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Running head: PTSD treatment mediators

The Temporal Sequence of Change in PTSD Symptoms and Hypothesized Mediators in Cognitive Processing Therapy and Written Exposure Therapy for PTSD

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Abstract

We examined whether extinction or changes negative trauma-related beliefs occur either prior to or concurrently with changes in posttraumatic stress symptoms among individuals who received either Cognitive Processing Therapy (CPT) or Written Exposure Therapy (WET) using statistical methods that permit proper discernment of temporal sequence. Community participants with PTSD (N = 126) were evenly randomized to 12 sessions of CPT or 5 sessions of WET. We assessed within- and between-session changes in arousal and valence and changes in trauma-related beliefs 6-, 12-, 24-, 36- and 60-weeks following the first treatment session. Between-session change in post-session emotional valence temporally preceded PTSD symptom reduction among participants who received WET but did not predict subsequent symptom reduction. Although negative trauma-related beliefs changed in parallel with and correlated with PTSD symptom reduction in both conditions, this change did not temporally precede symptom reduction. Our results are inconsistent with those from prior studies and suggest these constructs may more appropriately be characterized as correlates, rather than mediators, of symptom reduction. These results highlight the value of discernment of the temporal sequence of change between hypothesized mediators and symptoms and underscore that we still have much to learn about how evidence-based treatments reduce PTSD symptoms.

Keywords: mediation; PTSD; exposure-based treatment; cognitive therapy

The Temporal Sequence of Change in PTSD Symptoms and Hypothesized Mediators in Cognitive Processing Therapy and Written Exposure Therapy for PTSD

Trauma-focused psychotherapies, such as Cognitive Processing Therapy (CPT; Resick et al., 2016), Prolonged Exposure (PE; Foa et al., 2019), and Written Exposure Therapy (WET; Sloan & Marx, 2019) are consistently associated with large-magnitude reductions in posttraumatic stress disorder (PTSD) symptoms (for a review see, Cusack et al., 2016; Steenkamp et al., 2015). Despite the large-magnitude effects these interventions have on symptoms, a significant minority of individuals do not experience clinically significant benefit from these treatments (e.g., Steenkamp et al., 2015). Trauma-focused psychotherapies for PTSD are grounded in clear and long-standing theories about the underlying processes, based upon both human and animal models of behavior, that lead to significant symptom reductions. Research on how these treatments cause symptom reduction is critical to maximizing effectiveness of these interventions.

Exposure-focused interventions such as WET and PE are theorized to cause PTSD symptom reduction through extinction – or the diminishing conditioned response to a conditioned stimulus in the absence of an unconditioned stimulus. Based in emotional processing theory (Asnaani et al., 2016; Foa et al., 2006; Foa & Kozak, 1986), imaginal exposure to the trauma memory and in-vivo exposure to feared environmental stimuli (i.e., conditioned stimuli) in the absence of the unconditioned stimulus (i.e., trauma) is hypothesized to cause extinction, which in turn leads to PTSD symptom reduction. Within this framework, exposure is the mechanism that causes extinction, that in turn leads to symptom reduction (see Supplemental Figure 1). In support of the extinction model, several prior studies have demonstrated that between-session decreases in self-reported distress during imaginal exposure predict PTSD

symptom decreases in PE from pre- to post-treatment (Bluett et al., 2014; Gallagher & Resick, 2012; Harned et al., 2015; Jaycox et al., 1998; Rauch et al., 2004; Sripada & Rauch, 2015) and 2-weeks (van Minnen & Hagenaars, 2002) and 1-month (van Minnen & Foa, 2006) following treatment completion. Similarly, Wisco, Baker, and Sloan (2016) found that between-session decreases in subjective arousal were associated with PTSD symptom decreases pre- to post-treatment among a community sample of adults with PTSD who received Written Exposure Therapy (WET; Sloan & Marx, 2019). Recent work has extended these findings beyond self-reported distress to changes in trauma-potentiated startle (Maples-Keller et al., 2019; Robison-Andrew et al., 2014; Rothbaum et al., 2014) and physiological responses to script-driven imagery (Wangelin & Tuerk, 2015).

Cognitively focused interventions such as CPT (Resick et al., 2017) and Cognitive Therapy for PTSD (Ehlers et al., 2005) are theorized to cause PTSD symptom reduction by causing changes in distorted trauma-related beliefs, or dysfunctional perceptions of the trauma and its sequelae. These interventions use a series of techniques to explicitly challenge distorted trauma-related beliefs. Within this framework, challenging distorted trauma-related beliefs is the mechanism that causes reduction in these beliefs, that in turn leads to symptom reduction. In support of this hypothesized mediator, prior studies have shown changes in these distorted beliefs, as assessed using questionnaire measures, are associated with PTSD symptom change among individuals who received these treatments (Dillon et al., 2020; Holliday et al., 2018; Kleim et al., 2013; Schumm et al., 2015). Specifically, these studies have used questionnaire measures that ask participants to rate the degree to which they agree with a series of common distorted trauma-related beliefs (e.g., self-blame, difficulty trusting others, increases in perceived danger in the world), and find an association between decreased agreement with such beliefs and

reduction in PTSD symptoms. Similarly, Gallagher and Resick (2012) found that changes in hopelessness mediated the effect of CPT, relative to PE, on PTSD symptoms among a female community sample. Some studies have examined the differential role of specific domains of beliefs in predicting treatment outcome. Holliday and colleagues (2018) found that changes in self-blame, but not other domains of distorted trauma-related beliefs, predicted changes in PTSD symptoms. Likewise, Dillon and colleagues (2020) found that other-blame did not predict subsequent PTSD symptom reduction, and that changes in self-blame and PTSD symptoms were dynamically linked (i.e., changes in each construct predicted subsequent change in the other construct). Finally, Schumm and colleagues (2015) found that patient ratings of self-blame and other-blame cognitions were associated with subsequent PTSD symptom decreases in a trial of CPT.

Although extinction is the theorized mediator of exposure-based interventions such as PE and WET, exposure is designed to produce corrective information about stimuli, responses, and their meanings (Foa et al., 2006) and there is replicated evidence that these exposure-based PTSD treatments produce changes in distorted trauma-related beliefs (e.g., Foa & Rauch, 2004). Moreover, in recent years, there has been some suggestion that changes in distorted trauma-related beliefs may also be a mediator of symptom change in these treatments. Specifically, several studies have found that decreases in distorted trauma-related beliefs predict PTSD symptom reduction among individuals who received PE (McLean, Su et al., 2015; McLean, Yeh et al., 2015; McLean et al., 2019; Zalta et al., 2014).

Conversely, extinction has yet to be examined as a potential mediator in CPT. This may be due, at least in part, to the treatment protocol not requiring routine collection of state distress ratings during treatment. Although the focus of CPT is on challenging distorted trauma-related

beliefs, it includes components that could be interpreted as involving exposure. For example, the original version of CPT includes two impact statements in which the participant writes about why they think the traumatic event occurred and the effects of the event on beliefs in numerous areas (e.g., safety, trust), as well as two detailed written accounts of the event including visceral sensory details (e.g., smells, sounds), that participants are ask to read daily between sessions. It is therefore possible that extinction plays a role in reducing symptoms in CPT.

