Journal of Affective Disorders 338 (2023) 163–170

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Therapists' oxytocin response mediates the association between patients' negative emotions and psychotherapy outcomes

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ARTICLE INFO

Keywords:
Negative emotions
Oxytocin
Depression
Attachment

ABSTRACT

Background: Existing literature suggests that patients' experiences of emotions, especially negative emotions, predict outcomes in psychotherapies for major depressive disorder. However, the specific mechanisms underlying this effect remain unclear. Based on studies pointing to the role of oxytocin (OT) in attachment relationships, we proposed and tested a mediation model where the therapists' hormonal responses, as represented by increases in their OT levels, mediates the association between negative emotions and symptomatic change.
Method: OT saliva samples (pre- and post-session, $N = 435$) were collected on a fixed schedule over 16 sessions from the therapists of 62 patients receiving psychotherapy for major depression. The Hamilton Rating Scale for Depression was administered to the patients before the sessions, and the patients reported their in-session emotions after the sessions.
Results: The findings support the proposed within-person mediation model: (a) higher levels of negative emotions in patients predicted greater increases in therapist OT levels pre- to post-session throughout treatment; (b) greater OT levels in therapists, in turn, predicted reduction in patients' depressive symptoms on the subsequent assessment; and (c) the therapists' OT levels significantly mediated the association between patients' negative emotions and reduction in their depressive symptoms.
Limitations: This design precluded establishing a time sequence between patients' negative emotions and therapists' OT; thus, causality could not be inferred.
Conclusion: These findings point to a possible biological mechanism underlying the effects of patients' experiences of negative emotions on treatment outcomes. The findings suggest that therapists' OT responses could potentially serve as a biomarker of an effective therapeutic processes.

1. Introduction

Major Depressive Disorder (MDD), a severe emotional disorder, is a leading cause of disability worldwide (World Health Organization, 2020). The treatment of Major Depressive Disorder (MDD) is effective for only about 50 % of all patients (Cuijpers et al., 2014, 2019). This underscores the need to improve current treatment by better identifying the mechanisms responsible for therapeutic change in MDD (Kazdin, 2007). Negative emotions are central to understanding the mechanisms underlying depression and its treatment (Rottenberg, 2017). Most psychotherapy models emphasize the importance of experiencing and exploring negative emotions within sessions. For example, one of the primary goals of psychodynamic approaches is to experience previously avoided affective experiences and adaptively express them within an interpersonal context (Svartberg et al., 2004; Whelton, 2004).

Accumulating evidence on treatment for MMD has shown that greater experiences of emotions, and specifically negative emotions, predict better treatment outcomes (Fisher et al., 2016; Pascual-Leone and Greenberg, 2007; Town et al., 2017; Town et al., 2022). A recent meta-analysis reported significant medium-to-large effect size between patients' emotional expressions and outcomes (Peluso and Freund, 2018). Kramer and colleagues found that depressed patients who

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https://doi.org/10.1016/j.jad.2023.06.013
Received 28 December 2022; Received in revised form 18 May 2023; Accepted 4 June 2023
Available online 7 June 2023

experienced negative emotions, and specifically grief, during psychodynamic treatment sessions had better treatment outcomes (Kramer et al., 2015). However, the specific mechanisms that underlie the effectiveness of experiencing negative emotions remain unclear.

Several theories attempt to account for the *intrapersonal* mechanisms underlying the beneficial effects of experiencing negative emotions, but have neglected the possible *interpersonal* mechanisms. Three of the most commonly described theories are inhibition theory, exposure theory, and cognitive processing accounts. For example, according to Exposure Theory (Bootzin, 1997), when patients repeatedly confront their negative experiences throughout treatment, this repetition and exposure eventually lead to a reduction in the intensity of these emotions through habituation. Support for this theoretical assumption derives mostly from studies on expressive writing in which depressed patients who were asked to write about their negative experiences showed a greater decrease in their depressive symptoms compared to participants who were asked to write about a neutral topic (e.g., Frattaroli, 2006; Reinhold et al., 2018). However, given that, unlike writing tasks, emotions in psychotherapy arise within the interpersonal therapeutic encounter, it is imperative to investigate the potential interpersonal mechanisms of change in the treatment of depression.

