Do Changes in Trauma-related Beliefs Predict PTSD Symptom Improvement

in Prolonged Exposure and Sertraline?

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Public Health Significance Statements

Changing trauma-related negative beliefs may be an important pathway to PTSD symptom improvement for cognitive behavioral psychotherapies such as prolonged exposure (PE) but is perhaps less central for pharmacotherapy using selective serotonin reuptake inhibitors (SSRIs). Consistent with specificity to PTSD, there was less evidence for the role of change in trauma-related beliefs for depression symptoms. Processes that promote symptom improvement may differ between PE and SSRIs whereby change in PE may occur through specific learning processes surrounding adaptively shifting views about oneself, the world, and others.

Abstract

Objective: Negative trauma-related belief change has been found to predict subsequent

improvement in symptoms of posttraumatic stress disorder (PTSD) in prolonged exposure (PE)

and other therapies, consistent with several psychological theories of treatment change (e.g., Foa

& Kozak, 1986). However, belief change has not been examined in selective serotonin reuptake

inhibitors such as sertraline. We examined processes associated with symptom improvement in

two treatments for PTSD, hypothesizing that belief change would robustly predict PTSD

improvement in patients treated with PE but not those treated with sertraline, reflecting

moderation by treatment. *Method:* Patients with chronic PTSD ($N = 134$; 78% female, 71.6%

Caucasian, $M = 38.1$ years, $SD = 11.8$) received 10 weeks of PE or sertraline in a randomized

controlled trial. Patients reported PTSD and depression symptoms, and trauma-related beliefs

(Post-Traumatic Cognitions Inventory; Foa et al., 1999) at pre-treatment, every treatment

session, and post-treatment. *Results:* Using time-lagged mixed regression models, change in

trauma-related beliefs predicted subsequent PTSD symptom improvement, an effect moderated

by treatment and particularly strong in PE ($d = 0.93$) compared to sertraline ($d = 0.35$). Belief

change also predicted depressive symptom improvement but more modestly and bi-directionally,

with no difference by treatment modality. *Conclusions:* Trauma-related belief change precedes

PTSD improvement more robustly in PE than sertraline and with greater specificity compared to

depressive symptoms. These findings highlight potentially divergent processes contributing to symptom change in these PTSD treatments, with belief change as a key mechanism of PE.

Keywords: PTSD, exposure, selective serotonin reuptake inhibitors, sertraline, beliefs, process of change

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Do Changes in Trauma-Related Beliefs Predict PTSD Symptom Improvement in Prolonged

Exposure and Sertraline?

       The past three decades of research on the treatment of mental health disorders has yielded

a variety of empirically-supported psychotherapeutic and pharmacological treatments (Nathan &

Gorman, 2015). However, we still know relatively little about *how* these interventions work, in

terms of the mechanisms of acute and enduring symptom improvement (Kazdin, 2007; Murphy,

Cooper, Hollon, & Fairburn, 2009). As stated succinctly by McNally (2007): "Theoretical

agnosticism about mediating mechanisms is acceptable only when treatment works with flawless

fidelity" (p. 751). Persistent evidence across a variety of disorders of incomplete or non-response

to treatment (e.g., Hirschfeld et al., 2002; Taylor, Abramowitz, & McKay, 2012), as well as

relapse and recurrence after treatment (e.g., Bruce et al., 2005; Mueller et al., 1999), underscores

the need to move beyond theory and toward empirical tests of potential treatment mechanisms.

By identifying mechanisms linked to symptom improvement, researchers and clinicians can

maximize the likelihood of successful and effective treatment across patients (Murphy et al.,

2009). Mechanism research has been highlighted as a research funding priority (Cuthbert &

Insel, 2013), with a particular emphasis on integration of psychological and neurobiological

indices and identification of common processes across related disorders and treatments (e.g.,

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Hofmann, Ellard, & Siegle, 2012).

Cognitive behavioral therapies (CBTs) are empirically-supported for many disorders (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012) and dominate the literature on theoretical mechanisms of psychotherapeutic symptom change. Although specific treatment protocols vary both across and within disorder, CBT for anxiety and traumatic stressor disorders commonly involve some form of structured exposure exercises. Contemporary theories of exposure-based treatments draw on the behavioral and learning roots of these therapies in emphasizing altering the meaning of conditioned associations (conditioned stimuli [CS]-unconditioned stimuli [US]) as a central mechanism of treatment, fostering new inhibitory learning (e.g., Bouton, 1991, 2004; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Foa, Huppert, & Cahill, 2006). Consistent with these models, many contemporary theories posit that changes in disorder-specific negative or distorted beliefs may act as potential mechanisms of the observed treatment effects (e.g., Beck, Emery, & Greenberg, 2005; Hoffman, 2008).