To firmly establish a mediator of change for any treatment, several criteria must be satisfied. Kazdin (2007) catalogued these criteria in a seminal paper. These criteria include: 1) plausibility (i.e., a reasonable explanation is provided for how a given mediator could cause symptom change), 2) strong association (i.e., a robust link between an intervention and a given mediator as well as between change in a given mediator and symptom change), 3) gradient (i.e., a dose-response association between a mediator and symptom change), 4) experimental manipulation (i.e., target a given mediator to examine its effect on outcome), 5) timeline (i.e., whether change in a mediator temporally precedes symptom change), 6) specificity (i.e., a specified mediator and not other constructs accounts for symptom change), and 7) consistency (i.e., results are replicated).

At this writing, these criteria have yet to be comprehensively applied to the aforementioned hypothesized PTSD psychotherapy mediators. Extinction and decreases in distorted trauma-related cognitions have generally been accepted as plausible mediating constructs for PE and CPT, respectively (e.g., Asnaani et al., 2016; Resick et al., 2017). Evidence of strong association and gradient has been shown for extinction in PE (e.g., van Minnen & Foa, 2006) and WET (Wisco et al., 2016), and for changes in negative trauma-related beliefs in CPT (e.g. Schumm et al., 2015) and PE (e.g., McLean et al., 2019). Although prior research has

attempted to examine temporal sequence (i.e., whether change in a mediator temporally precedes symptom change), the analytic methods typically used in these studies are insufficiently able to determine the order in which variables change. Specifically, although lagged mixed-effects modeling can be used to examine if changes in a proposed mediator predicts subsequent changes in symptoms (e.g., Zalta et al., 2014), this approach cannot shed light on the order of change (i.e., which construct changes first or if constructs change simultaneously). Accordingly, even if changes in a hypothesized mediator predicts subsequent changes in symptoms, symptom change could temporally precede or occur in parallel with the hypothesized mediator in treatment. This distinction is critical to distinguishing between mediators and correlates of symptom reduction. The one exception to this is Dillon and colleagues (2020); this study used bivariate latent difference score modeling, and appropriate analytic technique for determining sequence of change. However, this study found evidence of a reciprocal association rather than a unidirectional effect.

In the current study, we used data analytic methods for properly determining the temporal precedence in change of several constructs representing those previously proposed mediators of change (extinction and changes in negative trauma-related beliefs) and relation between mediators and symptom reduction. We examined these potential mediators using data from a randomized controlled trial that compared CPT and WET. Based on the theoretical framework for each intervention, we generated two hypotheses. First, we hypothesized that extinction would temporally precede PTSD symptom change in WET and changes in trauma-related beliefs would temporally precede PTSD symptom change in CPT. Second, we hypothesized that extinction would predict subsequent PTSD symptom change in WET and changes in trauma-related beliefs would predict subsequent PTSD symptom change in CPT.

Method

Participants and Procedures

As reported previously (Sloan et al., 2018), 126 treatment-seeking adults participated in the study and were evenly randomized to WET (n = 63) or CPT (n = 63). Just over half of the sample identified as male (n = 66; 52.38%) and the mean age of participants was 43.86 (SD = 14.58). The sample was racially diverse; 69 participants (54.76%) identified as White, 43 (34.13%) identified as African American/Black, 7 (5.56%) identified as "other," 4 (3.17%) identified as American Indian/Alaskan Native, 2 (1.59%) identified as Asian, and 1 (0.79%) identified as Pacific Islander/Native Hawaiian. Most participants identified as non-Hispanic (n = 111; 88.10%). We did not find any significant between-condition differences in demographic characteristics (see Sloan et al., 2018). All participants were required to meet *DSM-5* (American Psychological Association [APA], 2013) criteria for PTSD, and those who were currently taking psychiatric medications were required to be stable for at least four weeks prior to baseline assessment. We utilized minimal exclusion criteria in order to recruit a maximally diverse and representative sample: we excluded if they were at high risk for suicide, were actively psychotic or manic, or had severe cognitive impairment. Participation was also prohibited if the individual currently met criteria for substance dependence or was currently engaged in PTSD-focused psychotherapy. We operationalized high risk for suicide as scoring ≥ 17 on the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998); no participants were excluded based on this criterion.

Individuals completed a baseline assessment to confirm eligibility and were then randomized to either WET or CPT. WET consists of five weekly sessions in which patients complete 30 minutes of writing about a single traumatic event at each session, according to

specific prompts. There are no homework assignments between the treatment sessions. CPT consists of 12 sessions, delivered once or twice per week, in which patients are taught to identify and challenge dysfunctional cognitions related to their trauma, as well as broader dysfunctional cognitions about themselves, others, and the world. Patients are assigned homework (written narratives and worksheets) to be completed between sessions. The CPT protocol that includes written trauma accounts was used in this study. Both treatments were delivered by doctoral-level psychologists who had completed formal training in each of the treatments and were supervised on an ongoing basis by the treatment developers. Therapists delivered both treatments (i.e., therapist crossed design) and adherence to the protocols was rated as high by independent evaluators (see Sloan et al., 2018).

We structured assessments to occur at the same time for both treatment conditions. Structuring assessments in this manner ensured that any between-condition differences that might have been observed would not be due to differences in time in treatment. We scheduled post-baseline assessments at 6-, 12-, 24-, 36-, and 60-weeks following the first treatment session. It was anticipated that the 6-week assessment would best represent a post-treatment assessment for participants assigned to WET, whereas the 12-week assessment would best correspond to post-treatment for participants assigned to CPT. The 6-week assessment was an appropriate representation of post-treatment for WET, as all the participants who were assigned to WET completed treatment by the 6-week assessment. However, the time to complete CPT was variable, ranging from 6 weeks to 20 weeks. Clinical interviews were administered by master's level or higher independent evaluators. Additionally, we administered measures of PTSD symptoms and valence and arousal at each session (see Supplementary Table 1 for a schedule of assessments). All study procedures were approved by the local Institutional Review Board and

all participants provided written informed consent; we protected privacy rights for all participants.

Measures

Outcome Measures

We measured PTSD symptoms using the Clinician Administered PTSD Scale for *DSM-5* (CAPS-5; Weathers, Blake et al., 2013) at baseline and 6-, 12-, 24-, 36- and 60-weeks following the first treatment session and the PTSD Checklist for *DSM-5* (PCL-5; Weathers, Litz et al., 2013) at baseline and 6-, 12-, 24-, 36- and 60-weeks following the first treatment session as well as at each treatment session. When administering the CAPS-5, clinicians rated each PTSD symptom on a five-point scale from *absent* to *extreme*, incorporating both symptom frequency and intensity. The sum of the items creates a total score reflecting overall PTSD symptom severity; higher scores indicate worse symptom severity. The CAPS-5 has shown strong test-retest reliability, internal consistency, and discriminant validity (Weathers et al., 2018). In this study, inter-rater reliability of the CAPS-5 was high ($\kappa = .85$).

