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The relationship between posttraumatic and depressive symptoms during virtual reality exposure therapy with a cognitive enhancer

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ABSTRACT

Two studies suggest that reductions in posttraumatic symptoms (Aderka et al., 2013) and cognitions (Zalta et al., 2014) precede reductions in depressive symptoms during prolonged exposure (PE) therapy for posttraumatic stress disorder (PTSD) in female assault survivors. The present study explored the temporal relationship between posttraumatic and depressive symptoms in a randomized trial of D-Cycloserine (DCS) versus placebo augmented virtual reality exposure (VRE) therapy for chronic World Trade Center-related PTSD following the September 11, 2001 terrorist attacks. Twenty-five male and female participants were randomly assigned to receive either 100 mg DCS (N = 13) or placebo (N = 12) 90 min before 12 weekly VRE sessions. Participants contributed a total of 280 weekly PTSD Checklist (PCL; Weathers et al., 1993) and Beck Depression Inventory-second edition (BDI-II; Beck et al., 1996) symptom scores. Two sets of mediation analyses for longitudinal mixed models assessed the effects of 1) lagged PCL on BDI-II (Model 1), and 2) lagged BDI-II on PCL (Model 2) in the VRE-DCS and VRE-Placebo treatment groups, respectively. Results revealed reciprocal relations between posttraumatic and depressive symptoms during VRE treatment, although reductions in posttraumatic symptoms led to subsequent reductions in depressive symptoms to a greater extent than the converse. These effects were stronger in the DCS-enhanced group. Findings suggest that VRE primarily decreases posttraumatic symptoms, which in turn leads to decreased depressive symptoms, and that DCS may strengthen these effects.

1. Introduction

Numerous studies have documented high rates of major depressive disorder (MDD) among individuals with posttraumatic stress disorder (PTSD). A meta-analysis examining the prevalence of MDD among those with PTSD reported that 52% of individuals with current PTSD also met criteria for MDD (Rytwinski, Scur, Feeny, & Youngstrom, 2013). Compared to individuals with PTSD alone, those with comorbid MDD evidence greater levels of healthcare utilization (Adams & Boscarino, 2006), subjective distress (Ikin, Creamer, Sim, & McKenzie, 2010), and functional impairment (Momartin, Silove, Manicavasagar, & Steel, 2004). Comorbidity is also associated with increased PTSD and depression symptom severity (Nixon, Resick, & Nishith, 2004), suicidality (Gradus et al., 2010), and chronicity (Green et al., 2006), and lower natural remission rates for both disorders (North, Kawasaki, Spitznagel, & Hong, 2004; O'Donnell, Creamer, & Pattison, 2004; Shalev et al., 1998).

Studies examining the relationship between posttraumatic and depressive symptoms have involved varied methodologies, time-frames, and samples, rendering clear conclusions difficult. For instance, some studies suggest that depressive symptoms increase the severity of subsequent posttraumatic symptoms (Schindel-Allon, Aderka, Shahar, Stein, & Gilboa-Schechtman, 2010; Shalev et al., 1998), while other studies suggest that posttraumatic symptoms precede and increase subsequent depressive symptoms in adults (Curry, Aubuchon-Endsley, Brancu, Runnals, & Fairbank, 2014; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Nickerson et al., 2013) and youth (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998). Yet other studies suggest reciprocal relationships between posttraumatic and depressive symptoms (Erickson, Wolfe, King, King, & Sharkansky, 2001) or that posttraumatic and depressive symptoms vary concurrently over time (Schindel-Allon et al., 2010). However, the above studies have not explicitly focused on the association between posttraumatic and depressive symptoms during treatment, and the complex relationship between PTSD onset/

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maintenance and MDD onset/maintenance may or may not relate to change dynamically over treatment.

Several studies have focused on posttraumatic and depressive symptom change over the course of trauma-focused psychotherapy. Prolonged exposure (PE) and Cognitive Processing Therapy (CPT) have been validated as effective treatments for PTSD across a diverse range of traumas and populations (Chard, 2005; Monson et al., 2006; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010; Resick, Nishith, & Griffin, 2003; Resick, Nishith, Weaver, Astin, & Feuer, 2002) and been shown to reduce posttraumatic and depressive symptoms (Foa et al., 2005; Foa & Rauch, 2004; Powers et al., 2010; Rauch et al., 2009; Resick et al., 2008; Resick et al., 2003; Resick et al., 2002; Tuerk, Yoder, Ruggiero, Gros, & Acierno, 2010).

