Choosing the right track: improving PTSD treatment outcomes for patients with childhood abuse-related posttraumatic stress disorder

Hoeboer, C.M.

Chapter 7

Temporal relationship between change in subjective distress and PTSD symptom decrease during prolonged exposure therapy for posttraumatic stress disorder

Published as: Hoeboer C.M., Oprel, D.A.C., Schoorl M., Van der Does A.W., Van Minnen A., & De Kleine, R.A (2021). Change in subjective distress as mechanism of change in prolonged exposure therapy for posttraumatic stress disorder. *Behavior therapy.*

Abstract

Objective: There is growing evidence that change in distress is an indicator of change during Prolonged Exposure (PE) for posttraumatic stress disorder (PTSD). However, temporal sequencing studies investigating whether change in distress precedes PTSD symptom decline are lacking. These studies are essential since the timeline between indicators of change and treatment outcome is a key assumption for mediation. The aim of the present study was to assess the temporal relationship between within- and between-session change in subjective distress and PTSD symptom decrease.

Method: We analyzed session data from 86 patients with PTSD. Data were analyzed using dynamic panel models. We distinguished temporal effects (within-persons) from averaged effects (between-persons).

Results: Results regarding the temporal effect showed that within-session change in subjective distress preceded PTSD symptom improvement while the reversed effect was absent. Averaged within-session change in subjective distress was also related to PTSD symptom improvement. Results regarding the temporal effect of between-session change in subjective distress showed that it did not precede PTSD symptom improvement. Averaged between-session change in subjective distress was related to PTSD symptom improvement.

Conclusions: This study provides evidence for within- but not between-session change in subjective distress as indicator of change during PE. We also found that the way of modeling potential indicators of change affects results and implications. We recommend future studies to analyze mediators during treatment using temporal rather than averaged effects.

Keywords: PTSD, prolonged exposure, working mechanism, change in distress, temporal sequencing, dynamic panel model

Introduction

Prolonged Exposure (PE) is a widely researched and effective psychotherapy for Posttraumatic Stress Disorder (PTSD), but remission rates leave ample room for improvement (Lee et al., 2016a; Mavranezouli et al., 2020; Watts et al., 2013). Investigating indicators of mechanisms of change, i.e. processes responsible for symptom change, will lead to a better understanding of the theoretical underpinnings of PE and may provide directions for further improvements (Kazdin, 2007; Kindt, 2014). Emotional Processing Theory (EPT) has long been the dominant theory on PE's mechanisms of change (Foa & Kozak, 1986). In short, EPT proposes that prolonged exposure to fear-evoking stimuli leads to emotional processing which in turn leads to symptom alleviation. Emotional processing is not directly measurable (Foa & McLean, 2016), but within-session change in subjective distress and between-session change in subjective distress are suggested to be indicators of change as they indicate emotional processing taking place (Foa & Kozak, 1986; Foa & McLean, 2016).

A large body of work supports the proposition that between-session change in subjective distress[2] is related to positive treatment outcome in patients with PTSD (e.g., Cooper et al., 2017a; see Table 1 for overview), although this work has also been criticized (e.g., Craske et al., 2008). Reasons for this criticism include limited use of complete session data - either by averaging session data or only considering the first and last sessions - and the categorization of outcome in (responder) categories which do not allow for a direct evaluation of the relationship between the indicators of change and outcome (Craske, et al., 2008). Moreover, given that many previous studies had small samples to begin with (see Table 1), results may be unreliable. Most studies found no evidence that within-session change in subjective distress and symptom improvement are related. But note, that these studies suffered from the same limitations as studies into between-session change in subjective distress. Importantly, nearly all of the previous studies considered the *averaged* effect of change in subjective distress (across individuals), referring to the relationship between averaged change in subjective distress across all sessions and treatment outcome. The *temporal effect* of change in subjective distress, referring to the relationship between change in subjective distress at timepoint X and outcome at timepoint X+1 within a person, has rarely been investigated (see Table 1). Temporal effects, however, are much more likely to reflect indicators of change than averaged effects, so the omission of temporal effects is problematic (Falkenstrom, Solomonov, & Rubel, 2020; Kazdin, 2007).