The PCL-5 is a 20-item self-report measure of *DSM-5* PTSD symptoms; respondents rate the degree to which they were bothered by each symptom on a 5-point Likert scale ranging from *not at all* to *extremely*. Total scores range from 0-80; higher scores indicate worse overall symptom severity. The PCL-5 has demonstrated strong psychometric properties among numerous populations, including criterion-related validity and test-retest reliability (Blevins et al., 2015; Bovin et al., 2016; Wortmann et al., 2016). Internal consistency for the PCL-5 total score was excellent ($\alpha > .90$ at all time points). We administered the PCL-5 at each treatment session for safety monitoring purposes and to examine PTSD symptom change during the course of treatment.

Mediator Measures

We measured state arousal and valence use the Self-Assessment Manikin (SAM; Bradley & Lang, 1994). The SAM is a brief measure of state arousal and valence; respondents rate each dimension of emotion on a 9-point pictorial scale. For the arousal subscale, low scores indicate low arousal and high scores indicate high arousal. For the valence scale, low scores indicate a highly pleasant valence and high scores indicate a highly unpleasant valence. The SAM is a widely used measure of emotional responding and has strong criterion-related validity evidence (Bradley & Lang, 1994; Backs et al., 2005). In this study, we administered the SAM before and after each treatment session only. We examined between-session changes in post-session arousal and valence ratings as well as between-session changes in within-session changes (calculated as post-session rating minus pre-session rating) to quantify extinction. Decreasing arousal and valence scores across sessions indicates decreasing post-session arousal and decreasing post-session unpleasantness, respectively, across sessions. Negative values for within-session change in arousal and valence scores indicates decreasing arousal and decreasing unpleasantness, respectively, from before to after a given session. Decreasing within-session changes in arousal and valence scores across sessions indicates decreasing changes in arousal and unpleasantness, respectively, from before to after session, across sessions. Our research group has used this measure to quantify extinction in past research (e.g., Wisco et al., 2016).

Our use of the SAM to measure emotional responding is somewhat of a departure from existing research. Nearly all existing research has relied on the Subjective Units of Distress Scale (SUDS; Wolpe, 1958). Although a well-validated measure of global distress, this measure does not capture established, meaningfully distinct components of emotional responding. As demonstrated by Bradley and Lang (1994), arousal and valence are only loosely associated

components of emotion; this was consistent in our study (e.g., pre-session valence and arousal ratings, collapsed across conditions, were not significantly associated; $r = .142$, $p = .115$). Given the absence of existing research on how these distinct constructs change during treatment or are associated with treatment outcome, we did not propose distinct hypotheses for how valence and arousal would function differentially in this capacity.

Finally, we measured distorted trauma-related beliefs using the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999). The PTCI is a 36-item self-report measure of three categories of beliefs impacted by trauma exposure: negative cognitions about the self (e.g., "I can't deal with even the slightest upset"), negative cognitions about the world (e.g., "I have to be on guard all the time"), and self-blame (e.g., "The event happened because of the way I acted"). Respondents rate the degree to which they agree with a series of statements corresponding to these beliefs on a 7-item Likert scale ranging from *totally disagree* to *totally agree*. Items are summed to total scores for each domain; higher scores indicate more severe negative beliefs. We administered the PTCI at baseline and 6-, 12-, 24-, 36- and 60-weeks following the first treatment session. The 21-item negative cognitions about self, 7-item negative cognitions about the world, and 5-item self-blame scales all demonstrated strong internal consistency ($\alpha > .85$ at all time points). Most prior PTSD treatment research examining trauma-related beliefs as a potential treatment mediator has used the PTCI.

Data Analytic Strategy

We quantified extinction as within- and between-session changes in state arousal and valence measured using the SAM. We quantified changes in distorted trauma-related beliefs using changes in PTCI scores. Because the PTCI was not administered at each session, we were only able to examine changes in beliefs from baseline to 6-, 12-, 24-, 36- and 60-weeks

following the first treatment session. Because the SAM was only administered at each session, we were only able to examine extinction from sessions 1-5 in WET and sessions 1-12 in CPT.

To determine temporal sequence of change, we used mean scores at each assessment point to calculate standardized mean gain scores (ESsg; Lipsey & Wilson, 2001). ESsg provides a standardized metric that can be interpreted in a similar fashion to Cohen's *d*, but includes a correction for repeated measurement. We used these effect size analyses to quantify sequential and cumulative changes in each construct over time to examine the temporal sequence of change between hypothesized mediators and symptoms.

We used latent growth curve modeling to examine how hypothesized mediators and symptoms changed over time. We examined individual growth curve models separately for each construct. Using the baseline and 6-, 12-, 24-, 36- and 60-week assessments, we examined change over time using slope factors. Specifically, we fixed the loading of each construct at baseline to the slope factor to 0 and at the 60-week assessment to 1.0, while freely estimating the loadings of each construct at the 6-, 12-, 24-, 36-week time points to the slope factor. These models allow for examination of total change in constructs over time (slope factor mean) and individual variability in change over time (slope factor variance). Next, we used parallel process growth curve models to examine associations between intra-individual change in each construct over time. We handled missing data using full information maximum likelihood estimation (FIML) for all analyses and conducted all analyses using Mplus version 8 (Muthén & Muthén, 1998-2017).

Results

Temporal Sequence of Change

We present FIML estimated means, SDs, and change scores for measures administered at baseline and 6-, 12-, 24-, 36- and 60-weeks following the first treatment session in Table 1. We observed the largest changes in CAPS-5 scores between the 6- and 12-week assessment in CPT and between baseline and the 6-week assessment in WET. As shown in Figure 1, effect size analyses indicated that, among participants randomized to CPT, decreases in trauma-related beliefs paralleled PTSD symptom decreases over time but plateaued after the 24-week assessment, whereas PTSD symptoms continued to decrease through the 60-week assessment. Among participants randomized to WET, decreases in trauma-related beliefs lagged behind PTSD symptom decreases over time. Collectively, PTSD symptom decreases temporally preceded or paralleled change in trauma-related beliefs in both conditions.

We report FIML estimated means, SDs, and change scores for session data in Table 2. As can be seen in the table, observed large- and medium-magnitude effect sizes for PCL-5 during the 12 sessions of CPT and 5 sessions of WET, respectively, indicate participants experienced substantial symptom improvement during treatment. PCL-5 scores evidenced the greatest between-session decreases from sessions five to six in CPT and from sessions three to four in WET. These periods correspond to when trauma accounts are completed in CPT and shifting from trauma narrative account to focusing on the impact of the event in WET.

As shown in Table 2, effect size results for post-session arousal and valence ratings indicate participants experienced large-magnitude between-session decreases in both constructs in WET and medium-magnitude decreases in CPT. Results for within-session change in arousal and valence ratings varied by condition. Effect size results in CPT indicate participants did not experience substantial within-session changes in either construct; in WET, participants experienced a medium-magnitude decrease in within-session arousal and valence.

As shown in Figure 2, between-session decreases in arousal and valence parallel PTSD symptom reduction early in CPT, but plateau later in treatment while PTSD symptoms continue to decrease. Similarly, changes in post-session arousal parallel PTSD symptom reduction in WET. However, changes in post-session valance parallel PTSD symptom reduction early in WET, but evidence larger decreases than PTSD symptoms for sessions 3-5. Accordingly, between-session changes in post-session valence appear to temporally precede PTSD symptom change symptoms in WET.