Two studies by Aderka and colleagues (Aderka, Foa, Applebaum, Shafran, & Gilboa-Schechtman, 2011; Aderka, Gillihan, McLean, & Foa, 2013) have investigated the relationship between changes in posttraumatic and depressive symptoms during PE. In the first of these studies, Aderka et al. examined the relationship between posttraumatic and depressive symptoms in children and adolescents undergoing PE for a range of traumas. The authors found that changes in posttraumatic symptoms accounted for 64.1% of changes in depressive symptoms, whereas changes in depressive symptoms accounted for only 11% of changes in posttraumatic symptoms, suggesting that PE may work by first reducing PTSD symptoms, leading to a subsequent reduction in depressive symptoms (Aderka et al., 2011). In a second study, Aderka and colleagues examined the interrelationship between posttraumatic and depressive symptoms during PE and PE with added cognitive restructuring in female assault survivors. The authors found a similar pattern of findings during PE, such that changes in posttraumatic symptoms accounted for 80.3% of changes in depressive symptoms whereas changes in depressive symptoms accounted for only 45% of changes in posttraumatic symptoms. In contrast, during PE with cognitive restructuring, the authors found a more reciprocal relationship between posttraumatic and depressive symptoms, such that changes in posttraumatic symptoms accounted for 59.6% of changes in depressive symptoms and changes in depressive symptoms accounted for 50.7% of changes in posttraumatic symptoms. The authors interpreted this finding as suggesting that PE may act first on unique PTSD factors, such as fear, which in turn lead to changes in shared PTSD/depression factors, such as negative beliefs about oneself. For instance, exposures may help an individual feel less fearful. As fear declines and an individual gains a sense of mastery and competence, her beliefs about herself may become more positive. In contrast, PE with cognitive restructuring, which teaches patients specific techniques to identify and challenge distorted thoughts in written homework, may act more directly on shared PTSD/depression factors, such as negative beliefs about oneself (Aderka et al., 2013). Although the authors were not able to test these different directional pathways directly, their findings raise the possibility that change may occur through different mechanisms in PE and more cognitively-based treatments.

In preliminary support of this notion, a study examining the association between posttraumatic and depressive symptoms in CPT found a similar pattern of change as that observed in PE with cognitive restructuring. In this analysis of female assault survivors, multilevel mediation analyses revealed that in contrast to the sequential pattern of change observed in PE in which reductions in posttraumatic symptoms led to subsequent changes in depressive symptoms, changes in PTSD and depression symptoms occurred concurrently (Liverant, Suvak, Pineles, & Resick, 2012). The authors suggested that CPT may act on a shared mechanism that affects both posttraumatic and depressive symptoms, similar to Aderka et al. (2013)' suggestion that PE with cognitive restructuring may target shared PTSD/depression factors (Aderka et al., 2013). However, it is also possible that potential heterogeneity in the mediational methods used by Aderka et al. (2013) and Liverant et al. (2012) may have contributed to differences in findings between exposure and more cognitively based treatments.

Although not focused on posttraumatic and depressive symptoms per se, a few other studies have examined features related to PTSD and depression during PE. Previous research has shown that decreases in PTSD symptoms are associated with decreases in suicidal ideation during PE (Gradus, Suvak, Wisco, Marx, & Resick, 2013; Harned, Korslund, & Linehan, 2014) and CPT (Gradus et al., 2013). Using time-lagged models, Cox and colleagues (Cox et al., 2016) found that decreases in PTSD symptoms occurred before and predicted future decreases in suicidal ideation during PE, while the converse was not true. Finally, Zalta et al. (2014) found that reductions in PTSD-related cognitions led to subsequent reductions in depression symptoms in female assault survivors receiving PE.