From an evolutionary perspective, negative emotions are thought to have been designed to impel people to seek help from others and to signal others that one is in need for help (Nesse, 2000; Plutchik, 2001). This view is congruent with the Behavioral Systems Theory (Mikulincer and Shaver, 2003) which posits that when people experience negative emotions, their relationship partners (parents, the romantic partner, etc.) often respond by activating the caregiving system, which prompts them to provide support and comfort. For example, a crying infant alerts parents to the needs of the infant and elicits parental proximity and caregiving (Zeifman, 2001). According to the biobehavioral model, the activation of the caregiving system manifests in biological changes in the caregiver in response to the other's distress through increased release of Oxytocin (OT). These biological changes increase the probability of providing care and support to the other (Bornstein, 2013; Feldman, 2012). This may suggest that an increase in the release of OT could potentially serve as a biomarker for the activation of the caregiving system and for caregiving behavior in therapists as well.

Previous studies have confirmed that OT is a key component enhancing caregiving responsiveness and empathy (e.g., Strathearn, 2011; Swain et al., 2012). For example, OT promotes responsiveness to infant crying by increasing activation in brain regions involved in empathy (Naber et al., 2010; Riem et al., 2011; Swain et al., 2012). This responsiveness to the expressed distress has a positive long-lasting impact on well-being (Leerkes et al., 2009; McElwain and Booth-LaForce, 2006; Zeifman, 2001).

In psychotherapy, therapists' caregiver responses within the therapeutic dyad have been conceptualized as curative as well (Bowlby, 1988; Wiseman and Egozi, 2021). This conceptualization suggests that similar to the parent-infant relationship, therapists respond to patients' negative emotions by an activation of the caregiver system, as manifested in OT reactivity, and that this type of response may enhance treatment outcomes (Wiseman and Egozi, 2021). Indeed, the therapists' behavioral responsiveness to patients' needs is crucial to improving treatment outcomes, just as it is important to the infant-parent relationship (Wu and Levitt, 2020). However, whereas studies have investigated the effects of parents' hormonal responses, the possible effects of therapists' hormonal responses on treatment outcomes remain understudied.

Recent studies have shown that not only behavior but also physiology, and specifically hormonal responses play a crucial role in therapeutic change (Fischer and Zilcha-Mano, 2022). However, most studies on the role of OT in psychotherapy have focused exclusively on patients' OT and have neglected the possible influence of therapists' OT on therapeutic processes and change. One exception is a recent study which found that OT synchrony between patients and therapists was associated with more effective treatment (Zilcha-Mano et al., 2021a). This finding highlights the potential role of therapists' OT in psychotherapy. However, the extent to which therapists' OT is related to better treatment outcomes and whether therapists' OT responses are triggered by patients' emotions require further elucidation.

The present study was designed to explore the biological mechanisms underlying the association between patients' in-session negative emotions and treatment outcomes. Specifically, we tested whether therapists' OT responses would mediate the association between patients' negative emotions and treatment outcomes. We focused on the OT response as a biomarker of an interpersonal mechanism given the vast literature pointing to its primary role in the activation of the caregiving system, and in increasing empathy and caregiving behavior in response to others' distress and negative emotions (Barchi-Ferreira and Osório, 2021; Gangestad, 2016; Swain et al., 2012).

We analyzed a mediation model with the following hypothesized pathways:

1. Higher levels of negative emotions in patients predict higher post-session increases in therapists' OT (controlling for pre-session OT).
2. Higher OT levels in therapists predict decreased subsequent depression severity.
3. Therapists' post-session OT levels mediate the association between negative affect and depression severity throughout treatment.

2. Method

2.1. Participants

The initial sample was composed of 83 patients enrolled in a 16-session manualized psychotherapy for MDD, as part of a rigorously conducted randomized control trial (RCT) comparing supportive and supportive-expressive (SE) treatment (Zilcha-Mano et al., 2021b). The inclusion criteria for participating in the RCT were: (a) MDD diagnosis, based on structured clinical interviews for DSM–5, with scores above 14 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) on two evaluations, 1 week apart, and current MDD, based on the MINI (International Neuropsychiatric Interview; Sheehan et al., 1998); (b) if on medication, patients' dosage had to be stable for at least 3 months prior to the start of the study, and they needed to be willing to maintain a stable dosage for the duration of treatment; (c) aged 18 to 60; (d) Hebrew language fluency; (e) provision of written informed consent. Exclusion criteria were (a) current risk of suicide or self-harm (HRSD suicide item>2); (b) current substance abuse disorder; (c) current or past schizophrenia or psychosis, bipolar disorder, or severe eating disorder, requiring medical monitoring; (d) history of organic mental disease; (e) currently in psychotherapy. The study was approved by the associated institutional review board, and all patients gave their informed consent in writing before screening. The mean age was 31.2 (SD = 8.63); 51 participants were female and 34 of the dyads were same sex (41 %). Fifty-six patients (67.5 %) had a comorbid anxiety disorder, including generalized anxiety disorder (62.3 %), social anxiety (31.9 %), agoraphobia (20.2 %), and panic disorder (2.9 %). Of the patients, 10.1 % had a posttraumatic stress disorder, and 5.8 % an obsessive-compulsive disorder. The patients' mean levels on the17-item HRSD at intake was 21.41 (SD = 3.76). Six treating psychotherapists, with a mean of 14.41 years of experience, participated in this study.