Prediction of Subsequent Change

We present univariate growth curve models with and without covarying for treatment condition in Supplemental Table 2. All models provided adequate fit to the data. Significant negative slopes indicated both CAPS-5 and PTCI scores decreased significantly between baseline and the 60-week assessment. Next, we examined a parallel process growth curve model of change in CAPS-5 and PTCI scores between baseline and the 60-week assessment with and without covarying for treatment condition. Both models provided adequate fit to the data. A significant treatment condition effect indicated that participants in CPT experienced greater reductions in PTCI scores from baseline and the 60-week assessment.

We examined the association between PTSD symptom changes and changes in distorted trauma-related beliefs using a parallel process growth curve model (Supplemental Table 3). This model estimated change in CAPS-5 and PTCI scores and the correlation between slopes for each construct. Decreases in PTCI scores were significantly and strongly correlated with CAPS-5 decreases between baseline and 60-weeks ($r = .785$, $p < .001$); those who experienced the greatest reductions in distorted trauma-related beliefs experienced the greatest symptom reduction across conditions.

We examined univariate growth curve models for PCL-5 and post-session valence scores across treatment conditions during the first five treatment sessions in both conditions (Supplemental Table 2). The univariate model for PCL-5 scores provided poor fit to the data. However, the model for post-session valence scores provided good fit to the data and indicate a significant decrease in valence scores from sessions one to five across conditions. A significant condition effect indicated that participants in the WET condition experienced greater reductions in post-session valence scores from sessions one to five.

We examined the association between PTSD symptom changes and changes in valence across the first five sessions using a parallel process growth curve model (Supplemental Table 3). This model estimated change in PCL-5 and post-session SAM valence scores and the correlation between slopes for each construct. This model provided adequate fit to the data. However, changes in PCL-5 and SAM valence scores were not significantly correlated (r = .368, p = .126). When we constrained the model to participants in the WET condition, this model provided adequate fit to the data and PCL-5 slope and valence slope were positively and significantly correlated (r = .403, p = .032), indicating individuals who experienced the greatest between-session change in post-session valence (i.e., experienced decreasingly unpleasant emotional responding at the end of sessions) experienced the greatest PTSD symptom reduction during treatment, suggesting extinction as a potential mediator in WET.

Visual review of session data indicated a threshold effect, such that participants who experienced a decrease in valence experienced the greatest symptom reduction, whereas those who experienced no change or an increase in negative valence experienced the least symptom improvement; session PCL-5 scores and CAPS-5 scores for these two groups are illustrated in Figure 3. Participants who experienced a decrease in negative valence experienced slightly larger

PCL-5 score decreases during treatment and larger CAPS-5 score decreases, particularly at the 12-week assessment, but CAPS-5 scores became comparable by the 36- and 60-week follow-up assessments. Taken together, these results suggest that extinction represents a predictor of early symptom improvement but does not function as the main mediator of longer-term symptom reduction in WET.

Discussion

In this study, we examined whether extinction and changes in negative trauma-related beliefs occurred either prior to or concurrently with changes in posttraumatic stress symptom severity among individuals with received either CPT or WET using statistical methods that permit proper discernment of temporal sequence. Change in distorted trauma-related beliefs paralleled PTSD symptom reduction and correlated significantly with symptom reduction for both conditions but did not temporally precede PTSD symptom reduction in aggregate. Between-session change in post-session self-reported emotional valence temporally preceded PTSD symptom reduction among participants who received WET and correlated with symptom reduction during treatment but did not predict subsequent symptom reduction. Our results are inconsistent with those from prior studies and suggest these constructs may more appropriately be characterized as correlates of, rather than mediators of, symptom reduction in WET and CPT. These results highlight the importance of discernment of temporal sequence of change between hypothesized mediators and symptoms. These results raise questions regarding our understanding of precisely how these widely used PTSD interventions achieve symptom reduction and the theoretical foundations thereof.

To the best of our knowledge, this is the first study to discern the sequence of change in symptoms and hypothesized mediators for PTSD interventions using proper analytic methods.

Prior research has relied on lagged multilevel modeling to examine if change in a presumed mediator predicted subsequent symptom change. As noted earlier, this approach is helpful in determining if change in one construct is associated with subsequent change in another (e.g., do early decreases in negative trauma-related beliefs predict later decreases in PTSD symptoms). However, this approach cannot determine the order in which two constructs change. Accordingly, a construct that changes in parallel to PTSD symptoms and predicts subsequent change could be mistakenly assumed to be a mediator, despite not changing temporally prior to symptoms. The findings of this study highlight the importance of such a distinction and indicate these constructs do not satisfy the temporal precedence criterion.

This finding is perhaps most surprising for extinction, which is widely accepted as a mediator of multiple interventions. As summarized by Craske and colleagues (2008), evidence for extinction is inconsistent across interventions for several psychiatric disorders, including PTSD (e.g., reported symptom decreases despite absence of between-session decreases in physiological reactivity). These inconsistencies have given rise to the inhibitory learning framework that distinguishes the roles of fear reduction and learning in treatment. Results from this study suggest examining inhibitory learning as a potential mediator of treatment outcome may be a promising future direction in PTSD treatment research.

Results from this study suggest the examined mediators satisfy the strong association and gradient criteria for treatment mediators, but not timeline. Given the study design, we were able to examine experimental manipulation as a criterion in that we could examine if WET and CPT exhibited distinct mediators. However, absence of any constructs that satisfied both gradient and timeline criteria prevented examination of either experimental manipulation or specificity criteria. Only after these criteria are satisfied can the consistency criterion be examined.

Although we should strive to better understand why our PTSD treatments work, it is important to do so while being mindful of challenges in measuring internal cognitive, affective, and physiological processes of interest both during and between treatment sessions. All PTSD treatment mediator research thus far has measured negative trauma-related beliefs using questionnaire measures and most of the research examining extinction as an underlying mediator has also relied on questionnaire measures. As a field, we have assumed these questionnaire measures are capable of quantifying granular changes in complex, abstract constructs over brief time periods. Further, we assume that participants can consistently report subtle changes in these constructs, an assumption that has long been challenged (Nisbett & Wilson, 1977). This obstacle is even more at issue in psychotherapy research as individuals with psychopathology are more likely to have deficits in emotional awareness and clarity (e.g., Grabe et al., 2014). Between-modality (i.e., comparing questionnaire, interview, and behavioral measures) examinations of subjective distress do not support the assumption that such measures can be used interchangeably (e.g., Marx et al., 2012). Although between-modality approaches to distorted trauma-related beliefs are more elusive, we assume similar challenges exist in asking respondents to rate distorted beliefs repeatedly during and after treatment. Indeed, some research groups have utilized more innovative approaches to examining potential mediators, including biological mediators (e.g., cortisol; Rauch et al., 2015) and behavioral measures of treatment outcome (e.g., script driven imagery; Wangelin & Tuerk, 2015). However, these measures of mediators and outcome suffer from many of same limitations as other measurement approaches described here. Collectively, more innovative approaches are needed to determine when, and to what degree, these constructs change during and after treatment.