Determining the course of posttraumatic and depressive symptom change during therapy is important for several reasons. First, such research may increase our understanding of the structural relationship between PTSD and depression and clarify whether these two conditions are best conceptualized as distinct entities or manifestations of a common factor representing general distress post-trauma. Second, clarifying patterns of posttraumatic and depressive symptom change during treatment may have clinical implications. A potential challenge facing clinicians treating individuals with comorbid PTSD and depression is whether to target symptoms of PTSD or depression first. Although the research reviewed above has begun shedding light on this question, additional studies are needed to confirm these findings and determine patterns of symptom change across different treatment modalities.

One treatment modality that has received increasing attention and empirical support over the last two decades is virtual reality exposure (VRE) therapy. Virtual reality (VR) technology integrates visual computer graphics with multiple sensory cues in order to create an evocative environment that may augment a patient's imaginative capacity with visual, auditory, olfactory, and haptic computer-generated experiences. The therapist asks the patient to recount the details of his trauma aloud, while the patient proceeds through detailed virtual simulations of the traumatic event that are closely monitored by the therapist. The therapist controls what the patient experiences by using preprogrammed keys on the keyboard, which allows the therapist to tailor treatment to the needs of the individual patient and therapy to proceed at a pace that is tolerable for that individual. Emotional processing theory (Foa & Kozak, 1986) proposes that fear reduction occurs during exposure therapy when two conditions are met: First, the fear structure, or memory of the traumatic event, is activated through emotional engagement, and second, corrective information is incorporated into the memory structure. Given that avoidance of trauma-related memories, thoughts, and cues are inherent to PTSD, some patients may struggle to engage emotionally during exposure, which has been shown to predict poor treatment outcome (Jaycox, Foa, & Morral, 1998). VRE may promote emotional engagement by providing a sensory-rich environment in which patients are able to encounter and gain mastery of their trauma.

Although it is possible that patterns of posttraumatic and depressive symptom change during VRE are similar to those during PE, research to date has yet to study the association between posttraumatic and depressive symptoms over the course of VRE. Without empirical studies, it is challenging to draw conclusions regarding the temporal pattern of posttraumatic and depressive symptom change during VRE. The present study extends previous research by exploring the temporal relationship between posttraumatic and depressive symptoms during VRE therapy for PTSD with or without D-Cycloserine (DCS).

The current study is an analysis of data from a randomized double-blind trial of DCS versus placebo augmented VRE therapy for chronic World Trade Center (WTC)-related PTSD following the September 11, 2001 terrorist attacks (Difede, Cukor, et al., 2014; Difede, Olden, & Cukor, 2014). DCS is a partial agonist at the *N*-methyl-D-aspartate (NMDA) receptor that has been found to facilitate extinction learning and memory in rodent models (Davis, Ressler, Rothbaum, &

Richardson, 2006; Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002) and reduce treatment length for some anxiety disorders (Guastella et al., 2008; Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004). Findings from the parent study revealed that participants in the DCS-enhanced group showed statistically and clinically significantly greater improvement in PTSD symptoms over the course of the study, as well as on secondary outcomes of sleep, depression, and anger expression compared with the VRE-placebo group. In the present study, data from this RCT were reanalyzed to explore the temporal relationship between posttraumatic and depressive symptoms over the course of VRE treatment.

2. Material and methods

2.1. Participants

Full details of the study enrollment process are provided in Difede, Cukor, et al. (2014). Participants were 25 men and women from the original randomized intent-to-treat sample who met criteria for WTC-related PTSD, were in good health, and between the ages of 18–70 years (Difede, Cukor, et al., 2014). The final sample had a mean age of 45.8 (SD = 10.50), were predominantly Caucasian (84%), and male (76%). All participants provided written informed consent after the study procedures and possible side effects were fully explained. The study was approved by the Weill Cornell Medical College Institutional Review Board.

2.2. Measures

Each week, participants completed the PTSD Checklist (PCL) (Weathers, Litz, Herman, Huska, & Keane, 1993) and the Beck Depression Inventory-second edition (BDI-II) (Beck, Steer, & Brown, 1996).