2.2. Treatment

Patients received 16 sessions (50-min per session) of Supportive-Expressive treatment (Luborsky, 1984; Luborsky et al., 1995), a time-limited psychodynamic therapy adapted for depression, either in an expressive-focused condition (including the use of expressive techniques such as interpretation, confrontation, clarification), or a supportive-focused condition (including the use of supportive techniques, such as

affirmation and empathic validation). For the expressive-focused condition, the Luborsky (1984) and Luborsky et al. (1995) manualized treatment was used. The supportive condition included all supportive techniques detailed in the manual used by Luborsky (1984) and Luborsky et al. (1995), but prohibited the use of any expressive techniques, as detailed in Leibovich et al. (2018).

To evaluate the therapists' competence and adherence to the treatment approach, four trained PhD/MA clinical psychology students coded video recordings of the therapy sessions using the Penn Adherence-Competence Scale (PACS; Barber and Critis-Christoph, 1996). The PACS has three subscales: general therapeutic behavior (ICC = 0.71 for amount and ICC = 0.76 for quality), the supportive component (ICC = 0.86 for amount and ICC = 0.83 for quality), and the expressive component (ICC = 0.91 for amount and ICC = 0.83 for quality). A total of 161 sessions were coded (80 SET and 81 ST), and the interrater reliability was assessed using a two-way mixed ANOVA with absolute agreement (Shrout and Fleiss, 1979).

2.3. Procedure and materials

The study procedure is depicted in Fig. 1. OT saliva levels were assessed at eight time points during the therapeutic process, before and after sessions 4, 8, 12, and 16. Salivary OT measurements are minimally intrusive and therefore well-suited for psychotherapy research. This technique has been validated in various contexts and found to be interrelated with OT levels in plasma (Feldman et al., 2011). The participants were requested to avoid eating and drinking (other than water) for 30 min before arrival, and to rinse their mouth 10 min before saliva collection. They were also asked to avoid romantic or intimate contact for 30 min before arrival. The evaluator assessing weekly depression symptoms also collected the OT samples. Both the evaluator and the therapist wore gloves during saliva collection. Saliva was obtained by asking the participants to chew on a roll-shaped saliva collector for 2 min to stimulate salivation until the roll became saturated. No social interaction or communication took place during saliva collection. The roll-shaped saliva collector was checked visually for blood. The samples were stored in a freezer at −20 °C and analyzed in batches. All samples were analyzed by RIAgnosis (RIA; Munich, Germany). The RIA analysis method does not use plates. The concentrations of salivary OT were computed using radioimmunoassay (de Jong et al., 2015). Intra- and inter- assay variabilities of <10 % were assessed; the detection limit ranged from 0.1 pg to 0.5 pg, depending on the age of the 125I-labeled tracer.

A total of 435 OT samples collected from the therapists of 62 patients were used in the analyses, so that for most therapists, four timepoints were collected, with two samples collected at each time point (pre- and post-session samples). There were 12.2 % missing observations. OT samples were not collected from 21 patients because their treatment was conducted remotely due to the COVID-19 pandemic.

2.3.1. Positive and Negative Affect Scale (PANAS; Watson et al., 1988)

To assess the patients' retrospective reports on their negative emotions during the therapy sessions, we administered the Negative Affect subscale of the PANAS. The PANAS is a self-report questionnaire consisting of 20 items, 10 of which assess the subjective experience of positive affect (PA; e.g., interested, enthusiastic, active) and 10 assess the subjective experience of negative affect (NA; e.g., irritable, upset, scared). Patients were asked to rate the extent to which they experienced each of these emotions *during the session*. Items were rated on a scale from 1 (very low or not at all) to 5 (very much). A mean negative emotion score was calculated for each session throughout treatment. The internal reliability range for NA was 0.81–0.87.

2.3.2. Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960)

To assess symptomatic change, the HRSD, a semi-structured clinical interview administered at baseline and before each session was conducted. The HRSD assesses the severity of depression in patients diagnosed with a depressive disorder. It contains 21 ratings measured on three-point (0 to 2) or five-point (0 to 4) scales. The first 17 items are used for scoring the instrument, whereas the final four items provide more details on the clinical characteristics of the depression. The total score consists of the sum of the responses, and ranges from 0 to 52 points, with higher scores corresponding to greater severity of depression. This measure has good psychometric properties, with a Cronbach alpha between 0.76 and 0.95 (Trajković et al., 2011).

