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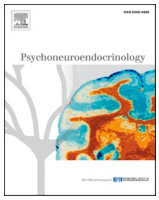

Cortisol interdependence during psychotherapy in major depressive disorder

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ABSTRACT

The current study explored cortisol interdependence between patients and therapists during psychotherapy, the possible moderating effect of patient alliance ratings on this interdependence, and the associations between cortisol interdependence and treatment outcome. While cortisol interdependence was explored in other interpersonal contexts, its presence in psychotherapy has remained unexplored. We hypothesized that (a) patients' and therapists' cortisol levels at pre-session will predict their own and their partner's subsequent cortisol levels at post-session, (b) patient ratings of their relationship with their therapists will moderate these partner effects, and (c) cortisol interdependence will be associated with better treatment outcome. Fifty dyads undergoing 16 weeks of psychodynamic treatment for major depressive disorder participated in this study. Patient-therapist salivary cortisol samples were collected at eight time points, alongside a post-session patient-rated alliance questionnaire and a symptom severity interview. For analyses we employed the actor-partner interdependence model. Results revealed that (a) patients' and therapists' cortisol levels before sessions predicted their own post-session cortisol changes. However, significant cortisol interdependence was observed in patients' pre-session cortisol levels predicting therapists' post-session cortisol levels. Furthermore, (b) poorer alliance ratings associated with more pronounced cortisol interdependence, and (c) in dyads where patient pre-session cortisol predicted therapist's post-session cortisol, a better treatment outcome was found. This study found novel evidence of cortisol interdependence in psychotherapy and is partially in line with other studies inspecting cortisol interdependence in adjacent research fields. These findings emphasize the intricate psychophysiological interactions within therapeutic relationships and their associations with treatment outcome.

1. Introduction

Arousal levels in psychotherapeutic interventions, defined as activation and readiness of physiological and psychological systems (Pfaff, 2006), have been widely studied (Yalom et al., 1977; Lane et al., 2015). Recent studies emphasize a two-person perspective in psychotherapy, focusing on interdependence of arousal between patients and therapists (Aron and Lechich, 2012; Kivlighan et al., 2014), revealing their mutual influence (Bryan et al., 2018; Wieder and Wiltshire, 2020). Cortisol, a common marker for arousal, has been investigated in interdependence research mainly in parent-child and romantic partner relationships (Bernard et al., 2017; Liu et al., 2013). However, little is known about patient-therapist cortisol interdependence during therapy sessions. The present study seeks to shed light on whether such interdependence exists, focuses on one potential moderator of it, and explores whether cortisol interdependence associates with treatment outcome.

Exploring cortisol interdependence in psychotherapy holds promise. Cortisol's secretion in response to social stress (Dickerson and Kemeny, 2004) and emotional arousal (Wieder and Wiltshire, 2020), common in psychotherapeutic contexts, highlights its regulatory roles (Harrewijn et al., 2020). Studies emphasize cortisol's robust predictive power for interpersonal linkage, making it a relevant measure between patients

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and therapists (Timmons et al., 2015). Given that psychotherapy fundamentally revolves around interpersonal relationships, these findings underscore the relevance of employing cortisol as an arousal measure, especially in the context of Major Depressive Disorder (MDD). Recognizing the global impact of MDD (Gutiérrez-Rojas et al., 2020), studies aim to identify factors improving treatment outcomes. Studies investigating cortisol in psychotherapy for MDD, focusing on individual levels, found increased cortisol levels in MDD (Marx et al., 2023) predicting unfavorable outcomes (Fischer et al., 2017). Notably, studies point at cortisol decrease as a possible product of therapy sessions for patients (Kim et al., 2009;Erbay et al., 2018)) and therapists (Miller et al., 2010; Schumacher et al., 2014). Despite accumulating individual-level findings, a gap exists in understanding cortisol dynamics at the two-person level in psychotherapy. Theories for a two-person approach highlight the mutual influence between patients and therapists in creating therapeutic change (Mitchell and Aron, 1999; Aron, 2013). While no studies have explored cortisol interdependence in psychotherapy, research in developmental psychology and interpersonal settings offers valuable insights.

Studies investigated the existence of cortisol interdependence between parents and their children, or between romantic partners. Most findings support the existence of such interdependence, so that one person's cortisol levels predict the other person's subsequent cortisol levels, and vice versa ((Ludmer) Nofech-Mozes et al., 2020; Meyer and Sledge, 2020). However, variability in the level of interdependence was found between studies. For example, some studies found that only one person's cortisol levels predicted the subsequent cortisol levels of the other's, but not the other way around (Bernard et al., 2017; Bader et al., 2021). Due to heterogeneous findings in the literature, many studies turned to exploring constructs that may explain variability in cortisol interdependence. Research on cortisol interdependence suggests that the parent-child relationship's quality may explain variability in interdependence, with lower relationship quality correlating with increased cortisol interdependence (Borelli et al., 2019; Hibel et al., 2019). Similarly in romantic relationships, a systematic review by Meyer and Sledge (2020) highlights ten studies focusing on relationship quality as a moderator for cortisol interdependence. These studies demonstrated a negative association between romantic partners' relationship quality and cortisol interdependence.