2.3. Equipment

A Dell (http://www.dell.com) 530 workstation with dual 2-gigabyte central processing units, 2 gigabytes of RAM, a Wildcat 5110 video card, Windows 2000 operating system, and MultiGen-Paradigm Inc., Vega VR software (http://www.multigen.com) was coupled with a 10242 × 768 resolution Kaiser XL-50 VR helmet, with 40° horizontal field of view (http://www.keo.com/proviewxl3550.htm). A PolhemusTM Fastrak position tracking system was used to measure the position of the participant's head (http://www.polhemus.com), allowing the virtual scene to move as the participant did.

2.4. Intervention

Participants received 12 weekly 90-min VRE therapy sessions. For a full description of the treatment protocol, see Difede, Cukor, et al. (2014). In sessions 2–11 participants engaged in VRE, which consisted of narrating the details of their trauma in first-person present tense while immersed in a VR simulation of the WTC attacks. During VRE, participants wore a head-mounted VR helmet containing two miniature LCD computer screens in front of their eyes. The VR-WTC environment developed for the study consisted of 11 VR scenarios that gradually increased in detail and intensity to allow for graded hierarchical exposure. Participants were instructed to narrate their trauma aloud while progressing through this sequence of VR scenarios over the course of treatment. The therapist controlled what the patient experienced by using preprogrammed computer keys, allowing her to tailor the pace of treatment for each patient. The graded sequence of VR scenarios began with a jet flying over the WTC towers without crashing and normal city street sounds present. In each subsequent scenario, visual (e.g., hole in WTC tower, smoke), and auditory effects (e.g., explosion, screaming) were gradually added until the final scenario, in which the full sequence was depicted.

In session 5, the concept of cognitive distortions was introduced, and participants were provided with a list of cognitive distortions and helped to identify cognitive distortions in their thoughts. Beginning in session 5, participants were also taught how to challenge distorted cognitions using thought records and were asked to complete thought records identifying and challenging distorted thoughts for homework during the remainder of treatment. Participants were randomly assigned to take either 100 mg DCS or matching placebo capsules containing lactose 90 min prior to sessions 2–11.

2.5. Analytic approach

Participants contributed a maximum 12 weekly PCL and BDI scores for the analysis for a total of 280 observations (22 completers contributed 264 observations and 3 dropouts contributed 16 observations). This sample size provides sufficient power to estimate small time effects on changes in clinical outcomes in each group (VRE-DCS and VRE-Placebo) as well as explore mediational hypotheses (Diggle, Heagerty, Liang, & Zeger, 2002; Fritz & MacKinnon, 2007).

The temporal relationship between changes in posttraumatic and depressive symptoms was evaluated using two sets of mediation analyses for longitudinal mixed models (Kenny, Korchmaros, & Bolger, 2003). Specifically, we assessed the effects of 1) lagged PCL on BDI-II (Model 1), and 2) lagged BDI-II on PCL (Model 2 – reverse model) in each treatment group (VRE-DCS and VRE-Placebo). First, we established the shape of change (i.e., linear, quadratic) for each outcome variable, with time measured as session number. Next, in order to establish mediation we evaluated whether the following mediation criteria were met: 1) outcome variable was associated with time variable (total effect, Path C, coefficient β_C), 2) time variable was significantly associated with lagged mediator (Path A, coefficient β_A); 3) lagged mediator was significantly associated with outcome (Path B, coefficient β_B) after controlling for time; and 4) the relationship between outcome and time was significantly attenuated after controlling for lagged mediator (direct effect, Path C' coefficient $\beta_{C'}$; Fig. 1). Full mediation is established when coefficient $\beta_{C'}$ is attenuated, as compared to coefficient β_C, and no longer statistically significant. Partial mediation occurs when coefficient $\beta_{C'}$ is attenuated but still significant. The total mediation effect was computed as 100*(total effect-direct effect)/total effect (Kenny et al., 2003). In addition, in line with advances in mediation