Another critical issue to consider when examining PTSD treatment mediators is that the proposed mediator should be distinct from the assessed treatment outcome. Unfortunately, this is often not the case in research conducted to date. The *DSM-5* definition of PTSD includes emotional and physiological reactions to trauma reminders (symptoms B4 and B5) and negative trauma-related beliefs (symptoms D2 and D3). Accordingly, some of the observed overlapping patterns in change may be attributable to construct overlap.

A third issue to consider is that the PTSD treatment mediator literature has conflated mechanisms with mediators. For example, emotional processing theory posits that exposure to trauma-related stimuli provides corrective information about stimuli, responses, and their meanings that, in turn, reduces PTSD symptoms. To test this theory, researchers have examined change in subjective distress during imaginal exposures. Rather than formally testing the hypothesized mechanism, this approach measures a downstream indicator and potential mediator. Demonstrating that subjective distress or trauma-related beliefs change does not determine how or why these constructs changed. In this sense, dismantling studies may be the most direct approach to delineating the specific mechanisms of symptom reduction (e.g., Resick et al., 2008).

Finally, consistent with Kazdin's (2007) specificity criterion, PTSD psychotherapy mediator research has focused on identifying a single mediator for interventions. Even manualized psychosocial interventions involve specific and non-specific processes (e.g., therapist and client characteristics, attitudes, and expectancies, therapeutic alliance, therapeutic expectations; Wampold, 2015), sequences of distinct intervention components (e.g., impact statement, ABC worksheets, trauma account, subsequent worksheets, and second impact statement in CPT), and most have intervention components that occur outside of the therapy

room (e.g., listening to imaginal exposure recordings in PE, completing worksheets between sessions in CPT; see Stirman et al., 2018). Furthermore, PTSD itself is a remarkably heterogeneous disorder with regard to both the range of Criterion A events that may be experienced and the combinations of symptoms that can give rise to a diagnosis (Galatzer-Levy & Bryant, 2013). Given the complexity of our interventions and the disorder itself, isolating a single mediator of symptom change will likely continue to prove challenging. Kazdin's specificity criterion may be worth revisiting in this regard. Rather than identifying a single mediator and a single mechanism across an entire intervention, perhaps sequences of processes (e.g., exposure leading to both extinction and changes in distorted trauma-related beliefs) may warrant exploration.

Collectively, these limitations indicate identifying specific mediators for trauma-focused psychotherapies for PTSD will continue to prove difficult. Kazdin emphasized that mediator research is so important due to the potential for improving treatments by manipulating an identified mediator to make interventions more efficient, stronger in dose, or more targeted to specific symptoms. However, these criteria have seen limited practical application, likely due at least in part to the previously described challenges. Which criteria, how many criteria, and to what extent each criterion must be satisfied before potential mediator should be manipulated to examine benefit remain unanswered empirical questions. A more iterative process of trial and error could potentially accelerate advances in improving interventions for PTSD.

To be clear, we are not suggesting evidence-based treatments for PTSD are inherently problematic because we struggle to identify the mediators by which they reduce symptoms. These psychotherapies unquestionably improve the lives of many of those who receive them and they should be the first choices for mental health professionals who treat those suffering from

PTSD. However, outcomes vary, and some individuals do not experience clinically significant benefit (Cusack et al., 2016; Steenkamp et al., 2015). Improving outcomes will likely require a clearer understanding of how these treatments cause symptom reduction.

Caveats of these findings aside, results from this study show that both interventions cause substantial reductions in distorted trauma-related beliefs that parallel PTSD symptom reduction, particularly early in treatment. Given that existing research has not utilized methods for evaluating temporal course of change, it is difficult to relate these findings to the broader literature. Another finding from this study that warrants acknowledgement is evidence of extinction in CPT. As noted earlier, extinction has yet to be examined as a potential treatment mediator for CPT, perhaps due in part to absence of distress measurement in the treatment manual. Although the observed moderate-magnitude decreases in post-session arousal and valence ratings lagged behind symptom reduction, these results indicate participants found sessions less distressing over time. Although this does not appear to function as a mediator of treatment outcome, diminished distress following a session discussing trauma-related issues is a meaningful outcome in and of itself.

Several limitations are worthy of consideration when interpreting results from this study. First, like prior studies, our investigation relied on self-report questionnaires to measure the variables of interest. Second, although we administered measures with a frequency that is typical of contemporary clinical trials, many of the examined constructs may fluctuate to a greater extent than is captured by weekly assessment during treatment (e.g., day to day, within-day). Future approaches may consider assessment approaches suited to measure symptom and mediator change in more granular detail (e.g., ecological momentary assessment). Third, like other existing treatment mediator research, this study examined hypothesized treatment mediators that

overlap substantially with symptoms. Fourth, this study, like all others in psychotherapy mediator research, was unable to link unique mediators to specific intervention mechanisms. Future research should consider other methods to target specific mediators, ideally dismantling studies. Finally, participants in this study reported PTSD symptoms stemming from a wide range of index traumas (e.g., combat, motor vehicle accidents, sexual assault). It is possible that this heterogeneity in trauma event types, as well as other sample characteristics, may cause these results to not generalize to other populations (e.g., veterans).

In conclusion, our results are inconsistent with those from prior studies and suggest extinction and changes in distorted trauma-related beliefs may more appropriately be characterized as correlates of, rather than mediators of, symptom reduction in WET and CPT. These results highlight the importance of discernment of temporal sequence of change between hypothesized mediators and symptoms and indicate that we still have much to learn about the processes by which our evidence-based treatments reduce PTSD symptoms. Future research in this area should emphasize addressing the numerous limitations described in this study, including conceptual overlap between mediators and symptoms, measurement challenges, and distinguishing between mechanisms and mediators of therapeutic processes. Finally, future research should examine newer theoretical models, particularly inhibitory learning (Craske et al., 2014). Efforts to improve PTSD treatments will be impeded until we better understand why these treatments work.

Data Transparency Statement

Previously published manuscripts from this dataset do not overlap with the current manuscript and focus on distinct constructs and processes. We do not have any previously published or currently in press works stemming from this same dataset other than those disclosed in our cover letter.

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Table 1.

Full Information Maximum Likelihood Estimates of Means, Standard Deviations, and Change Scores for CAPS-5 and PTCI Scores

		Cognitive Processing Therapy						Written Exposure Therapy					
		FIML estimates		Sequential		Cumulative		FIML estimates		Sequential		Cumulative	
Outcome	Time	Mean	SD	ESsg	SEsg	ESsg	SEsg	Mean	SD	ESsg	SEsg	ESsg	SEsg
CAPS-5	Base	37.10	6.09	-	-	-	-	36.13	6.01	-	-	-	-
	6 wk	32.82	5.73	-0.36	0.36	-0.36	0.36	30.54	5.53	-0.53	0.52	-0.53	0.52
	12 wk	25.31	5.03	-0.64	0.59	-0.96	0.89	26.81	5.18	-0.28	0.24	-0.82	0.89
	24wk	21.21	4.61	-0.18	0.17	-1.09	1.00	25.95	5.09	-0.11	0.11	-0.93	0.95
	36 wk	21.49	4.64	-0.03	0.06	-1.17	1.17	24.50	4.95	-0.10	0.11	-1.09	1.17
	60 wk	19.48	4.41	-0.15	0.14	-1.37	1.47	22.34	4.73	-0.14	0.14	-1.27	1.42
PTCI	Base	130.81	11.44	-	-	-	-	124.13	11.14	-	-	-	-
	6 wk	125.02	11.18	-0.10	0.14	-0.10	0.14	117.93	10.86	-0.14	0.16	-0.14	0.16
	12 wk	107.08	10.35	-0.47	0.42	-0.53	0.63	118.70	10.90	0.04	0.08	-0.14	0.18
	24wk	88.52	9.41	-0.42	0.37	-0.97	1.36	109.75	10.48	-0.18	0.16	-0.35	0.37
	36 wk	91.09	9.54	0.03	0.07	-0.78	0.98	109.80	10.48	-0.06	0.10	-0.36	0.38
	60 wk	91.10	9.54	0.00	0.07	-0.75	1.10	102.62	10.13	-0.11	0.11	-0.56	0.63

