support will be needed for researchers to be able to follow these recommendations. Regarding grant funding, the National Institute of Mental Health is incentivizing researchers to identify and manipulate mechanisms of change (National Institutes of Health, 2021). Study designs that manipulate therapy procedures, like dismantling and single-subject ABAB designs, can also help map procedures onto change in putative mechanisms. Advanced statistical training is needed in graduate programs and throughout researchers' careers to stay up to date on analytic approaches. Professional associations could hire experts to lead workshops in advanced statistical mediation approaches and even provide post-workshop consultation. The expertise of a few needs to become more widespread so more researchers can better answer important questions of mechanisms of change in treatment.

The study of mediators of change in psychotherapy is complicated, and establishing a mechanism of change even more so. The field is moving toward study designs that will make answering these questions more feasible, and statistical techniques are advancing rapidly. There is no doubt that the field's ability to answer these questions will continue to improve over time.

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Elizabeth Alpert and Denise Sloan conceptualized the systematic review. Elizabeth Alpert drafted the protocol, and Chelsea Shotwell Tabke, Travis Cole, and Denise Sloan reviewed and edited the protocol. Elizabeth Alpert conducted literature searches and oversaw project administration. Elizabeth Alpert, Chelsea Shotwell Tabke, Travis Cole, and Denise Sloan screened studies for preliminary eligibility, and Elizabeth Alpert, Chelsea Shotwell Tabke, and Travis Cole conducted full study coding. Daniel Lee contributed to coding statistical methodologies, as well as conceptualizing the presentation of the results. Elizabeth Alpert, Chelsea Shotwell Tabke, and Travis Cole drafted the manuscript, and all authors reviewed and edited the manuscript. All authors contributed to and have approved the final manuscript.

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Disclaimer

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Declaration of Competing Interest

The author have no conflicts of interest to declare.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpr.2023.102300.

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