Establishing a timeline between an indicator of change and symptom change is in fact a crucial *prerequisite* for establishing mediation (Hayes, 2013; Kazdin, 2007; Kumpula et al., 2017) and the direction of the relationship between change in subjective distress and symptom change is as yet unclear. Previous results showing that averaged between-session change in subjective distress and symptom change are related may refer to three different

[2] Note that in previous work, the terms *habituation* or *extinction* have been interchangeably used to describe subjective change in distress levels during exposure sessions, while these terms actually refer to theoretically distinct mechanisms. To avoid theoretical confusion , we use the descriptive term change in subjective distress throughout this manuscript

associations: between-session change in subjective distress *precedes* symptom improvement, *co-occurs* with symptom improvement or *follows* symptom improvement. Only the first is relevant from the perspective of mechanisms of change. Secondly, temporal relations are clinically relevant as they provide information about change processes on an individual level. In contrast, averaged effects may be influenced by (unchangeable) covariates at the individual level and are therefore less informative for change processes. For example, patients with high intelligence might have more between-session change in subjective distress and more symptom improvement while these are temporally unrelated to each other. Thirdly, using temporal data has statistical advantages as it results in more power than averaged data and takes covariates at the person level into account. When averaged relationships are generalized to temporal relationships, these covariates may result in biased conclusions (Hamaker, 2012). For example, on average, a higher number of PE sessions might be related to worse treatment outcomes (between-persons). However, this might be due to covariates at the person level, e.g., persons who respond well may finish treatment early. If this averaged result is generalized to a temporal effect one might falsely conclude that providing more PE sessions to a patient leads to poorer treatment outcome.

Almost all studies on the effect of change in subjective distress as indicator of change during PE have used averaged-person data, raising doubts about the conclusions. The only exception is a study about the effect of within-session change in subjective distress on symptom change during D-cycloserine- versus placebo-enhanced PE (de Kleine, Smits, Hendriks, Becker, & van Minnen, 2015). This study is one of only two studies (de Kleine, Hendriks, Becker, Broekman, & van Minnen, 2017; de Kleine et al., 2015) that found a significant relationship between within-session change in subjective distress and PTSD symptom improvement. This raises the question whether earlier null-findings on the effect of within-session change in subjective distress on symptom change might be explained by the data-analytic strategy. Ideally, a study using temporal data would also report on averaged-person relationships as 'control analysis', as this allows a better comparison to previous findings in this field.

The aim of the current study was to investigate whether within- and between-session change in subjective distress is related to PTSD symptom improvement using temporal data. We studied the timeline between change in subjective distress and symptom improvement using dynamic panel models. These models allow for distinguishing temporal effects from averaged effects without violating assumptions (a problem with mixed-model analyses; see Allison, Williams, & Moral-Benito, 2017; Hamaker & Muthen, 2019; Leszczensky & Wolbring, 2019). Based on the premises of EPT, we expected change in subjective distress, both within- and between-sessions to predict next session change in PTSD symptoms. To test temporality, we reversed predictors and outcome, and expected that PTSD symptoms would not – or to a lesser extent – predict subsequent changes in subjective distress within- or between-sessions. To allow comparison with previous studies, we also assessed the averaged-person effect of change in subjective distress within- and between-sessions to elucidate whether

the use of temporal data leads to different results than the use of averaged data. Based on previous findings (Cooper et al., 2017a), we expected averaged change in subjective distress between-sessions, but not within-sessions, to predict PTSD symptom decrease.

Table 1. Evidence for the effect of within- and between-session change in distress as mediators of prolonged exposure