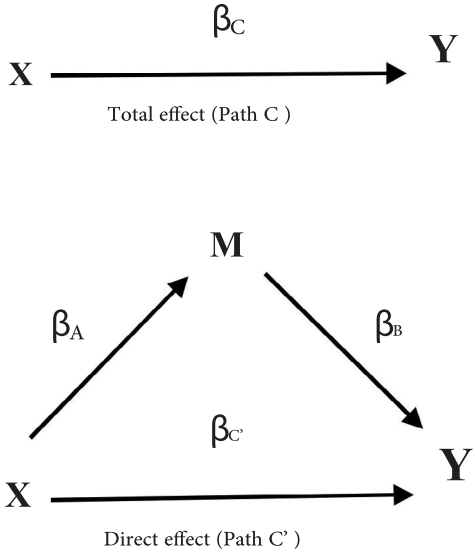

Fig. 1. Mediation models with lagged M as a mediator of the effect of X on Y. X denotes independent variable (time), M is the lagged mediator (Model 1: lagged PCL, Mod-el 2: lagged BDI-II), Y denotes outcome variable (Model 1: BDI-II, Model 2: PCL). Indirect effect is represented by $\beta_A * \beta_B$.

analysis, we assessed the significance of the indirect effect represented by $\beta_A * \beta_B$ using the distribution-of-the product method (Tofighi & MacKinnon, 2011). All models included random effects for intercept and slope and were estimated via restricted maximum likelihood method (REML) using SAS 9.2 software. Rmediation R package was used to compute 95% confidence intervals for the indirect effect. The analysis adhered to the intent-to-treat principle.

3. Results

3.1. Overall treatment effects in the VR-DCS and VR-Placebo groups

Results from the primary analysis of the effect of DCS on the efficacy of VRE therapy are reported elsewhere (Difede, Cukor, et al., 2014). Briefly, the difference between the VR-DCS and VR-Placebo groups in posttraumatic and depressive symptoms increased over time, with small-medium effect sizes at posttreatment (PCL: Hodge's d = 0.20; BDI-II: Hodge's d = 0.63), and large effect sizes at 6-month follow-up (PCL: Hodge's d = 1.19; BDI-II: Hodge's d = 1.62).

3.2. Mediational analysis of weekly posttraumatic and depressive symptoms (PCL and BDI-II)

The first set of analyses examined whether weekly lagged PCL scores predicted subsequent BDI-II scores (Model 1). There was a statistically significant linear effect of time on BDI-II scores in the VRE-DCS and VRE-Placebo groups indicating a significant decrease in depressive symptoms over the course of treatment (total effects, Paths C, VRE-DCS: $\beta_C = -0.84$, $p < 0.001$ and VRE-Placebo: $\beta_C = -0.43$, $p < 0.001$, Table 1). Likewise, time significantly predicted a decrease in lagged PCL scores in both groups (Paths A, VRE-DCS: $\beta_A = -1.58$, $p < 0.001$ and VRE-Placebo: $\beta_A = -1.51$, $p < 0.001$, respectively). Lastly, the effect of lagged PCL scores on BDI-II scores was statistically significant after controlling for the effect of time in the models (Paths B, VRE-DCS: $\beta_B = 0.25$, $p < 0.001$ and VRE-Placebo: $\beta_B = 0.11$, $p = 0.005$). 95% confidence intervals for indirect effects confirmed statistically significant indirect effect in both groups (VRE-DCS: $\beta_A * \beta_B = -0.40$, 95%CI [−0.61, −0.21] and VRE-Placebo: $\beta_A * \beta_B = -0.17$, 95%CI [−0.59, −0.32]). Percent mediation in the VRE-DCS group was 50.24, and 37.12 in the VRE-Placebo group. However, the direct effect (Paths C') remained statistically significant in the VRE-DCS group ($p = 0.033$) and marginally significant in the VRE-Placebo group ($p = 0.070$), indicating that posttraumatic symptoms partially mediated the relationship between time and depressive symptoms.