In the case of posttraumatic stress disorder (PTSD), negative trauma-related beliefs about oneself, others, and the world have a prominent role in many psychological models (Ehlers & Clark, 2000; Foa, Huppert, & Cahill, 2006; for a recent review, see LoSavio, Dillon & Resick, 2017). Some studies have shown that peritraumatic endorsement of these beliefs predicts subsequent development of PTSD (e.g., Ehring, Ehlers, & Glucksman, 2008; Shahar, Noyman,

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Schindel-Allon, & Gilboa-Schechtman, 2013), as well as severity and maintenance of PTSD symptoms (e.g., Bryant & Guthrie, 2007; Dunmore, Clark, & Ehlers, 1999; Foa & Cahill, 2001; Lancaster, Rodriguez & Weston, 2011). The interplay between beliefs and PTSD symptoms has been characterized as a "vicious cycle" leading to worsening impairment over time (Shahar et al., 2013). Reductions in these beliefs occur across successful PTSD treatments with a variety of cognitive-behavioral psychotherapies (Foa & Rauch, 2004; Kleim et al., 2013; Resick et al., 2002; Taylor et al., 2003; Zoellner, Feeny, Efthekari, & Foa, 2011). Changes in trauma-related beliefs have therefore been emphasized as an important target of some psychological treatments for PTSD as a potential mediator of symptom change (LoSavio et al., 2017).

Prolonged exposure therapy (PE) is a gold standard treatment for PTSD with strong empirical support across a variety of samples and trauma types (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). PE was developed based on earlier behavioral therapies and on the foundation of emotional processing theory (Foa & Kozak, 1986). Historically, emotional processing theory has primarily emphasized behavioral and learning models of fear conditioning and extinction (e.g., Lang, 1979). However, recent updates have more clearly highlighted the importance of change in trauma-related beliefs as a key process in recovery from PTSD (Foa et al., 2006; Foa & McLean, 2016). In PE, change in negative thinking patterns is thought to be facilitated by providing disconfirming information through exposure exercises. For instance, a

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belief that one is weak and incompetent might be counteracted by evidence of mental strength and skillfulness, as demonstrated through repeatedly recounting one's life-saving actions throughout the trauma. Several studies have shown that negative trauma-related cognitions are substantially reduced after PE and correlated with PTSD symptom change (e.g., Foa & Rauch, 2004; Hagenaars, van Minnen, & de Rooij, 2010; Nacasch et al., 2015). Trauma-related belief change has also been found to mediate symptom change in some (Mueser et al., 2008; Nacasch et al., 2015; Zoellner et al., 2011) but not all (Hagenaars et al., 2010) studies of PE. Careful assessment of the temporal sequence of cognitive and symptom change is critical to ascertaining whether belief change might "drive" symptom improvements (e.g., Kazdin, 2007; Murphy et al., 2009) in PE and other PTSD interventions. Using time-lagged, repeated measures analyses, a series of recent studies have found that belief change predicts subsequent improvements in PTSD symptoms in CBT treatments for adults (Kleim et al., 2013; Kumpula et al., 2016; McLean, Su, & Foa, 2015; Oktedalen, Hoffart & Langkaas, 2015; Schumm, Dickstein, Walter, Owens & Chard, 2015; Zalta et al., 2014) and adolescents (McLean, Yeh, Rosenfield, & Foa, 2015). Most of these studies have shown that belief change precedes symptom improvement, with just one showing a more reciprocal relationship between beliefs and symptoms (McLean, Su et al., 2015). Thus, there is preliminary evidence that trauma-related belief change precedes, and perhaps drives, symptom improvement in CBT for PTSD. This is consistent with the view of belief

change as a process which underlies successful recovery from PTSD, regardless of whether this is achieved via PE, another treatment, or naturalistic improvement (Foa et al., 2006). Consistent with this theory, belief change has been found to precede PTSD improvement in other empirically-supported psychotherapies, including other CBTs like Cognitive Processing Therapy (Kleim et al., 2013; Schumm et al., 2015) and non-CBT approaches that are not clinically or theoretically focused on modifying trauma-related cognitions (e.g., McLean, Yeh et al., 2015; McLean, Su et al., 2015).