Study	Year	Sample size	Mechanism of change	Within person data mechanism	Within person data outcome	Within-session	Between-session
Norr et al.	2019	108	Within and Between	Not used	Not used	-	+/-
Reger et al.	2019	96	Between	Used	Not used	NA	+
Rauch et al.	2018	97	Within and Between	Used	Not used	-	+
Hendriks et al.	2018	69	Within and Between	Not used	Not used	-	+
Badour et al.	2017	46	Within and Between	Not used	Not used	-	+
De Kleine et al.	2017	50	Within and Between	Not used	Not used	+	+
Wisco et al.	2016	22	Between	Used	Not used	NA	+
Harned et al.	2015	16	Within and Between	Not used	Not used	-	+
Nacasch et al.	2015	39	Within and Between	Not used	Not used	-	+
Sripada et al.	2015	12	Within and Between	Used	Not used	-	+
De Kleine et al.	2015	67	Within and Between	Used[1]	Used[1]	+	+
Bluett et al.	2014	88	Between	Not used	Not used	NA	+
Gallagher et al.	2012	88	Between	Not used	Not used	NA	+
Van Minnen et al.	2006	92	Within and Between	Not used	Not used	-	+
Rauch et al.	2004	69	Between	Not used	Not used	NA	+
Van Minnen et al.	2002	34	Within and Between	Not used	Not used	-	+

[1]Used for within-session but not for between-session change in distress

NA = Not applicable; + = significant finding; - = non-significant finding; +/- = mixed finding

Method

Participants

We used the data from the IMPACT study (Oprel et al., 2018), a multicenter randomized controlled trial comparing PE with intensified PE (iPE) and phase-based treatment

compromising Skills Training in Affective and Interpersonal Regulation followed by PE (STAIR+PE). The trial is registered at the clinical trials registry, number NCT03194113. All participants (1) met DSM-5 diagnosis of PTSD established with the Clinician Administered PTSD Scale (CAPS-5) with moderate-severe PTSD-symptoms (CAPS-5 score ≥ 26) following repeated interpersonal childhood physical/sexual abuse by a primary caretaker or an authority figure and had at least one specific memory of the traumatic event (Boeschoten et al., 2015), (2) were between 18 and 65 years old and (3) spoke Dutch. Participants were excluded when they (1) were involved in a compensation case or legal procedures concerning admission or stay in The Netherlands, (2) were pregnant, (3) engaged in severe non-suicidal self-injury (NSSI) which required hospitalization during the past three months, (4) engaged in severe suicidal behavior defined by either a suicide attempt during the past three months or acute suicidal ideations with serious intent to die with a specific plan for suicide and preparatory acts, (5) had a severe disorder in the use of alcohol or drugs in the last three months according to the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), (6) suffered from cognitive impairment (estimated IQ < 70), (7) changed psychotropic medication in the two months prior to inclusion or (8) engaged in any current psychological treatment. Informed consent was obtained prior to randomization from all participants. For this article, we included participants from the exposure only conditions[3]: PE (n = 48) and iPE (n = 51). Patients also had to complete at least two PE sessions with measurements of subjective distress levels and PTSD symptoms, such that a timeline could be established (n_{PE} = 44, n_{iPE} = 42). Most patients were female (79%) and patients had an age between 20 and 60 years old (M = 36.8, SD = 11.5). Almost half (40%) of the patients had a non-western cultural background, 20 percent of the patients were highly educated (i.e. higher vocational education or university), 43 percent of the patients were employed and 51 percent of the patients used psychotropic medication. Patients suffered on average from 3.0 comorbid axis-1 diagnoses (*SD* = 1.9) in addition to the PTSD diagnosis and 47 percent of the patients suffered from severe suicidality according to the MINI (Sheehan et al., 1998). Moreover, 62 percent of the patients met criteria for a personality disorder according to the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-2; Weertman et al., 2003). We refer to the design paper for detailed information about the design, recruitment, participants, procedure or therapy (Oprel et al., 2018) and to the main outcome paper for detailed information about the study sample (Oprel et al., 2021). The study was approved by the Medical Ethical Committee of Leiden University Medical Center (NL57984.058.16).

Procedure

After enrollment, patients were randomized to PE, iPE and STAIR+PE (1:1:1 ratio) by an independent researcher based on a computerized randomization sequence of permutated blocks of six participants stratified by gender. Prolonged exposure (PE) was delivered in 16

[3]The STAIR+PE condition is excluded because it is based on the notion that skills training in the first phase of treatment will increase the tolerability of PE and therefore influences the proposed working mechanism of PE. This precludes conclusions about the working mechanism of PE.