2.3.3. Data availability statement

The study analysis code is available at: https://osf.io/6qspk/. When this study was carried out, the informed consent form for the participants stated that we would keep the data strictly confidential and would not be shared. Therefore, the data are not available.

2.4. Statistical analysis

To test whether post-session therapist OT levels mediated the association between negative affect and depression severity (HRSD score), we compared the fit of two models: a random-intercept cross panel model (RI-CLPM; Falkenström et al., 2022; Hamaker et al., 2015) and a latent curve model with structured residuals (LCM-SR; Curran et al., 2014). These models are similar in many respects. Both models allow testing for temporal precedence through the inclusion of autoregressive and cross-lagged parameters, and they also separate stable between-person differences from within-person fluctuations. However, the LCM-SR, in addition to the random intercept factors, includes slope factors that detrend the observed means. The need for detrending has elicited recent debate (Falkenström et al., 2017). Detrending is considered more robust against unobserved confounding factors, at the same time, it can potentially reduce the ability to detect significant effects (Falkenström et al., 2017). Thus, to enhance the robustness of our findings, we opted to replicate the results using both approaches.

The random intercept in the RI-CLPM represents the between-person variance in the means. The within-person deviation scores are latent variables defined by the time-specific residuals from the between-person model. In the model, this was done by fixing the factor loading of the random intercepts to 1. That is, similar to person-mean centering in multilevel modeling, the RI-CLPM estimates cross-lagged coefficients among within-person deviations from each person's mean over their own time-series. In contrast, due to the inclusion of a random slope factor centered on the first measurement occasion, the random intercept in the LCM-SR represents the between-patient variation in initial levels. The random slope represents the between-person variation in the long-term trajectory of change. The within-person deviation scores are latent

Fig. 1. Study procedures for the pre- and post-session measurements across sessions.

variables defined by the time-specific residuals from each person's average trajectory over time. In the model, this was done by setting the factor loadings of the random slope to a sequence of linearly increasing values (0,1,2,3) which represent the slope of the linear function of time in the model. This modeling approach is depicted graphically in Fig. 2. The corresponding factor represents the linear change in the variables over time: for every one unit increase in time, the predicted value of the variable increases by the value of the slope. That is, similar to detrending in multilevel modeling, LCM-SR estimates whether an individual's level on a specific construct (such as depression) at a particular time is above or below what is anticipated based on this person's underlying trajectory. Thus, LCM-SR is a more conservative model that has a greater potential for causal interpretation since it accounts for confounders that are stable over time or cause linear (or non-linear) slopes over time. Studies have shown that therapist effects are unlikely to affect within-patient fluctuations in these models. Hence, we did not model them explicitly in this study (Falkenström et al., 2020a).

Our models included the same-session paths between negative affect and OT levels (path a), the time-lagged association between post-session OT levels and depression severity (path b), as well as the association between negative affect and subsequent depression severity (path c). We tested the mediation model by estimating the within-patient effects in the direct effect (path c'; negative affect predicting depression) and the indirect effect (the product of coefficients a × b, with OT mediating the affect-depression association). We also included the pre-session OT, centered around the mean as an exogenous variable in the model. Using model selection procedures commonly applied in mechanisms of change research, we made a series of modifications to the model by gradually relaxing stationarity assumptions and tested whether this would result in improved model fit (Falkenström et al., 2020b, 2022). Specifically, to calculate the mediation model path, we constrained paths a, b, and c to be equal over time. The other paths were left constrained to equality over time unless freely estimating the separate coefficients for each time point improved model fit. We calculated the 95 % confidence intervals with 1000 bootstrap samples to test the significance of mediation.

We handled missing data by basing estimates on all available information (i.e., intent to treat analysis), using Full Maximum Likelihood Estimation with robust standard errors. A model is considered to be well-fitting if the following are found to be present: a Chi-square test with a non-significant *p*-value (e.g., $p > .05$), along with Comparative Fit Index (CFI) values close to or above 0.95 and Root Mean Square Error of Approximation (RMSEA) values close to or below 0.06. We then calculated the Swain correction for Chi-square model fit in small samples (Herzog and Boomsma, 2009). Analyses were conducted in Mplus version 9 (Muthen & Muthen, Los Angeles, CA, USA); Swain correction was calculated in Stata v. 17 (StataCorp, 2019).

3. Results

Table 1 presents the means, variances, score range and distribution of the variables. Since both models produced similar pattern of results, and the LCM-SR is considered more robust against unobserved confounding factors, we only report the results of the LCM-SR. The results of the RI-CLPM are reported in the supplement.