Selective serotonin reuptake inhibitors (SSRIs) are efficacious in the treatment of a variety of mental health disorders, including unipolar mood disorders (e.g., major depressive disorder [MDD]; Hollon et al., 2005) and PTSD (Jonas et al., 2013; Lee, Schnitzlein, Wolf, Vythilingam, Rasmusson, & Hoge, 2016). One contemporary model of the therapeutic action of SSRIs posits that they intiate a cascade of intracellular effects that ultimately ameliorate a broad range of neuronal deficits most typified by decreased neurogenesis and disrupted neuroplasticity (Duman & Voleti, 2012), consistent with atrophy of the hippocampus observed in patients with depression (MacQueen & Frodl, 2011) and often observed in PTSD (Woon, Sood, & Hedges, 2010). SSRIs have both acute and sustained effects on a variety of emotional and cognitive processes (e.g., DiSimplicio, Norbury, & Harmer, 2012; Harmer, 2008). For instance, changes in negative self-schemas in depression have been linked to altered self-referential attention and

positive affect potentiated by SSRI treatment (Harmer, 2008), with comprehensive models

highlighting connections between pharmacologically-mediated neurobiological processes and

psychological constructs (e.g., Harmer, 2013; Pringle, Browning, Cowen, & Harmer, 2011).

Accordingly, although SSRIs do not directly involve provider-targeted efforts to modify trauma-

related beliefs, it is quite plausible that these beliefs improve across treatment and may in fact

promote PTSD improvement. Indeed, Dozois et al. (2014) found few differences in change on

self-reported core beliefs between depressed patients treated with both antidepressants and

cognitive therapy versus those treated with antidepressants alone. To our knowledge, no prior

study has evaluated the role of trauma-related belief change in symptom improvement in patients

with PTSD treated with SSRI monotherapy or compared this relationship to trauma-focused

psychotherapy. Thus, our study investigates whether the relationship between belief change and

PTSD symptom improvement differs by treatment modality, specifically comparing prolonged

exposure versus sertraline, an SSRI with established efficacy for PTSD (Lee et al., 2016).

Cognitive behavioral models of PTSD emphasize the disorder-specific nature of trauma-

related beliefs (e.g., Ehlers & Clark, 2000), so changes in these beliefs should mostly clearly

impact PTSD symptomatology. Although trauma-related cognitions are most robustly predictive

of development of PTSD, they also predict development of major depressive disorder (MDD) to

a lesser degree (Kleim, Ehlers, & Glucksman, 2012). MDD co-occurs in more than half of

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patients with PTSD (Rytwinski, Scur, Feeny, & Youngstrom, 2013) and depressive symptoms

typically improve after treatment with PE (Powers et al., 2010; Ronconi, Shiner & Watts, 2015).

The relationship between PTSD and depressive symptoms is complex both in terms of

conceptual overlap (Post, Zoellner, Youngstrom, & Feeny, 2011; Zoellner, Pruitt, Farach, & Jun,

2014) and patterns of change across treatment (Aderka, Gillihan, Mclean, & Foa, 2013). Two

studies have shown that changes in trauma-related beliefs predict subsequent improvements in

depressive symptoms in PE, with results differing in terms of whether this relationship is

stronger (Zalta et al., 2014) or weaker (McLean, Yeh et al., 2015) than the link between beliefs

and PTSD symptoms. SSRI treatments for PTSD and MDD likely share common pathways, with

recent analogue studies suggesting that both fear and mood regulation may be driven by a

common neural mechanism (e.g., Tronson et al., 2008). Thus, it is less likely that the relationship

between negative-trauma related beliefs and depressive symptom change would differ between

PE and sertraline. This comparison also helps to evaluate the specificity of the relationship

between trauma-related belief change and PTSD symptom improvement, a key criterion needed

to establish a mechanistic effect (Kazdin, 2007).