weekly sessions of 90 minutes. Intensive prolonged exposure (iPE) was delivered in 14 sessions of 90 minutes starting with three weekly sessions for four weeks followed by two sessions after one and two months. For practical reasons, iPE was alternately provided by two therapists. The treatment manual of PE and iPE was identical and largely based on the protocol by Foa et al. (2007). The exposure sessions involved psychoeducation in the first session and 60 minutes imaginal exposure and exposure in vivo from the second session onwards. During imaginal exposure, patients were instructed to repeatedly and vividly recount the most disturbing traumatic memories. During exposure in vivo, patients repeatedly approached trauma-related stimuli. Between sessions, patients listened to recordings of the imaginal exposure and performed in-vivo homework assignments. For this paper, data from session 15 and 16 of the PE condition were omitted, because these sessions did not include sufficient observations. The exposure sessions involved psychoeducation in the first session, 60 minutes of imaginal exposure in the second session and 60 minutes of the imaginal exposure and within-session exposure in vivo from the third session onwards. observations for the temporal models (only 18 patients [21%] completed session 15 and 15 patients [17%] completed session 16).

Measures

Weekly changes in PTSD symptoms were assessed during every session of PE and during session 1, 4, 7, 10, 12, 13, and 14 of iPE. Subjective distress levels were assessed during in-session exposure, every session from the second session onwards.

Table 2. Descriptive information about mechanisms of change and outcome as a function of session

	PCL-5			Within-session change in distress			Between-session change in distress		
Session	N	M	SD	N	M	SD	N	M	SD
1	85	54.29	12.72						
2	43	55.93	12.59	86	25.48	23.82			
3	44	54.25	15.74	85	24.94	26.54	85	7.01	14.90
4	83	50.61	15.32	83	22.35	21.00	82	1.77	15.64
5	42	46.95	17.87	79	23.99	21.72	79	5.72	14.74
6	40	46.10	18.42	73	21.63	20.73	74	3.95	21.51
7	73	42.93	18.83	73	20.41	18.76	72	-0.10	16.90
8	35	38.03	21.71	69	18.96	17.63	68	2.81	17.77
9	33	34.94	21.17	64	18.91	19.51	66	2.18	16.28
10	66	36.50	20.42	64	21.20	21.67	63	-0.05	14.96
11	27	32.93	23.60	63	19.52	17.89	62	4.21	19.30
12	62	32.08	20.07	60	19.67	21.30	59	5.24	17.42
13	62	30.35	20.95	56	15.02	16.58	55	6.69	23.53
14	55	30.80	23.10	46	15.07	19.22	48	5.44	21.97

PCL-5 = PTSD checklist for DSM-5

PTSD symptoms

The primary outcome of this study was self-reported PTSD symptom severity measured with the weekly version of the PTSD checklist for DSM-5: PCL-5 (Blevins et al., 2015) . The PCL-5 consists of 20 items scored on a five-point Likert scale, ranging from 0 (not at all) to 4 (extremely), with total scores ranging from 0-80. The PCL-5 demonstrated high internal consistency in previous studies, high test-retest reliability and convergent and divergent validity with other measures (Blevins et al., 2015; Van Praag, Fardzadeh, Covic, Maas, & von Steinbuchel, 2020) and showed substantial agreement with a clinical interview for assessing PTSD in a Dutch population (van der Meer, Bakker, Schrieken, Hoofwijk, & Olff, 2017). The PCL-5 demonstrated high internal consistency in previous studies (Cronbach's α = .94; Blevins et al., 2015). In the current sample, the PCL-5 had a high internal consistency at the first session (Cronbach's α = .89). For the standard PE condition, data was available for 44 patients who completed on average 12.07 sessions (range 3-16, total sum of sessions = 531). The PCL-5 was assessed at the start of every session and completed in 98.5% of the sessions (n = 523). For the iPE condition, data was available for 42 patients who completed on average 12.83 sessions (range 4-14, total sum of sessions = 539). The PCL-5 was assessed at the start of session 1,4,7,10,12,13 and 14 (total sum of sessions with PCL-5 = 265) and completed in 97.7% of the sessions (n = 259).