We estimated a null LCM-SR model, which assumes complete stationarity except for the means, which are specified as person-specific

Table 1
Descriptive statistics for patients' and therapists' variables.

	N	M	SD	Min	Max	Skewness	Kurtosis
NA4	83	17.06	5.71	10	38	1.12	1.32
NA8	79	16.01	5.75	10	35	1.30	1.37
NA12	72	15.36	5.43	10	34	1.21	1.05
NA16	68	14.09	5.13	10	38	2.31	6.55
Post-session OT4	62	11.05	2.93	2.3	20	0.24	1.77
Post-session OT8	58	10.89	2.34	1.6	19.1	−0.06	4.75
Post-session OT12	50	11.01	2.48	5.5	19.2	0.88	1.78
Post-session OT16	47	11.41	2.21	8.3	17.4	1.04	0.67
HRSD4	82	19.80	8.63	3	38	0.11	−1.03
HRSD8	79	16.39	8.33	1	35	0.32	−0.43
HRSD12	72	14.33	8.33	1	37	0.40	−0.53
HRSD16	68	10.48	6.98	0	30	0.75	−0.03

Note. NA= Negative affect; OT = Oxytocin; HRSD=Hamilton Rating Scale for Depression. The numerical value at the end of the label for each row indicates the week.

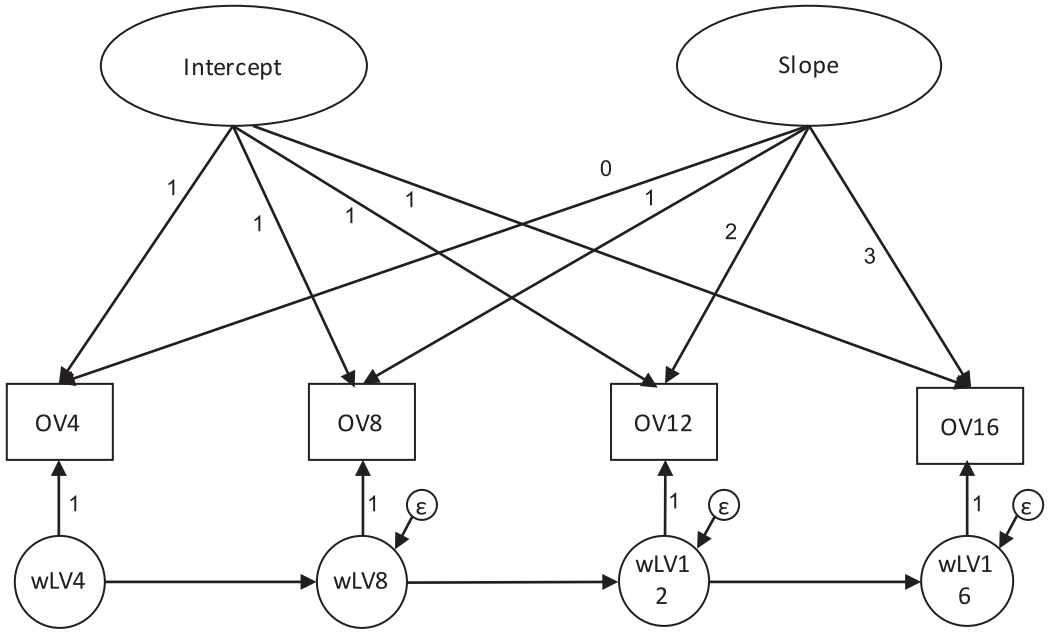

Fig. 2. Representation of the latent variables in the model. OV = Observed Variable; wOV = within-patient level latent variable. The random intercepts defined by factor loadings fixed at 1 to extract stable between-person differences. The factor loadings of the random slopes were set to 0,1,2,3 to extract each individual's linear trajectory. The within-patient scores are the latent variables defined by the time-specific residuals from the between-person model.

trajectories at the between-person level. This model fit was low ($\chi 2$ (93) = 117.0, p = .05; RMSEA = 0.06; CFI = 0.92; AIC = 5438.36). We then performed a series of model modifications to optimize the fit of the model to the data. Removing the HRSD predicting next session NA, and pre-session OT predicting next session HRSD improved the model fit. In addition, because of the negative variance of the slope of OT, we excluded it from the final model. This exclusion was consistent with our theoretical model in which we assumed a temporal increase in OT but not a gradual change over time. The fit of the final model was good ($\chi 2$ (97) = 108.70, p = .20; RMSEA = 0.04; CFI = 0.96; AIC = 5420.11). Higher negative emotions, as reported by the patients, predicted higher therapist OT levels on the post-session assessment, when controlling for the pre-session OT (a path: 0.11, SE = 0.05, p = .03, 95 % CI = [0.003, 0.20]). Higher therapist OT levels predicted lower depression severity in the next session (b path: -0.97, SE = 0.34, p = .005, 95 % CI = [−1.57, −0.22]). Finally, whereas the direct effect was nonsignificant (c path:0.03 SE = 0.27, p = .91, 95 % CI = [−0.60, 0.37]), the indirect effect was significant (c' path:-0.11, 95 % CI = [−0.24, −0.001]; see Fig. 3). We repeated the analysis, but this time incorporating the treatment group into the model. Including the treatment group either dramatically reduced model fit or resulted in a non-converging model due to the sparse data when adding more parameters. Thus, we did not include treatment in our final models.