In this study, we investigated the temporal relationship between change in trauma-related

beliefs and symptoms in patients with PTSD treated with PE or sertraline. We utilized time-

lagged regression models, which allowed for an estimate of the magnitude of the relationship

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between belief and symptom change at the session level, as well as a comparison of the direction of effect (i.e., whether belief change mediates symptom change or vice versa). We hypothesized that belief change would predict subsequent change in PTSD and depressive symptoms in both treatments. We further hypothesized a significant treatment interaction indicating stronger effects in PE than sertraline, in line with the important theoretical role of changing cognitions in PE and some prior evidence of its mediating effects on PTSD symptom improvements. Finally, we expected the relationship between trauma-related belief change and depressive symptom change to be comparable across both PE and sertraline, with no significant moderation by treatment.

Method

Participants

Two hundred participants were recruited for a multi-site trial comparing PE to sertraline in the treatment of PTSD (Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2017). Institutional review boards at both sites approved the trial. Participants were between 18 and 65 years of age and had a current primary DSM-IV diagnosis of chronic PTSD. Exclusion criteria included: current diagnosis of schizophrenia or other psychotic disorder, unstable bipolar disorder or depression with psychotic features, severe depression requiring immediate treatment (e.g., current actively suicidal with intent); serious self-injurious behavior or suicide attempt within the past three months; no clear trauma memory or primary trauma before age three; alcohol or

substance dependence within the previous three months; ongoing intimate relationship with the perpetrator (in cases of assault); unwilling or medically inadvisable to stop current CBT or pharmacotherapy, based on condition assignment; previous non-response to adequate trial of sertraline (8 weeks, 150mg/d) or PE (8+ sessions); or medical contraindication for initiating sertraline (e.g., pregnant/likely to become pregnant).

For the current study, we developed sample selection criteria based on a relevant theoretical models (Yang & Maxwell. 2014), precedent established by similar studies (e.g., Kleim et al., 2013), and review of patterns of missing data. There is growing recognition that some patients can provide more information about change mechanisms than others (e.g., DeRubeis, Gelfand, German, Fournier, & Forand, 2014), conditional in part on having received some dose of the treatment being investigated. In line with this, most well-powered studies of belief change as a treatment mechanism have focused on patients who attended a specific minimum number of sessions. Thus, patients who are excluded are those contributing little if any data to the primary treatment mechanism questions. This approach also addresses concerns about non-random missingness and estimation accuracy in clinical research models (e.g., Yang & Maxwell. 2014). The present study used the conservative criterion selected by Kleim and colleagues (2013) of including only patients who completed self-report ratings for at least five treatment sessions, resulting in a final sample of 134 patients ($n = 83$ in PE, $n = 51$ in sertraline).

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Of this sample, 73.9% (*n* = 99) were missing one or fewer sessions (mean missing = 0.89,

median = 0).[1] There was no difference in baseline symptoms or trauma-related cognitions

between patients who were excluded and those included in this sample. Demographic and

diagnostic characteristics of patients included in these analyses are presented in Table 1. The

sertraline condition was slightly older with a mean age of 40.8 (*SD* = 11.9) versus 36.3 (*SD* =

11.5) in PE, *t*(132) = -2.12, *p* =.04, *d* = 0.37), with no other differences in demographic

characteristics by treatment.

Interview Measures

      PTSD Symptom Scale – Interview Version (PSS-I; Foa, Riggs, Dancu & Rothbaum,

1993). The PSS-I is a 17-item clinician rated measure of PTSD symptoms used at baseline to

assess PTSD diagnosis and severity for inclusion criteria purposes. This measure has been

demonstrated to have good reliability and convergent validity (Foa & Tolin, 2000). In the current

study, approximately 10% of cases were re-rated for diagnostic reliability, which was excellent

(ICC = .99).

      Structural Clinical Interview for the DSM-IV (SCID-IV; First, Spitzer, Gibbon &

Williams, 1995). The SCID-IV was used to assess comorbid Axis I diagnoses in this sample for

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[1] Missing datapoints represented <8% of the analyzed sample versus >70% for those who were excluded. In the analyzed sample, the modal case of missingness involved a single session in early- or mid-treatment (i.e., not at the end of treatment) likely attributable to failure to fill out questionnaires.

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the purposes of inclusion and exclusion criteria.