Note. CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*; ESsg = standardized mean gain score; FIML = full information maximum likelihood; PTCI = Posttraumatic Cognitions Inventory; SEsg = standard error of the standardized mean gain score; SD = standard deviation.

Table 2.

Full Information Maximum Likelihood Estimated Means, Standard Deviations, and Change Scores for Each Construct by Session

		Cognitive Processing Therapy						Written Exposure Therapy					
		FIML estimates		Weekly		Cumulative		FIML estimates		Weekly		Cumulative	
Outcome	Session	Mean	SD	ESsg	SEsg	ESsg	SEsg	Mean	SD	ESsg	SEsg	ESsg	SEsg
PCL	1	42.68	13.55	-	-	-	-	42.14	15.19	-	-	-	-
	2	41.85	15.79	-0.06	0.08	-0.06	0.08	40.67	15.40	-0.10	0.11	-0.10	0.11
	3	39.93	14.33	-0.13	0.12	-0.26	0.23	39.09	17.55	-0.11	0.11	-0.20	0.20
	4	40.53	16.71	0.07	0.11	-0.16	0.18	35.60	17.54	-0.20	0.18	-0.42	0.40
	5	36.38	16.08	-0.21	0.18	-0.32	0.31	34.24	16.61	-0.12	0.13	-0.55	0.59
	6	32.42	14.47	-0.36	0.29	-0.76	0.70	-	-	-	-	-	-
	7	29.13	15.92	-0.19	0.16	-0.87	0.81	-	-	-	-	-	-
	8	30.34	15.95	0.01	0.09	-0.86	0.88	-	-	-	-	-	-
	9	28.71	18.01	-0.21	0.20	-0.99	1.05	-	-	-	-	-	-
	10	26.57	16.89	-0.03	0.06	-1.14	1.14	-	-	-	-	-	-
	11	22.25	15.49	-0.30	0.25	-1.49	1.70	-	-	-	-	-	-
	12	22.16	15.06	-0.20	0.21	-1.75	2.45	-	-	-	-	-	-
ARO-Post	1	4.50	1.84	-	-	-	-	5.13	2.01	-	-	-	-
	2	4.50	1.88	0.05	0.14	0.05	0.14	4.74	2.09	-0.20	0.30	-0.20	0.30
	3	4.87	2.38	0.21	0.25	0.19	0.27	4.57	2.31	-0.07	0.21	-0.24	0.37
	4	4.56	2.38	-0.13	0.19	0.03	0.13	4.34	2.35	-0.09	0.17	-0.35	0.55
	5	4.58	2.35	0.16	0.22	0.14	0.26	3.51	2.06	-0.45	0.53	-0.84	1.06
	6	3.95	2.41	-0.09	0.14	0.23	0.26	-	-	-	-	-	-
	7	4.12	1.96	0.12	0.19	0.28	0.25	-	-	-	-	-	-
	8	3.31	2.27	-0.13	0.20	0.39	0.38	-	-	-	-	-	-
	9	3.26	2.21	-0.15	0.19	0.61	0.57	-	-	-	-	-	-
	10	3.51	2.24	0.24	0.36	0.36	0.34	-	-	-	-	-	-
	11	4.00	2.32	0.06	0.17	0.35	0.34	-	-	-	-	-	-
	12	3.28	2.27	-0.33	0.73	0.63	0.75	-	-	-	-	-	-
ARO-Chng	1	-0.13	1.95	-	-	-	-	0.40	2.81	-	-	-	-
	2	-0.30	2.24	0.13	0.26	0.13	0.26	0.37	2.35	0.01	0.14	0.01	0.14
	3	0.60	2.62	0.38	0.45	0.37	0.61	-0.05	2.63	0.16	0.26	0.14	0.24

	4	0.03	2.25	0.34	1.87	0.01	0.15	-0.11	2.28	0.01	0.16	0.20	0.31
	5	0.11	2.15	0.08	0.37	0.05	0.17	-0.92	2.19	0.40	0.64	0.54	2.21
	6	-0.20	1.76	0.13	0.24	0.06	0.18	-	-	-	-	-	-
	7	0.30	1.88	0.18	0.58	0.17	0.34	-	-	-	-	-	-
	8	-0.90	2.05	0.44	2.98	0.28	2.59	-	-	-	-	-	-
	9	-0.67	1.76	0.01	0.16	0.39	3.89	-	-	-	-	-	-
	10	-0.19	1.79	0.45	0.90	0.07	0.62	-	-	-	-	-	-
	11	-0.40	1.91	0.24	1.26	0.16	0.22	-	-	-	-	-	-
	12	0.10	1.23	0.06	0.76	0.15	0.26	-	-	-	-	-	-
VAL-Post	1	4.60	1.98	-	-	-	-	6.03	1.79	-	-	-	-
	2	4.33	1.93	-0.12	0.19	0.12	0.19	5.89	1.60	-0.09	0.16	-0.09	0.16
	3	4.98	2.17	0.29	0.29	0.21	0.26	5.28	2.35	-0.30	0.54	-0.38	0.81
	4	4.77	2.20	-0.07	0.14	0.10	0.14	4.39	2.03	-0.41	0.47	-0.89	1.27
	5	4.97	1.89	0.07	0.14	0.08	0.14	4.40	2.38	-0.00	0.14	-0.81	6.41
	6	4.54	2.19	-0.30	0.34	0.20	0.22	-	-	-	-	-	-
	7	4.89	1.78	0.09	0.15	0.06	0.12	-	-	-	-	-	-
	8	4.01	2.02	-0.28	0.31	0.20	0.19	-	-	-	-	-	-
	9	4.03	1.85	0.08	0.16	0.17	0.18	-	-	-	-	-	-
	10	3.74	1.74	-0.16	0.18	0.36	0.34	-	-	-	-	-	-
	11	4.15	1.72	0.05	0.14	0.47	0.50	-	-	-	-	-	-
	12	3.29	1.70	-0.31	0.38	0.62	0.63	-	-	-	-	-	-
VAL-Chng	1	-0.41	1.81	-	-	-	-	1.02	2.54	-	-	-	-
	2	-0.42	1.95	0.01	0.15	0.01	0.15	1.10	1.67	0.04	0.17	0.04	0.17
	3	0.23	2.38	0.29	0.36	0.29	0.40	0.19	2.60	0.41	0.57	0.31	1.02
	4	-0.62	2.36	0.23	0.73	0.00	0.16	0.00	1.90	0.09	0.21	0.46	0.54
	5	-0.17	2.43	0.02	0.18	0.00	0.14	-0.42	1.79	0.16	0.33	0.54	1.32
	6	-0.41	1.42	0.08	0.21	0.12	0.53	-	-	-	-	-	-
	7	0.30	1.36	0.14	0.56	0.23	0.72	-	-	-	-	-	-
	8	-0.39	2.38	0.25	0.40	0.04	0.16	-	-	-	-	-	-
	9	-0.31	2.12	0.10	0.24	0.06	0.16	-	-	-	-	-	-
	10	-0.41	1.93	0.04	0.19	0.07	0.18	-	-	-	-	-	-
	11	-0.12	1.32	0.06	0.19	0.12	0.27	-	-	-	-	-	-
	12	-0.29	1.62	0.05	0.15	0.16	0.24	-	-	-	-	-	-