4. Discussion

This is the first study to test therapists' hormonal response as a possible biomarker of an *interpersonal* mechanism through which patients' negative emotions during therapy lead to symptomatic improvement. The results indicated that an increase in therapists' OT mediated the association between patients' negative emotions and improved depression severity. Given the well-documented role of OT in close relationships and interpersonal interactions (romantic partner: e.g., Algoe et al., 2017; parent-infant: e.g., Feldman et al., 2011), these findings hint that therapists' OT response may serve as an interpersonal route by which negative emotions lead to therapeutic change. These results also support the potential evolutionary function of negative emotions in signaling need for help (Nesse, 2000), by suggesting that this signaling may be reciprocated by OT release and caregiving behavior within the therapeutic context.

Consistent with the first hypothesis, the results showed that in sessions in which the patients reported experiencing more negative emotions, there was a greater increase in their therapists' OT levels. This result is congruent with previous reports suggesting that caregivers' OT levels increase when they are involved in attachment interactions (e.g., Feldman et al., 2011; Strathearn, 2011). Given the role of the therapists as an attachment figure (Mikulincer et al., 2013), this finding may suggest that the therapists' caregiving system was activated in response to their patients' distress. This finding is also aligned with previous work showing an increase in parents' OT levels in response to infant cues of distress in a healthy population (Galbally et al., 2011; Naber et al., 2010). In contrast, depressed mothers with neglecting parenting behaviors tended to have deficits in their OT release in response to their infants' distress (Feldman, 2017; Strathearn, 2011). Therefore, an increase in therapists' OT in response to patients' negative emotions may be a biomarker of the activation of the therapists' caregiving system signaling the emergence of a good, healthy therapeutic interaction.

Consistent with the second hypothesis, an increase in the therapists' OT from the beginning to the end of one session predicted lower depressive symptoms in later sessions throughout treatment. One possible explanation for this finding is that OT may facilitate responsiveness, empathy, and more attuned behavior toward the patient. All these behaviors were found to be related to better treatment outcomes (Atzil-Slonim et al., 2019; Elliott et al., 2018; Håvås et al., 2015). Support for this explanation comes from a recent review of 44 studies on the relationship between empathy and OT which found that an increase in OT release over time, but not OT baseline levels, was associated with greater empathy (Barchi-Ferreira and Osório, 2021). Similarly, previous studies have found that increased parents' OT levels were significantly related to more affectionate contact behaviors and greater responsiveness in their interactions with their infant (Scatliffe et al., 2019) and infants' secure attachment (Kohlhoff et al., 2022).

The significant mediation effect suggests that therapists' hormonal response to patients' negative emotions had a positive effect on treatment outcomes. Previous studies have found that therapists' cognitive and emotional response to patients' emotions during treatment was related to outcomes (Kimerling et al., 2000; Ogrodniczuk et al., 2008). The results of the current study suggest that in addition to the therapists' emotional involvement, their physiological responses may also have played a role in the therapeutic process and should be further studied. Thus, this study is one of the first to suggest that biological measures may serve as precise markers of interpersonal processes that mediate treatment response in psychotherapy. At the same time, the nonsignificant direct association between negative emotions and outcome may imply that merely experiencing negative emotions during a session is not beneficial in and of itself, but rather than its effect on treatment outcomes depends on the therapists' responses to these emotions. This explanation is in line with the literature on interpersonal emotion regulation which emphasizes the undeniable influence of others on the ways in which people are able to experience, express, and regulate their own emotions (Hofmann, 2014; Zaki and Williams, 2013; Beckes and Coan, 2011). Previous studies have suggested that healthy close relationships promote emotion-regulation and that these processes are instantiated across multiple channels, including biological and physiological channels (e.g., Helm et al., 2014; Saxbe et al., 2018).