Self-Report Measures

      PTSD Symptom Scale – Self-Report (PSS-SR; Foa et al., 1993). The PSS-SR is a 17-item self-report version of the PSS-I. Symptoms are rated on a 4-point scale from 0 (*not at all)* to 3 (*very much*) and are summed to provide a total score. The measure has good reliability and convergent validity (Foa, Cashman, Jaycox & Perry, 1997) and was internally consistent in this sample at pre-treatment, $\alpha = .85$, with a one-week test-retest reliability of .80.

      Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Erbaugh, 1961). The BDI is a 21-item self-report measure of depression, assessing cognitive, affective and vegetative symptoms. Each question includes four response options (0-3), with more severe symptoms reflected in higher scores. The BDI demonstrates good reliability and validity (Beck, Steer & Garbin, 1988) and in the current study at pre-treatment, $\alpha = .88$, with a one-week test-retest reliability of .84.

      Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999). The PTCI is a 36-item self-report measure of negative trauma-related thoughts, with three factors capturing negative beliefs about the self, the world, and self-blame. Each item (e.g., *The world is a dangerous place*) is rated on a scale from 1 (*totally disagree*) to 7 (*totally agree*), with higher scores reflecting more rigid endorsement of negative cognitions. This measure has excellent convergent

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and discriminant validity, internal reliability and good test-retest reliability (Foa et al., 1999) and

internal consistency at pre-treatment was $\alpha = .95$, with a one-week test-retest reliability of .91

Treatments

      PE consisted of 10 weekly sessions, 90-120 min in duration, based on a standard PE

treatment manual (Foa, Hembree, & Dancu, 2002). Masters or doctoral-level clinicians who were

trained in the delivery of PE provided treatment and received weekly supervision. In sertraline,

patients met with board certified psychiatrists for 10 weekly sessions of up to 30 min duration

(45 min for the first session). Patients started sertraline at 25mg/day, with a goal of increasing

dose to up to 200mg/day, as tolerable and clinically indicated using a standard titration algorithm

(Marshall, Beebe, Oldham, & Zaninelli, 2001). The average final dose of participants in this

subsample was 155mg/day ($SD = 59.0$). Treatment adherence ratings were made based on the

treatment manual (Foa et al., 2002; Marshall et al., 2001) with 10% of videotapes from the

overall study reviewed by trained raters. No protocol violations were detected, and both

treatments scored 90% or above on essential treatment components.

Procedure

      Participants provided written informed consent prior to enrollment. Participants

completed an initial intake evaluation to assess eligibility, at which time they were assessed with

the PSS-I and SCID-IV. Eligible participants were assigned to treatment using a computerized

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urn randomization stratified by PTSD severity and current anti-depressant status. BDI, PSS-SR, and PTCI ratings were collected at pre-treatment, every treatment session, and post-treatment, and were based on a one-week timeframe, so as to preclude overlapping assessment periods. Although this approach is commonly used in similar treatment research (e.g., Kumpula et al., 2016; Zalta et al., 2014), these measures were originally developed for longer assessment intervals (e.g., 1 month for PTCI; Foa et al., 1999).

Statistical Approach

To test the relationship between symptom change and change in trauma-related beliefs at the session level, we utilized time-lagged, repeated-measures regression (e.g., Rovine & Walls, 2006). This statistical approach allows for an examination of potential temporal relationship between two variables, examining the strength of the relationship between a predictor at Time X, and a dependent variable at Time X+1, while also controlling for the autocorrelation with that predictor at Time X (for additional detail, see Strunk et al., 2012). Scores from the BDI, PSS-SR, and PCTI included up to 12 time points: at pre-treatment, for each of 10 sessions of treatment, and at the post-treatment assessment. For each of these variables, we created a set of dependent variables (Time 2 to Time 12) and a set of lagged predictors (Time 1 to Time 11) combined in a single dataset. All models were tested in PROC Mixed with restricted maximum likelihood in

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SAS 9.2 (SAS Institute, Cary NC) to account for missing variables.

We conducted four main sets of analyses: (1) PTCI predicting next-session PSS-SR, (2) PSS-SR predicting next-session PTCI, (3) PTCI predicting next-session BDI, and (4) BDI predicting next-session PTCI. We also included a time covariate, which was significantly predictive in all models, indicating substantial reductions in PSS-SR and PTCI over treatment. Moderator analyses were conducted after first testing for main effects of treatment (PE versus sertraline), which were not significant in any model. In summary, the models predicted time-varying outcome variables by a lagged predictor, covarying time and the outcome auto-correlation (i.e., prior session score).