Change in subjective distress within and between sessions

During the 60 minutes of imaginal exposure of PE (every session except the first session), participants' subjective distress was assessed with subjective units of distress (SUDs). Every 10 minutes, the participants rated their subjective distress on a scale from 0 (no distress) to 100 (maximum distress). The SUD peak was indicated by the highest subjective distress score within a session and SUD end was indicated by the last observed subjective distress score within a session. In line with EPT (Foa & McLean, 2016) and previous work (Harned et al., 2015; Hendriks et al., 2018; Nacasch et al., 2015), change in subjective distress within-session was indicated by the difference between the SUD peak and SUD end of a session. Change in subjective distress between sessions was indicated by the change in SUD peak ratings over two subsequent sessions. In 21 sessions (2.1% of the total exposure sessions) the therapist or patient refrained from performing any exposure in-session, so there was no SUDs data available for those sessions. Of all sessions wherein exposure took place for PE (n = 474), SUDs data were available for 96.0% (n=455) of the sessions. Of all sessions wherein exposure took place for iPE (n = 489), SUD data were available for 97.8% of the sessions (n= 478). For the temporal analyses, we used the data per session for within- and between-session change in subjective distress. For the averaged analyses, data of within- and between-session change in subjective distress was averaged over all sessions per person.

Statistical analyses

The data analysis plan was pre-registered at OSF (Center for Open Science; Hoeboer et al., 2020b). We used dynamic panel models based on maximum likelihood estimation (Allison et al., 2017) following recent recommendations for models with lagged dependent variables

(Falkenstrom et al., 2020; Xu, DeShon, & Dishop, 2019). Models were fitted using structural equation models (SEM) with R package Lavaan and dpm (Rosseel, 2012). In these models, results are corrected for stable, unobserved heterogeneity between persons and reverse causation (Allison et al., 2017). We corrected for the autoregressive effect of the outcome variable (the effect of the outcome at time point X-1 on the same outcome at time point X) and used cross-lagged effects of predictors (the effect of the predictor at time point X-1 on outcome at time point X). We used fixed effect models which included a random intercept that was allowed to correlate with predictors, thereby correcting for the effect of clustering without violating the assumption of independent errors. Missing data was handled using full information maximum likelihood (FIML). The temporal relationship between mediators and outcome is by default estimated with the fixed effect model of the dynamic panel model. We included bootstrapped standard errors in all analyses to account for violations to the normal distribution of the data. This was especially relevant for the analyses with change in subjective distress as dependent variable. The assumptions of all models were met.

Temporal analyses

In the first analysis, we assessed a dynamic panel model with the PCL-5 scores as dependent variable and with the autoregressive effect of the PCL-5 and cross-lagged *within*-session change in subjective distress as independent variables. For example, PCL-5 scores in session 4 were predicted by PCL-5 scores in session 3 and within-session change in subjective distress (SUD_{peak} -SUD_{end}) during session 3. In the iPE condition, participants had multiple sessions per week, while the PCL-5 was administered once per week. Therefore, only the SUDs data that was directly linked to PCL-5 assessment was used from this condition (e.g. session 3 included no PCL-5 score so within-session change in subjective distress from session 2 was not used).

In the second analysis, we assessed a dynamic panel model with PCL-5 scores as dependent variable and with the autoregressive effect of the PCL-5 and cross-lagged *between*-session change in subjective distress as independent variables. To illustrate, PCL-5 scores at session 4 were predicted by PCL-5 scores at session 3 and the change in peak distress between session 2 and 3 ($SUD_{peak\ session2} - SUD_{peak\ session3}$).

As the two exposure conditions differed in their delivery format (weekly vs. intensive) and the delivery format might affect change mechanisms, we ran two additional analyses to investigate the effect of condition on the relationship between change in distress and PCL-5 outcomes. These analyses were carried out using the same model as for the primary analyses, but additionally included condition (PE versus iPE) and the interaction effect between condition and mediators. If condition proved to affect outcomes, analyses were carried out per condition.

To test temporality, we next ran dynamic panel models testing effects in the opposite direction. In the third analysis, we included *within*-session change in subjective distress as dependent variable and the autoregressive effect of *within*-session change in subjective distress and cross-lagged change in PCL-5 scores as independent variables. In the fourth analysis, we included *between*-session change in subjective distress as dependent variable

and the autoregressive effect of *between*-session change in subjective distress and cross-lagged change in PCL-5 scores as independent variables.