Note. ARO = arousal; Chng = change score; ESsg = standardized mean gain score; FIML = full information maximum likelihood; PCL = PTSD checklist; SEsg = standard error of the standardized mean gain score; SD = standard deviation; VAL = valence.

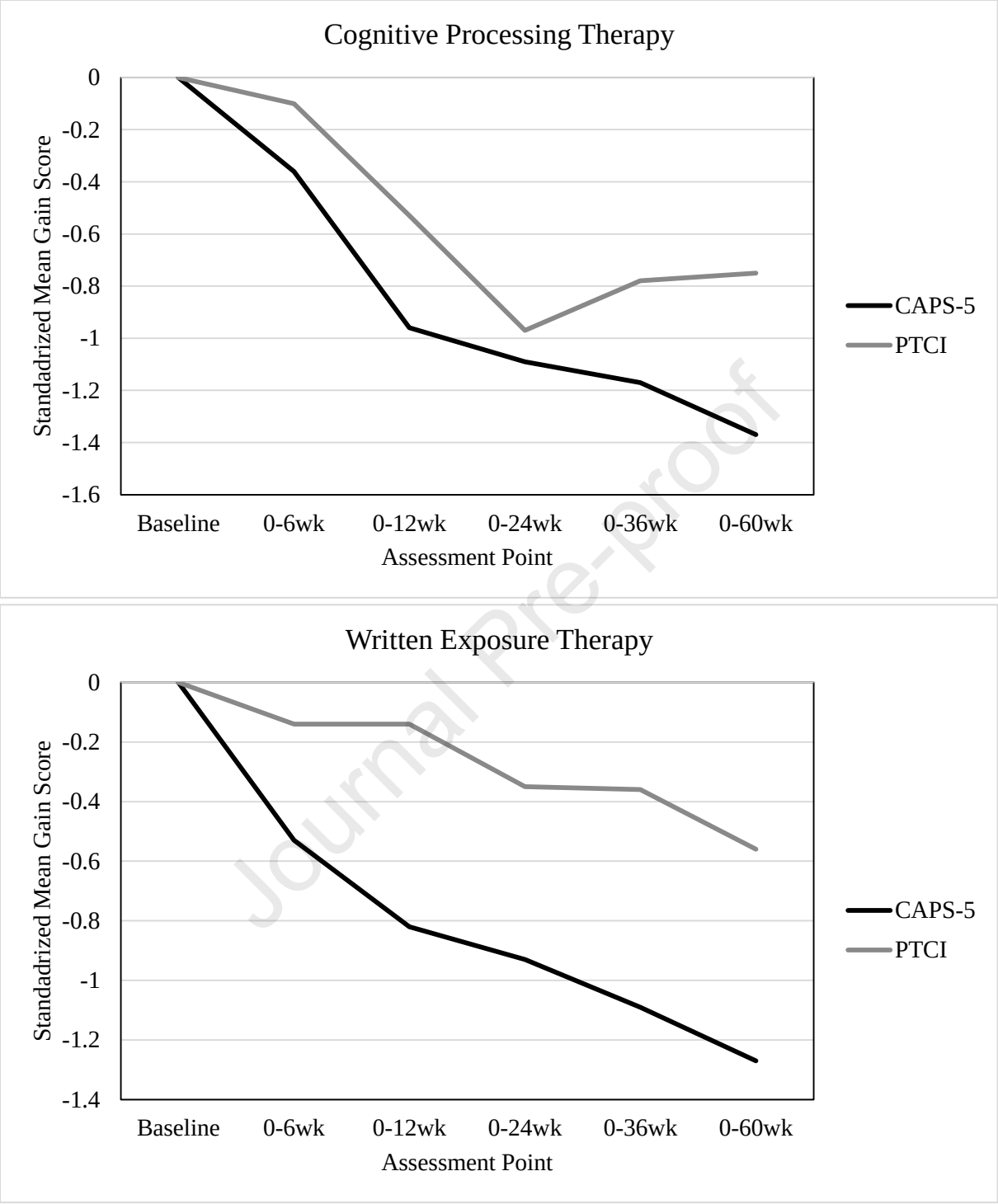
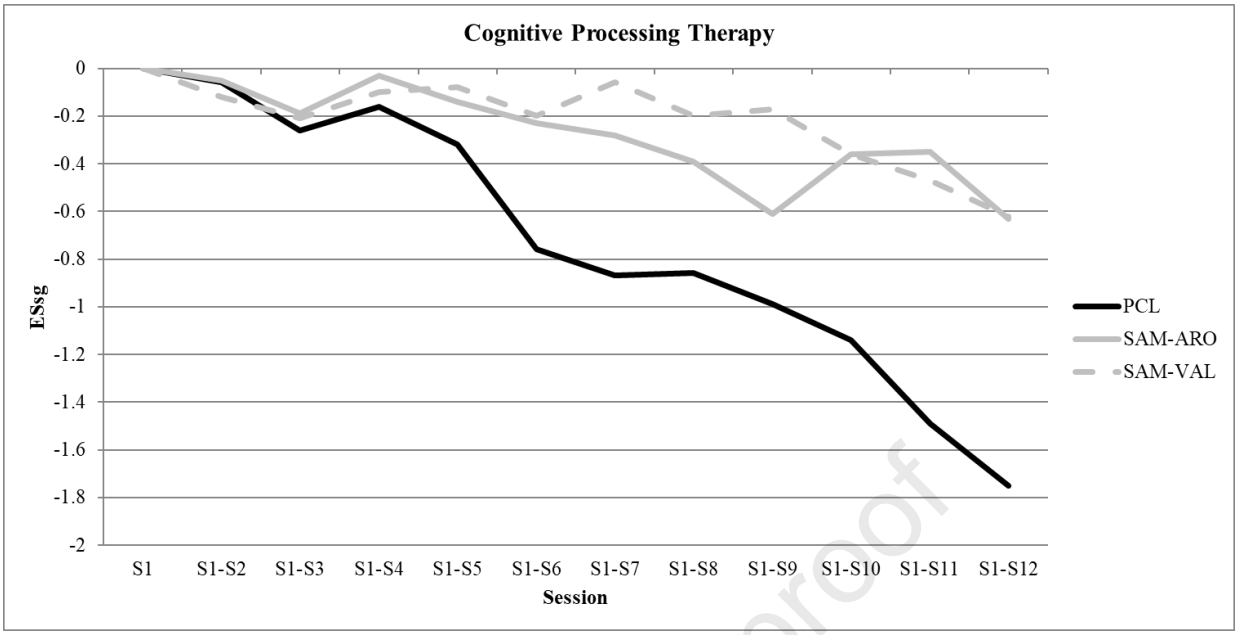


Figure 1. Temporal Sequence of Change in PTSD Symptoms and Negative Trauma-Related Beliefs.