4.1. Limitation and future directions

This study was limited by the study design and the procedures. First, OT was sampled in peripheral fluids (saliva). Second, while this is one of the largest samples of OT in the psychotherapy literature to date, the sample size still limited our statistical power. In addition, our design precluded establishing a time sequence between patients' negative emotions and OT reactivity. Therefore, it remains unclear whether negative emotions preceded OT reactivity or whether the therapists' empathy or other behaviors related to OT could have facilitated the patients' ability to feel safe to experience negative emotions. Currently, there is no technology that can continuously measure change in OT without interrupting the therapeutic encounter. However, future studies could code negative emotions at the beginning of each session, which would strengthen the assumption that negative emotions trigger therapists' OT and not the reverse. This study was also limited by the use of post-session retrospective self- reports to measure negative emotions. In addition to the bias that may result from a retrospective perspective, this measure focuses on patients' experience rather than the expression of negative emotions. Previous studies using the same self-report (PANAS) measure have found that therapists accurately tracked their patients' emotions (Atzil-Slonim et al., 2019), which may suggest that therapists are sufficiently sensitive to patients' cues. Nevertheless, future studies should replicate these findings with a more objective measure that assesses patients' emotions continuously throughout the session.

Finally, we did not include treatment group in our final models and thus are unable to draw conclusions on potential differences in the role of oxycontin in specific treatments. However, since one treatment (i.e. supportive expressive) is an augmentation condition and not distinct from the other treatment (i.e. supportive only), we did not expect treatment differences. In fact, we would predict that the supportive techniques, present in both conditions, would be linked to oxytocin levels. Further, in an exploratory analysis, adding treatment to our models reduced fit dramatically. Future studies with larger samples can explore this issue further. Despite these limitations, the use of a different perspective (self-report, objective physiology, and clinical interview) for