Results

Belief Change and PTSD Symptom Change

Results of the time-lagged session-to-session models involving PTCI and PSS-SR are presented in Table 2. For both the model of PTSD symptoms and PTCI, the linear effects of time and auto-correlation variables were significant. For the model with belief change as the dependent variable, the cross-lagged effect of PTSD severity (PSS-SR) on negative cognitions (PTCI) was negligible ($d < .01$), suggesting no relationship between preceding change in PTSD symptoms on subsequent change in beliefs (PTCI). For the model with PTSD symptoms as the dependent variable, the cross-lagged effect of PTCI in predicting subsequent PSS-SR was large

and statistically significant ($d = 0.81$), suggesting that change in beliefs generally preceded improvements in PTSD symptoms.

Moderation by treatment. In order to examine whether the relationship between belief change and PTSD symptom change differed by treatment modality, we tested Treatment x Predictor interactions in both of the models described above. In the model predicting change in PTCI, the Treatment by PSS-SR interaction was not statistically significant, $\beta = .03$, SE = .08, $p = .72$. Thus, there were no significant differences between treatments in the relationship between PSS-SR and subsequent PTCI change, which was generally negligible. In the model predicting change in PTSD symptoms, the Treatment x PTCI interaction was significant, $\beta = -.02$, SE = .01, $p = .03$. Probing this interaction, we examined the relationship between preceding beliefs change and next-session PTSD symptoms in each treatment separately. In sertraline, PTCI was associated with subsequent PTSD symptom improvement at a trend level with a small effect size, $\beta = .02$, $SE = .01$, $p = .08$, $d = 0.35$. In PE, the relationship was considerably stronger, with a large effect size ($\beta = .05$, $SE = .01$, $p < .0001$, $d = 0.93$). Therefore, the interaction reflects a difference in magnitude between treatments, with a small trend-level relationship of belief change preceding PTSD symptom change in sertraline versus a much more robust relationship in PE of belief change preceding PTSD symptom change.

Belief Change and Depressive Symptom Change

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Table 3 shows results for the time-lagged session-to-session models involving trauma-related negative beliefs (PTCI) and depression (BDI) change. As in the PTSD symptom models, the linear effects of time and auto-correlation variables were significant in both models. For the model predicting change in PTCI, the cross-lagged effect of BDI on PTCI was statistically significant with a small to medium effect size ($d = 0.30$), indicating that preceding depressive symptoms were modestly related to subsequent belief change. For the model with BDI as the dependent variable, cross-lagged PTCI scores were significantly predictive of subsequent BDI scores with a medium effect size ($d = 0.49$), suggesting that change in beliefs also preceded improvements in depression symptoms.

Moderation by treatment. We tested Treatment x Predictor interactions in both of the belief change and depressive symptom models. In the model predicting change in PTCI, the Treatment x BDI interaction was not a significant predictor of belief change ($\beta = .05$, $SE = .08$, $p = .54$). In the model predicting change in BDI, the Treatment x PTCI interaction was not significant in predicting subsequent BDI change ($\beta = .01$, $SE = .01$, $p = .42$), indicating that the relationship between depressive symptom improvement and belief change did not differ by treatment modality. Thus, unlike our PTSD symptom findings, there were no significant differences between treatments in the relationship between BDI and PTCI change, regardless of the direction of lagged effect being modeled.

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Discussion

Trauma-related belief change preceded PTSD symptom improvement more robustly in patients treated with PE versus those treated with sertraline. As hypothesized, the relationship between belief change and depression improvement was less substantial, with no clear direction of effect, and no difference between treatments. The robust link between belief change and PTSD change in PE is consistent with the emphasis on negative trauma-related beliefs in CBT treatments and related psychological models (Ehlers & Clark, 2000; Foa et al., 2006). Patients who received sertraline also saw reductions in trauma-related beliefs across treatment, temporally preceding PTSD symptom improvement, but this relationship was small to moderate.