Averaged analyses

To test whether using temporal data would lead to different results than using averaged-person data, we performed two analyses with averaged-person effects. The averaged-person effect was estimated using a fixed-effect model including person-averaged mediators. In the first analysis, we assessed a dynamic panel model with PCL-5 scores as dependent variable and with the autoregressive effect of PCL-5 scores and averaged change in subjective distress within-sessions as independent variables. In other words, we assessed the effect of the *average* change in subjective distress on PTSD symptom change over the course of treatment. In the second analysis, we assessed a dynamic panel model with PCL-5 score as dependent variable and with the autoregressive effect of PCL-5 scores and averaged change in subjective distress between sessions as independent variables.

Results

Fifty-five (64%) of the 86 patients who were included in this study completed fourteen sessions. The PCL-5 scores decreased during the course of treatment, from on average 54.24 (*SD* = 12.72) in the first session to on average 30.80 (*SD* = 23.10) in session fourteen. Within-session change in subjective distress showed a large variation between patients and was larger at the start of treatment ($M_{\text{session 2}}$ = 25.48; $SD_{\text{session 2}}$ = 23.82) compared to the end of treatment ($M_{\text{session 14}}$ = 15.07; $SD_{\text{session 14}}$ = 19.22). Between-session change in subjective distress also showed a large variation between patients without clear pattern over the course of treatment ($M_{session\ 3}$ = 7.01; $SD_{\text{session 3}}$ = 14.90 to $M_{session\ 14}$ = 5.44; $SD_{\text{session 14}}$ = 21.97; see Table 2 for more details).

Temporal analyses

We found that within-session change in subjective distress was significantly related to lower PTSD symptoms in the next session (i.e. the temporal effect): *b* = -.04, *SE* = .02, *z* = -2.17, *p* = .03, Cohen's *d* = .48, while correcting for the autoregressive effect of PTSD symptoms (see Table 3). This effect was not different for iPE compared to PE (*b* = .01, *SE* = .05, *z* = .27, *p* = .79). The reversed temporal effect of PTSD symptom change on next session's within-session change in subjective distress was not significant: *b* = -.08, *SE* = .09, *z* = -.85, *p* = .40, while correcting for the autoregressive effect of within-session change in subjective distress.

Table 3. Temporal effect of within-session change in subjective distress on next session's PTSD symptoms and reversed effect of PTSD symptom change on next session's within-session change in subjective distress

Temporal effects	Estimate	SE	*z*-value	*p*-value
Lagged within-session change in subjective distress	-.04	.02	-2.17	.03
Autoregressive effect PCL-5 score	.70	.06	12.37	< .001
Reversed effects				
Lagged change in PCL-5 score	-.08	.09	-.85	.40
Autoregressive effect within-session change in subjective distress	.11	.07	1.75	.08

PTSD = Posttraumatic Stress Disorder; PCL-5 = PTSD checklist for DSM-5

We found that between-session change in subjective distress was not significantly related to lower PTSD symptoms in the next session (i.e. the temporal effect): b = .003, SE = .02, z = .17, p = .86, while correcting for the autoregressive effect of PTSD symptoms (see Table 4). This effect was not different for iPE compared to PE (b = -.03, SE = .04, z = -.73, p = .47). The reversed temporal effect of PTSD symptom change on between-session change in subjective distress in the next session was also not significant b = .05, SE = .12, z = .39, p = .70, while correcting for the autoregressive effect of between-session change in subjective distress.

Table 4. Temporal effect of between-session change in subjective distress on next session's PTSD symptoms and reversed effect of PTSD symptom change on next session's between-session change in subjective distress

Temporal effects	Estimate	SE	*z*-value	*p*-value
Lagged between-session change in subjective distress	.003	.02	.17	.86
Autoregressive effect PCL-5 score	.66	.09	7.78	< .001
Reversed effects				
Lagged change in PCL-5 score	.05	.12	.39	.70
Autoregressive effect between-session change in subjective distress	-.41	.06	-7.56	< .001

PTSD = Posttraumatic Stress Disorder; PCL-5 = PTSD checklist for DSM-5

Averaged analyses

Averaged within-session (b = -.16, SE = .05, z = -3.06, p = .002, Cohen's d = .70) and between-session (b = -.53, SE = .20, z = -2.71, p = .007, Cohen's d = .61) change in subjective distress were both related to lower PTSD symptoms over the course of treatment while correcting for the autoregressive effect of PTSD symptoms.