The analysis of the reverse model (Model 2) examined the effect of changes in depressive symptoms on subsequent changes in posttraumatic symptoms using the same analytic approach. In both groups, the effect of weekly lagged BDI-II scores on PCL scores was statistically significant after controlling for the effect of time (Paths B, VRE-DCS: $\beta_B = 0.39$, $p < 0.001$ and VRE-Placebo: $\beta_B = 0.36$, $p < 0.005$). Likewise, the indirect effects were statistically significant in both groups (VRE-DCS: $\beta_A * \beta_B = -0.30$, 95%CI [−0.52, −0.10] and VRE-Placebo: $\beta_A * \beta_B = -0.18$, 95%CI [−0.42, −0.02]). The direct effect (Paths C') remained statistically significant in the both the VRE-DCS and VRE-Placebo groups ($p < 0.001$). These findings revealed that BDI-II scores partially mediated the effect of time on PCL scores, however the effects were much smaller in both the VRE-DCS and VRE-Placebo groups (percent mediation was 17.86 and 10.86, respectively) as compared to the mediation effects of lagged PCL scores on BDI scores. This analysis suggests that session-to-session decreases in PCL scores led to subsequent decreases in BDI scores to a greater extent than the opposite, most strongly in the VRE-DCS group.

4. Discussion

The present study explored the temporal relationship between posttraumatic and depressive symptoms during VRE therapy. Meditation analyses revealed a reciprocal relationship between posttraumatic and depressive symptoms during VRE treatment. However, while changes in posttraumatic symptoms mediated 50.2% and 37.1% of changes in depressive symptoms in the DCS-enhanced and placebo groups, respectively, changes in depressive symptoms mediated only 17.9% and 10.9% of changes in posttraumatic symptoms in the DCS and placebo groups, respectively. This suggests that reductions in posttraumatic symptoms led to subsequent reductions in depressive symptoms to a greater extent than the converse. Thus, although we found evidence for a bidirectional relationship between posttraumatic and depressive symptoms, this pattern of findings suggests that VRE

Table 1
Mediation Analysis: posttraumatic and depressive symptoms (PCL and BDI-II).

	Outcome	Predictor	*β*	*SE β*	*t*	*p*	ES
VR-DCS							
Model 1							
Total effect (Path C)	BDI-II	Time	−0.84	0.20	−4.16	< 0.001	
Path A*r	Lagged PCL	Time	−1.58	0.25	−6.38	< 0.001	
Path B*r	BDI-II	Lagged PCL	0.25	0.05	5.56	< 0.001	
Direct effect (Path C')	BDI-II	Time	−0.42	0.20	−2.16	0.033	50.24
Model 2(reverse model)							
Total effect (Path C)	PCL	Time	−1.22	0.20	−4.16	< 0.001	
Path Ar	Lagged BDI-II	Time	−0.76	0.25	−6.38	< 0.001	
Path Br	PCL	Lagged BDI-II	0.39	0.05	5.56	< 0.001	
Direct effect (Path C')	PCL	Time	−1.00	0.20	−2.16	0.001	17.87
VR-Placebo							
Model 1							
Total effect (Path C)	BDI-II	Time	−0.43	0.15	−2.97	< 0.001	
Path A°	Lagged PCL	Time	−1.51	0.30	−5.13	< 0.001	
Path B°	BDI-II	Lagged PCL	0.11	0.04	2.85	0.005	
Direct effect (Path C')	BDI-II	Time	−0.27	0.15	−1.83	0.070	37.12
Model 2(reverse model)							
Total effect (Path C)	PCL	Time	−1.67	0.30	−5.66	< 0.001	
Path Ar°	Lagged BDI-II	Time	−0.51	0.22	−3.13	0.002	
Path Br°	PCL	Lagged BDI-II	0.36	0.12	2.98	0.003	
Direct effect (Path C')	PCL	Time	−1.49	0.29	−5.20	< 0.001	10.86

Note. Indirect effects, VRE-DCS: *Model 1: $\beta_A * \beta_B = -0.40$, 95%CI (−0.61, −0.21), *rModel 2(reverse model): $\beta_A * \beta_B = -0.30$, 95%CI (−0.52, −0.10); VRE-Placebo: ° Model 1: $\beta_A * \beta_B = -0.17$, 95%CI (−0.59, −0.32), r° Model 2(reverse model): $\beta_A * \beta_B = -0.18$, 95%CI (−0.42, −0.02).

primarily decreases posttraumatic symptoms, which in turn leads to decreased depressive symptoms.