These findings are consistent with emotional processing theory in highlighting belief change as a precursor to PTSD recovery (Foa et al., 2006), regardless of how it occurs. Although belief change occurs with SSRIs, this treatment likely promotes symptom reduction via more general neurochemical changes in fear circuitry, consistent with the broad changes in functioning in response to SSRIs (Brady et al., 2000; Davidson et al., 2001). This is similar to the framework described by Mayberg and colleagues (Mayberg et al., 1999), whereby psychotherapies exert "top down" effects on symptomatology (i.e., cognitive / cortical processes regulating limbic response) versus more "bottom-up" or mixed effects of SSRIs (i.e., affecting brainstem nuclei with secondary effects on cortical sites). Models of SSRI treatment for mood and anxiety

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disorders have not traditionally emphasized a role for change in specific psychological processes, and only recently have efforts been made to incorporate these factors into cognitive neuropsychological models of treatment effects (e.g., Harmer, 2013; Pringle et al., 2011) or test modality-specific differences in their relation to treatment change (e.g., Dozois et al., 2014). SSRI-mediated neurological changes in emotionally-biased attention and self-referential processing (e.g., DiSimplicio et al., 2012) may promote more approach-oriented behaviors, which in turn could provide disconfirming evidence with respect to strongly held, erroneous negative beliefs. Alternatively, self-reported belief change may be an epiphenomenon of other change processes (e.g., Hofmann, 2008), such as reversal of neuronal deficits in key brain areas (Duman & Voleti, 2012), constituting a different level of measurement with respect to the neurobiological mechanisms by which SSRI treatment achieves its effects (Harmer, 2013)[2]. Regardless, most notably, these findings suggest that the change in negative beliefs is a more relevant marker of PTSD improvement in PE versus SSRI treatment.

The parallel examination of depressive symptoms provides an important comparison to the primary models of PTSD change. Notably, associations between trauma-related belief change and depression were more modest than those between PTSD and beliefs, consistent with the

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[2] We take care not to describe biological mechanisms as *underlying* belief change, or vice versa. See Miller (2010) for a detailed discussion of the potential problems with this term.

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trauma-specific ways of thinking emphasized by cognitive models of PTSD (e.g., Ehlers & Clark, 2000). Although certain symptoms of PTSD and MDD overlap (e.g., insomnia; Post et al., 2011), prior research has typically found stronger predictive relationships between trauma-related negative beliefs and PTSD symptoms versus depressive symptoms (Kleim et al., 2012). These findings also suggest change in beliefs and depressive symptoms had a more reciprocal temporal relationship, with belief change predicting subsequent depressive symptom improvement and vice versa. Most critically, the relationship between beliefs and depressive symptoms did not significantly differ between PE and sertraline, regardless of which temporal sequence was being tested. Thus, whereas the relationship between trauma-related belief change and PTSD symptom change was clearly unidirectional and considerably stronger in PE versus sertraline, the relationship between belief change and depressive symptom analyses were more modest, reciprocal, and comparable across treatments. This is in line with the specific role ascribed to negative trauma-related beliefs in the maintenance of PTSD symptoms in several cognitive behavioral models of PTSD (e.g., Foa et al., 2006; Hoffmann, 2008). These findings suggest trauma-related belief change likely exerts a more robust influence on PTSD symptoms, and perhaps especially so in PE.

Key strengths of this study include the theoretically important and unique comparison between PE and sertraline, the conservative analytic strategy, and use of a large and diverse

sample of male and female patients with heterogeneous target traumas. However, we strongly caution readers not to draw strong, causal inferences about the relationships depicted in these models, as these are fundamentally correlational. Although we utilize a conservative statistical method that controls for prior change and establishes temporal precedence, it is possible that common factors (e.g., supportive contact with study personnel) or modality-specific factors (e.g., content of in-session processing in PE) may help to explain both change in trauma-related cognitions and symptom change. Similarly, these analyses do not inform us as to *how* belief change may be occurring – that is, what precipitates or motivates such change. Other limitations of this study include unequal size of PE and sertraline conditions, a consequence of the design of the clinical trial from which data are drawn. This study also used DSM-IV symptom criteria for PTSD. As noted by Schumm and colleagues (2013), in the DSM-5 (American Psychiatric Association, 2013) cognitive alterations are now considered a symptom of PTSD. Future studies using DSM-5 criteria will need to carefully consider whether trauma-related negative beliefs are better represented as cognitive mechanisms, sequelae, or symptoms of PTSD. It is possible that future work in this area will be framed in terms of sequential symptom change rather than mechanisms *per se*.