Discussion

The main goal of this study was to test the effect of change in subjective distress during prolonged exposure (PE) therapy on PTSD symptom improvement using temporal analyses. The results indicated that within- and not between-session change in subjective distress preceded symptom improvement. These findings stand in contrast to the commonly expressed finding that between- and not within-session change in subjective distress is related to better treatment response (e.g., Asnaani, McLean, & Foa, 2016; Brown, Zandberg, & Foa, 2019; Cooper et al., 2017a; Foa & McLean, 2016). Importantly, in the current work we used a new-analytic framework (Allison et al., 2017) and distinguished temporal from averaged effects (Falkenstrom et al., 2020; Hamaker, 2012; Hamaker & Muthen, 2019) which probably explains the divergent findings.

Our first hypothesis, that within-session change in subjective distress would predict change in PTSD symptoms to the next session, was confirmed. Crucially, we did not find the reversed effect. Our findings thus point to within-session change in subjective distress as an indicator of change during PE, as it precedes and predicts symptom improvement (Kazdin, 2007). This finding is in line with EPT, but stands in contrast with most previous studies that examined the effect of within-session subjective change in distress on PE outcome (see Table 1). Notably, these studies used data-analytic strategies which only considered averaged effects. The only other study using temporal data for both within-session change in subjective distress and PTSD symptom change during PE found similar results (de Kleine et al., 2015). Our findings imply that within-session reduction of subjective distress precedes PTSD symptom change during PE. This is of clinical relevance, as in-session indices of change can guide clinicians in their implementation of PE.

In contrast to our expectations, we found that *averaged* within-session change in subjective distress was also related to change in PTSD symptoms. This is remarkable as the data-analytic strategy for this analysis was in line with earlier work, yet leading to a different outcome. Our finding implies that those with, on average, more within-session change in subjective distress showed more change in PTSD symptoms. One important factor that might explain our divergent findings is a difference in statistical power. Notably, about half of the previous studies that assessed within-session change in distress included small sample sizes with less than 40 patients (Harned et al., 2015; Jaycox et al., 1998; Nacasch et al., 2015; Sripada & Rauch, 2015; van Minnen & Hagenaars, 2002). Moreover, these studies mostly defined outcome as a pre-post difference rather than utilizing the repeated measurements per patient (resulting in far less power; e.g., Morgan & Case, 2013), Therefore, these studies lacked adequate power resulting in increased false positive and false negative findings (see for rationale: Button et al., 2013). In line, a recent meta-analysis on change in subjective distress on symptom improvement during PE concluded that there was insufficient power to establish the effect of within-session change in subjective distress on outcome (Rupp, Doebler, Ehring, & Vossbeck-Elsebusch, 2017).

Our second hypothesis, that between-session change in subjective distress predicts change in PTSD symptoms in the next session, was not confirmed, nor did we find the

reversed effect. This finding contradicts previous studies that consistently found between-session change in subjective distress to be related to PTSD symptom change (see Table 1). However, this difference might be explained by our different data-analytic method. Previous studies did not use temporal analyses but assessed averaged effects. Indeed, in line with previous work, we found that averaged between-session change in subjective distress predicted change in PTSD symptoms. As these analyses omit the temporal relationship between indicators of change and outcome, this relationship might be driven by a third factor related to both the indicator of change and outcome (i.e., personal characteristics such as learning ability) or time-congruency of both factors. The latter would imply that between-session change in distress might be a *proxy* of treatment response, rather than an indicator of change (Cooper et al., 2017a). To conclude, our results indicate that between-session reduction in distress does not precede PTSD symptom decline. These results are supported by previous work that showed that patients without between-session change in distress also improved over the course of treatment (e.g., Bluett et al., 2014).