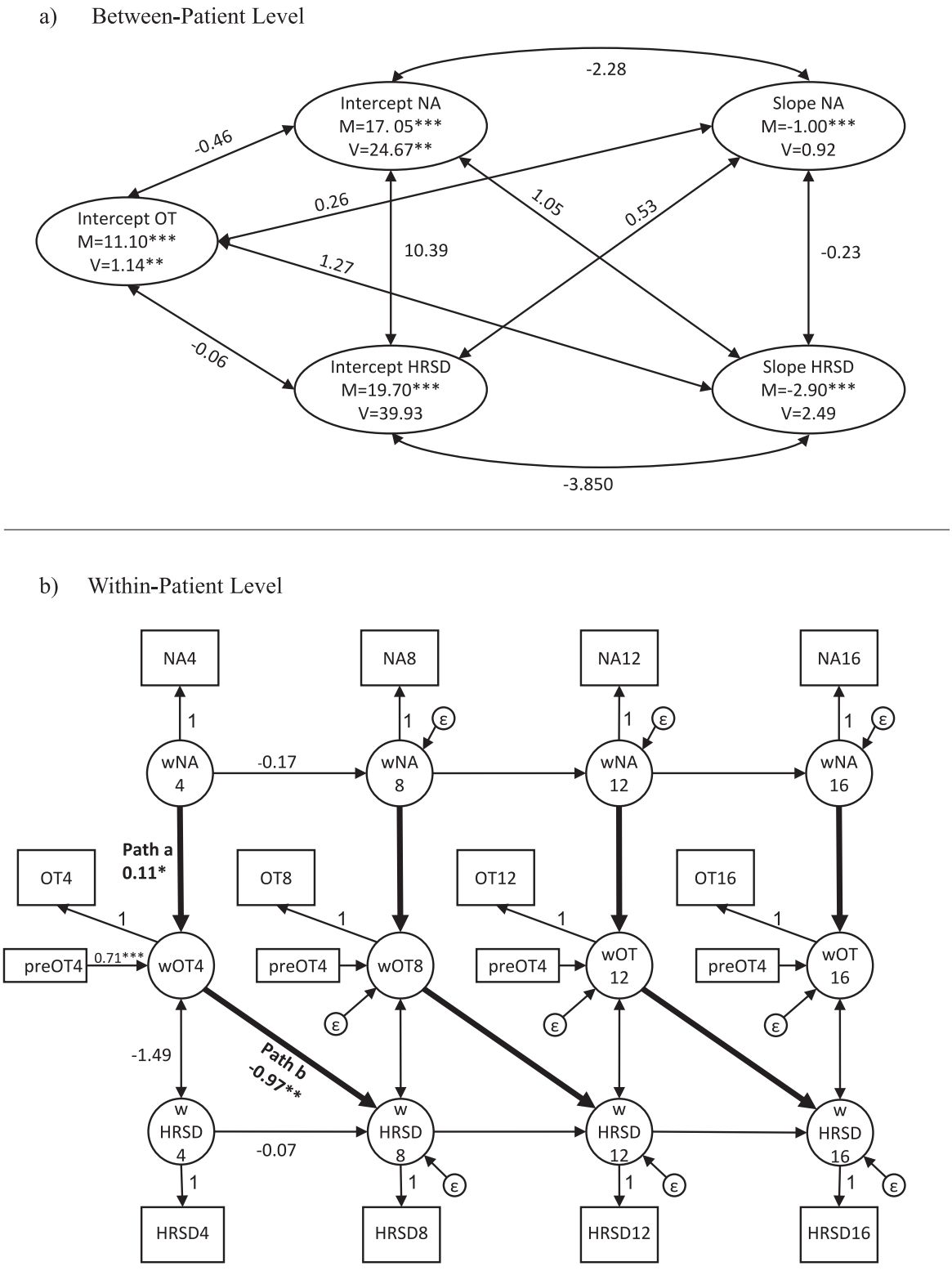

Fig. 3. Latent Curve Model with Structured Residuals (LCM-SR, Curran et al., 2014). Panel a- between-patient effects; Panel b- within-patient effects. The between and within effects were evaluated within the same model, but are depicted separately to simplify the presentation. NA = Negative affect; OT = Oxytocin; HRSD=Hamilton Rating Scale for Depression. The epsilons represent the residuals corresponding to each observed variable and that they are referred to as measurement errors. The following paths were included in the model, but are not presented in the graph: (1) path c: negative emotions predicting next session depressive symptoms, NA(t)→HRSD(t + 1), constrained to equality over time; (2) depressive symptoms predicting next session negative emotions, HRSD(t)→NA(t + 1) (3) pre-session OT predicting same session NA, preOT(t)→NA(t), constrained to equality over time; (4) pre-session OT predicting next session HRSD, preOT(t)→HRSD(t); (5) covariance between same-session NA and HRSD, NA(t) ←→ HRSD(t), constrained to equality over time.

each variable in the current study is also its strength.

Future studies should expand the findings by exploring the ways by which increases in therapists' OT affect treatment outcomes. In addition to its possible effect on promoting caregiving behavior, the effect of therapists' OT may also be related to its role in facilitating a similar increase in patients' OT. Previous studies have found that infants' OT reactivity during an interaction was correlated with their parents' OT reactivity; that is, infants whose parents exhibited higher OT also showed a similar increase in OT (Feldman, 2017; Feldman et al., 2010). Similarly, Zilcha-Mano et al. (2021b) reported that patient-therapist OT synchrony was related to a decrease in next session depressive symptoms. Atzil-Slonim et al. (2022) found that patient OT reactivity was associated with a decrease in next session symptoms. Thus, the therapists' increase in OT level may "pull" the patients' OT, such that the biological synchrony as well as the patients' increase in OT may have positive results in terms of symptom decrease. More research is needed to elucidate the role of therapists' OT and the various ways it affects treatment outcomes.

4.2. Conclusion

The current study contributes to the growing body of literature showing that therapists' and not only patients' physiological changes enter into the therapeutic process (Atzil-Slonim et al., 2022; Levi et al., 2021; Zilcha-Mano et al., 2021b). The model examined in the current study was based on the parent-infant relationship literature, and the findings are consistent with these works. This lends support to the claim that parental and therapist-patient attachment share some underlying mechanisms that are mediated by the oxytocinergic system. Findings of this study constitutes an important step forward by suggesting that therapists' OT response can be seen as an interpersonal mechanism by which experiencing negative emotions can contribute to decrease in patients' depression.

Funding

The study was supported by a grant from the Israeli Science Foundation (Grant 186/15).

CRediT authorship contribution statement

Hadar Fisher: Conceptualization, Writing – original draft, Formal analysis, Visualization, Writing – review & editing. **Nili Solomonov:** Formal analysis, Methodology, Writing – review & editing. **Fredrik Falkenström:** Formal analysis, Methodology, Writing – review & editing. **Ben Shahar:** Conceptualization, Methodology, Validation, Writing – review & editing. **Simon Shamay-Tsoory:** Conceptualization, Methodology, Validation, Writing – review & editing. **Sigal Zilcha-Mano:** Resources, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors have no competing interests to report.

Data availability

When this research was carried out, the informed consent form for the participants stated that we would keep the data strictly confidential and would not be shared. Therefore, the data are not available.

Acknowledgments

The authors thank all participants in this study. We also are grateful to all of our research collaborators.

Ethics approval

The study was conducted in accordance with APA ethical standards and was approved by the University of Haifa ethical committee (approval number: 118/15, Date: 10/10/2015).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.013.

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