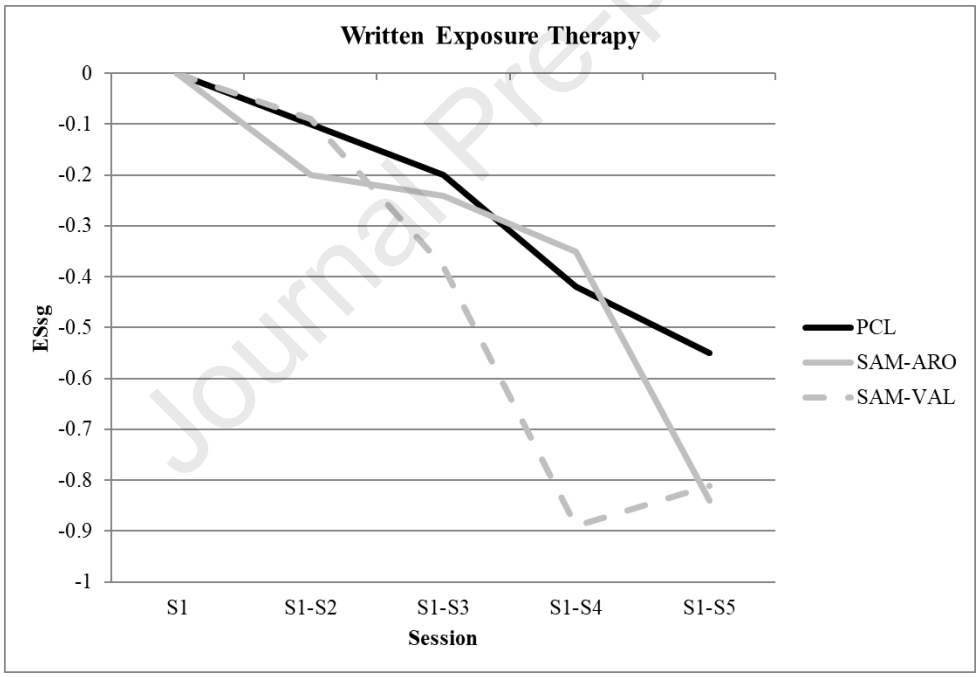


Figure 2. Temporal Sequence of Change in Arousal, Valence, and PTSD Symptoms

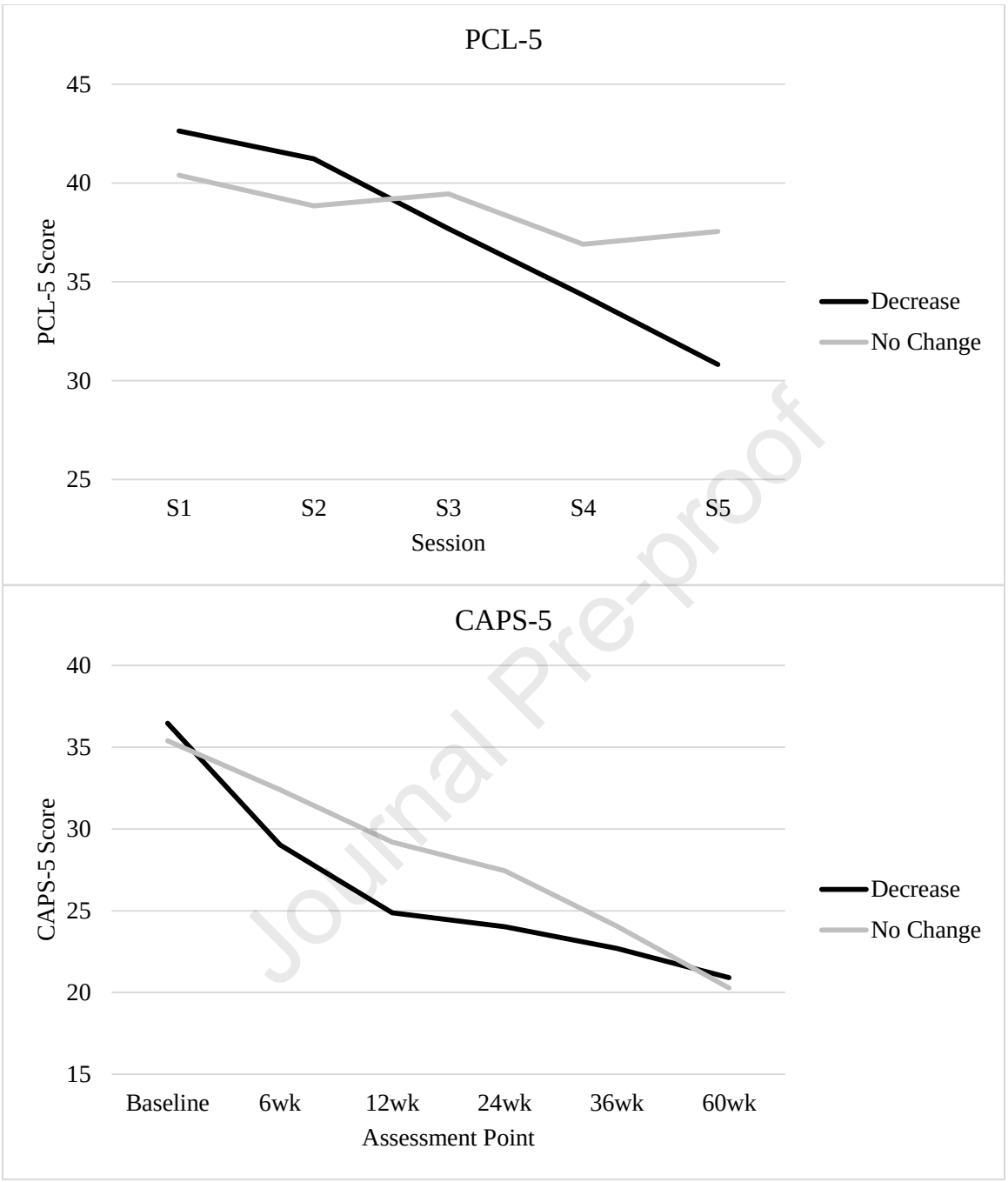


Figure 3. PCL-5 and CAPS-5 scores for participants who did and did not experience between-session decreases in valence in Written Exposure Therapy.

This study found that extinction and changes negative trauma-related beliefs, two hypothesized mediators of PTSD treatment outcome, exhibited a parallel pattern of change with symptoms. Accordingly, these constructs may more appropriately be characterized as correlates of, rather than mediators of, symptom reduction.