This is the first temporal sequencing study about within- and between-session change in subjective distress as indicators of change during PE. Although temporal precedence is a key assumption which is often overlooked when studying change processes (Kazdin, 2007), it does not in itself suggest a mechanistic relationship. To establish mechanisms of change additional evidence is required such as experimental evidence of cause (see Tryon, 2018). Note that our results also do not imply that within-session reduction of subjective distress is the only indicator of change during PE, as it is likely that multiple change mechanisms explain treatment outcome (Kredlow, de Voogd, & Phelps, 2020; Vervliet, Craske, & Hermans, 2013). Based on novel insights from emotional learning research, the inhibitory learning theory (ILT; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014) postulates that the learning and retrieval of inhibitory non-threat associations is crucially important for successful treatment outcome. Both EPT and ILT are rooted in extinction theory and partially overlap in theoretical mechanisms (Cooper et al., 2017a), but the theories differ with respect to their view on distress reduction as an index of meaningful change. In short, ILT proposes that distress reduction may be a by-product of inhibitory learning. ILT proposes new indices of meaningful change during exposure therapy such as expectancy violation or enhanced tolerance of distress (Bluett et al., 2014; Craske et al., 2008; Knowles & Olatunji, 2019; Sripada, Rauch, & Liberzon, 2016). Future studies might test whether these indices also precede and fuel PTSD symptom decrease, and how they relate to distress reduction. Moreover, EPT also proposes other indices of emotional processing such as emotional engagement. Strong empirical evidence for the relevance of emotional engagement is lacking (Cooper et al., 2017a), but so are temporal studies assessing its relevance. Thus, future studies might also examine such indices with temporal models.

An already previously established indicator of change during PE is the reduction of maladaptive trauma-related cognitions (Cooper et al., 2017a). In studies focusing on trauma-related cognitions (e.g. “the world is dangerous” or “I have no future”), mixed-effect models including temporal data have already been successfully used to establish the timeline

between these cognitions and PTSD symptom improvement (Cooper, Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2017c; Kumpula et al., 2017; Zalta et al., 2014). Changes in trauma-related cognitions were found to be related to symptom improvement during PE and to precede symptom improvement. Our current findings add to these findings as within-session change in subjective distress also predicted and preceded symptom improvement during PE. An important next step is to test several indicators of change simultaneously in one model, to better understand how they (interactively) lead to symptom PTSD change. In light of the recent developments in the availability of statistical algorithms to adequately model temporal data and lagged effects (e.g. using dynamic panel models; Rosseel, 2012), we also urge future studies into mechanisms of change to take temporality into account and distinguish averaged relationships (between-persons) from temporal relationships (within-persons). Note that already collected data might also be re-analyzed using temporal sequencing models to improve understanding about within- and between-session change in subjective distress as indicators of change during PE. Future studies might also consider the use of experience sample and ecological momentary assessments to establish a timeline between indicators of change and symptom change more precisely (see for example: Padovano & Miranda, 2018).

The current study has several limitations. Firstly, the intensified PE condition in our study did not have session data available for every exposure session and included only fourteen PE sessions. This resulted in less temporal precision in this condition, less data and consequently less power. Secondly, the panel data in our study was unbalanced due to missing data which is inherent to clinical trials but reduces statistical power (Moral-Benito, Allison, & Williams, 2019). This was especially problematic for session 15 and 16 of the PE condition which were therefore omitted for the analyses. Related to this, the current sample size did not allow for assessing multiple indicators of change in one dynamic panel model. Future studies may consider including other relevant predictors of symptom improvement in dynamic panel models such as homework adherence (Cooper et al., 2017b). Finally, the assessment method of change in distress in the current study (subjective self-reportage) differs from methods used in controlled laboratory research on underlying mechanisms of fear extinction which commonly include physiological indicators of distress (Carpenter, Pinaire, & Hofmann, 2019). Physiological measures of distress might, therefore, be an important additional indicator of change in distress and have already been shown to relate to treatment response in previous research (Wangelin & Tuerk, 2015).

To conclude, we found that within, but not between-session change in subjective distress predicted next session's change in PTSD symptoms using temporal data. Against contemporary belief, these results indicate that within-session change in subjective distress is an indicator of change during PE. This suggests that within-session change in subjective distress could be used to monitor treatment progress. Since this is the first study to investigate temporal relationships between change in subjective distress and PTSD symptom change, more research is needed to replicate these findings.