Our findings are consistent with two previous studies examining posttraumatic and depressive symptom change during PE in youth (Aderka et al., 2011) and adults (Aderka et al., 2013). In the first of these studies, Aderka and colleagues found support for a reciprocal relationship between posttraumatic and depressive symptom change during PE in children and adolescents, although changes in posttraumatic symptoms influenced subsequent changes in depression more than vice versa (Aderka et al., 2011). In the second of these studies, the authors reported a similar pattern of findings in adults during PE, and a more reciprocal relationship between posttraumatic and depressive symptoms during PE with cognitive restructuring (Aderka et al., 2013). While both of these studies found that changes in posttraumatic symptoms fully mediated the effects of PE on depressive symptoms, the current study found evidence of partial mediation. Although largely speculative at this point, one possible explanation for this difference may be that the treatment protocol in the current study involved some elements of cognitive restructuring, whereas the PE treatment protocol in Aderka et al. (2011) and one of the PE protocols in Aderka et al. (2013) – PE without cognitive restructuring – did not involve these elements. Although more and larger studies are needed to replicate this finding, at least one prior study suggests that PE with cognitive restructuring results in a more reciprocal relationship between posttraumatic and depressive symptoms than PAderka et al. (2013) found that changes in posttraumatic symptoms fully mediated the effect of treatment on depressive symptoms in PE, whereas posttraumatic symptoms only partially mediated the effect of treatment on depressive symptoms in PE with cognitive restructuring. The authors suggested that change may occur through different mechanisms in PE and more cognitively-oriented treatments (Aderka et al., 2013). As this is only one study, more research is needed before firmer conclusions can be drawn about mechanisms of change in PE and more cognitively-based treatments. However, Aderka et al.'s (2013) suggestion is consistent with at least one prior study on the relationship between posttraumatic and depressive symptom change during CPT, a cognitively-based treatment, which found evidence of concurrent change in posttraumatic and depressive symptoms (Liverant et al., 2012), rather than a sequential relationship as has been reported in PE. Given that so few studies have examined relationships between posttraumatic and depressive symptom change in PE and more cognitively-oriented treatments, additional large-scale studies using the same meditational methods are essential in order to better understand whether, and if so, how, the relationship between posttraumatic and depressive symptoms differs between exposure and more cognitively-based treatments.

Although reductions in posttraumatic symptoms impacted changes in depressive symptoms more than the converse in both the DCS and placebo groups, effect sizes were smaller in the placebo group. The most likely explanation for this may be that in the parent RCT, Difede, Cukor, et al. (2014) found that the DCS group showed significantly greater improvement in PTSD and depression symptoms overall. Participants in the DCS group had significantly higher rates of remission from PTSD and significantly greater reduction in depression symptoms than did participants in the placebo group. Thus, the stronger effect we report here for the DCS group may simply reflect the fact that this group showed greater improvement in PTSD and depression symptoms in the parent study.

As Aderka and colleagues have noted, a pattern of findings in which reductions in posttraumatic symptoms lead to successive reductions in depressive symptoms is in keeping with a number of different theories regarding the link between anxiety and depression (Aderka et al., 2011; Aderka et al., 2013). Exposure therapies directly target avoidance of trauma-related cues through imaginal and in vivo exposure. As individuals begin re-engaging in previously avoided activities, they may experience increased enjoyment of activities and subsequent reductions in anhedonia and depressed mood (Aderka et al., 2011; Aderka et al., 2013) as occurs in behavioral activation (Nickerson et al., 2013). In turn, improvement in depressive symptoms may enable individuals to participate more fully in and derive greater benefit from therapy, thereby further reducing posttraumatic symptoms. This pattern is consistent with a vulnerability model of depression in which anhedonia plays a precipitating role in the development of depression (Loas, 1996), although our findings relate to improvements in depression rather than its onset, as in Loas' model.