Our analyses focus on total scores of symptom and belief measures (i.e., PTCI, PSS-SR, BDI), as these had the most robust prior support and were most likely to be relevant to tests of

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moderation by treatment. As such, our findings do not speak to potential differences by subscales

or symptom clusters, as highlighted by a recent study showing stronger effects for self-relevant

trauma beliefs on PTSD gains (Kumpula et al., 2016). However, testing all possible

combinations of PTCI subscales and PSS-SR clusters across our four main models would greatly

raise the risk of a Type I error. Self-report measures were also adjusted to reflect a one-week

timespan interval, departing from longer durations specified during development of these

measures (e.g., Foa et al., 1993; Foa et al., 1999). Although this shorter interval is commonly

used in clinical research on belief change and PTSD (e.g., Zalta et al., 2014; Kumpula et al.,

2016), its influence on the psychometrics of these scales and measurement of processes across

time is not well established. However, the relationship between PTCI and PTSD symptoms has

been quite consistent across studies of PE despite method variance in assessments, including

studies separating assessment of beliefs and symptoms (e.g., Oktedalen et al., 2014) or using

longer intervals between assessments (e.g., 4 weeks; McLean et al., 2015). Finally, as most prior

studies of this kind have done (e.g., Kleim et al., 2013), we chose to focus on patients who

attended a minimum number of sessions, based on contemporary guidance for mechanism

research (Cohen & DeRubeis, 2016; DeRubeis et al., 2014). The analyzed sample had very little

missing data, whereas patients excluded from analyses often had more extensive missing data,

following patterns characteristic of attrition (i.e., consecutive missing sessions at the end of

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treatment). Accordingly, the present findings are most relevant to understanding change processes in patients who engaged with treatment and do not represent the entire randomized sample.

In summary, trauma-related belief change is linked to PTSD improvement across modalities yet more robustly predictive in cognitive behavioral therapy than SSRI treatment with sertraline, suggestive of different processes implicated PTSD symptom improvement. Notably, the relationship between belief change and depressive symptoms was not moderated by treatment nor clearly directional, highlighting the relatively more robust link between trauma-related cognitive change and PTSD improvements. Psychotherapy process research may illuminate the elements of treatment most strongly associated with belief change and suggest ways to enhance this process during treatment, such as by tailoring between-session activities (i.e., *in vivo* homework assignments) to focus on persistent negative beliefs. Similarly, novel research paradigms such as experience-sampling might offer insight into patients' subjective experience of changes in negative beliefs and PTSD improvement across shorter time intervals. Beyond their significance to theory and research on change mechanisms of PE and SSRIs, our findings also have clear clinical implications. In PE, failure to experience trauma-related belief change may be a warning sign of an impending clinical impasse or stagnation. Furthermore, belief change may be a critical pathway to overcoming such setbacks and enhancing treatment

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outcomes. Beyond routinely assessing beliefs across treatment, further study is needed as to the best approach to address such situations clinically within the context of PE. Strategies could include explicitly tracking change in each patients' most troubling or central negative belief as suggested by Kleim et al. (2013) or incorporating more explicit cognitive change techniques (i.e., cognitive restructuring; CR) from other trauma-focused CBTs during post-imaginal processing. However, the addition of CR to PE protocols does not enhance overall treatment response (Jonas et al., 2013). In fact, one study found that patients with more severe negative beliefs at baseline showed a worse response to combined PE plus CR than conventional PE (Moser, Cahill, & Foa, 2010). Although the addition of cognitive techniques may not be warranted for all cases, an additional possibility is that certain patients would benefit from these approaches, though who these patients are is not clear. Research on moderation of treatment mechanisms is lacking at present in the PTSD literature, but there is evidence from the depression literature that certain patient traits predict more robust response to cognitive techniques, including gender (e.g., Sasso, Strunk, Braun, DeRubeis & Brotman, 2015). Further study is needed in this area, and in terms of potential cascading temporal relationships between belief change, PTSD symptoms and depressive symptoms across treatment. In summary, this work adds to the growing body of research highlighting trauma-related beliefs as predictors of change in trauma-focused CBTs (Kleim et al., 2013; Kumpula et al., 2015; McLean, Su et al., 2015; Oktedalen et al., 2014;

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Schumm et al., 2013; Zalta et al., 2014) and further suggests that different change processes may

promote improvement in sertraline treatment.

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