Our findings also have clinical implications. In conjunction with previous research, the current study suggests that in the approximately half of individuals with PTSD who present with comorbid depression (Rytwinski et al., 2013), an initial treatment focus on PTSD may yield improvement in both PTSD and depression symptoms. Although a large body of research has shown that PE decreases posttraumatic and depressive symptoms across varied populations and settings (Harvey, Bryant, & Tarrier, 2003; Powers et al., 2010), understanding the relationship between posttraumatic and depressive symptoms during exposure therapy may offer insight into potential treatment mechanisms. For example, concurrent declines in posttraumatic and depressive symptoms over the course of VRE might suggest that VRE acts on a common posttraumatic/depressive factor, such as negative cognitions about oneself. Alternatively, a sequential relationship between PTSD and depression, such as that observed here, adds incrementally to the suggestion that exposure-based treatments, such as VRE, may primarily affect unique PTSD factors, such as fear, and that declines in fear may then lead to subsequent declines in common PTSD/depression factors, such as negative beliefs about oneself (Aderka et al., 2011; Aderka et al., 2013). This suggests that focusing on common PTSD/depression factors may not be necessary for depression to improve, and provides potentially meaningful information for clinicians struggling to decide on the best course of treatment for individuals with comorbid PTSD and depression. In order to determine the optimal course of treatment for patients with comorbid PTSD and MDD it would be necessary to compare patients with comorbid PTSD/MDD on their response to treatments targeting either PTSD (e.g., VRE) or MDD (e.g., CBT for depression) to investigate whether the extent of change in posttraumatic and depressive symptoms is similar across treatments.

Although we did not explore this, one theoretical model suggests that in order for fear to decrease, fear-relevant information associated with patient's memory of the traumatic event must be accessed so that new information can be incorporated into the trauma memory (Foa & Kozak, 1986). Treatments that are designed to engage the fear structure, such as PE or VRE for PTSD, are predicted to decrease fear. As fear declines, several theories offer explanations for how this reduction in fear may in turn lead to a reduction in depression. For example, according to the helplessness-hopelessness theory (Alloy, Kelly, Mineka, & Clements, 1990), as patients' fear and posttraumatic symptoms decrease in treatment and they are better able to handle situations and events, they may feel less helpless. Feeling less helpless and increasingly able to manage events may in turn reduce feelings of hopelessness or depression (Aderka et al., 2011; Aderka et al., 2013). While an MDD-focused treatment, such as CBT for depression, might target cognitions and some of the biological symptoms of MDD, it is not designed to engage the fear structure directly. Emotional processing theory (Foa & Kozak, 1986) posits that without directly engaging the fear structure there would not be an expected diminution in fear, and associated decrease in PTSD symptoms. Thus, for comorbid PTSD/MDD patients, it is possible that a treatment for depression that does not directly activate the fear structure may not result in as much of a decrease in PTSD symptoms as a PTSD-focused treatment does in depression symptoms; although empirical studies employing similar methodologies and analyses that compare treatments targeting either PTSD or MDD in comorbid patients are needed to determine this.

Several limitations of this study should be acknowledged. First, our sample was largely male. While previous research on PE has found similar relationships between posttraumatic and depressive symptoms in

female assault victims, it will be important to replicate the current findings using VRE in more diverse samples. Second, although effect sizes were moderate to large and multiple repeated observations were included, our sample size was relatively small. Given the small sample size and exploratory nature of the present study, future studies on VRE with larger samples are needed to support these findings. Nonetheless, every soundly constructed study has the potential to add incrementally to the knowledge base, increasing insight into patterns of symptoms change across treatment modalities and informing hypotheses regarding potential treatment mechanisms.

5. Conclusion

Despite these limitations, the present study adds to a growing literature suggesting that reductions in posttraumatic symptoms influence subsequent reductions in depressive symptoms to a larger extent than the converse during various forms of exposure therapy. Our findings suggest that VRE primarily targets posttraumatic symptoms, which in turn affects depressive symptoms. The current study explores the temporal relationship between posttraumatic and depressive symptoms during VRE, and extends prior research by suggesting that a similar pattern of symptom change occurs in VRE as has been observed in PE. From a clinical standpoint, our findings suggest that it may not be necessary to focus on common PTSD/depression factors for depression to improve, and that an initial treatment focus on PTSD may yield improvement in both PTSD and depression. Future research that examines patterns of symptom change during VRE may provide additional insight into mechanisms of change during VRE treatment for PTSD.

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