To date, no studies have investigated the existence of cortisol interdependence in psychotherapy. However, accumulating findings support patient-therapist interdependence on other constructs, mainly of self-report measures. Previous research suggests that patients and therapists are interdependent on their reported alliance strength (Kivlighan et al., 2014; Li, 2022). There are also a few studies examining patient-therapist interdependence based on measures other than self-report, including acoustic markers (Wieder and Wiltshire, 2020; Soma et al., 2020), which support the existence of patient-therapist interdependence in their arousal levels. Yet, little is known about the interdependence between patients and therapists in their cortisol levels, ands its associations with relationship quality or treatment outcome.

This study's overarching goal was to verify its conceptual model regarding patient-therapist cortisol interdependence. This study's conceptual framework (Fig. 1) is based on cortisol as a marker of the individual's arousal level (Thorn et al., 2009; Miller et al., 2015), and interdependence as reflecting arousal regulation between partners (Wieder and Wiltshire, 2020; Meyer and Sledge, 2020). This study's first goal was to explore cortisol interdependence between patients and therapists, utilizing the Actor Partner Interdependence Model (APIM; Kenny et al., 2006). The APIM allows to examine associations between individuals' independent variables and their dependent variables (actor effects), as well as associations between individuals' independent variables and the dependent variables of their interactional partners (partner effects). Building on research utilizing the APIM and its associated interpersonal moderating factors, this study's second goal was to investigate whether patient ratings of their relationship with their

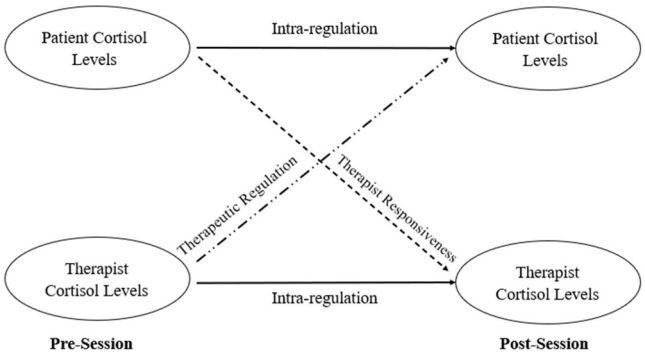

Fig. 1. *Conceptual Model – Intra- and Interpersonal Cortisol Changes and Associated Clinical Impact During a Psychotherapy Session. Note.* Continuous line – Intrapersonal changes in cortisol levels from pre- to post session. Intrapersonal changes represent intra-regulation dynamics within individuals. Dashed line – Interpersonal changes in cortisol concentrations, where patient pre-session cortisol levels associate with post-session subsequent cortisol levels of therapists. This interpersonal and interdependent cortisol change represent the therapist's responsiveness to the patient's arousal. Dashed-Dotted line – Interpersonal changes in cortisol concentrations, where therapist pre-session cortisol levels associate with post-session subsequent cortisol levels of patients. This interpersonal and interdependent cortisol change represent the therapeutic regulation that therapists provide for the patient's arousal. The presence of a partner effect denotes dyadic arousal regulation, while the absence of a partner effect, coupled with only actor effects, indicates the absence of dyadic arousal regulation. We hypothesize that the less patients were affected by their therapists or by therapy (actor effect; patients will be predictive of their own cortisol levels throughout treatment), a worse treatment outcome will be observed. We also hypothesize that the more therapists will be affected by the patient's cortisol levels (partner effect; therapist's responsiveness to patient cortisol levels), a better treatment outcome will be observed (Kramer and Stiles, 2015; Watson et al., 2020).

therapists moderate their cortisol interdependence. This moderation refers to how much the patient views their relationship with their therapists as meaningful. A gold-standard measure for patient-therapist relationship quality is the Working Alliance Inventory (Horvath and Greenberg, 1989). Based on findings concerning treatment outcomes and interdependence dynamics (Kivlighan et al., 2015; Laws et al., 2017), and cortisol levels (Fischer et al., 2017), this study's third goal was to explore whether cortisol interdependence associates with treatment outcome. Treatment outcome was assessed using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). We hypothesize that (a) patients' and therapists' cortisol levels at pre-session will predict their own (actor effects) and their partner's (partner effect) subsequent cortisol levels at post-session, (b) patient ratings of their relationship with their therapists will moderate partner effects, competing hypotheses exist on the direction of this moderation. One hypothesis, aligned with developmental and interpersonal studies, suggests that lower relationship ratings lead to increased cortisol interdependence. Conversely, psychotherapy studies propose that higher relationship ratings will result in heightened cortisol interdependence (Wiltshire et al., 2020). We also hypothesize that (c) better treatment outcome will be associated with increased partner effects (Fig. 1). To address these goals, the study utilized data collected from a randomized controlled trial (Zilcha-Mano et al., 2018; Zilcha-Mano et al., 2021) involving psychotherapy for MDD.

2. Material and Methods

2.1. Participants

The RCT recruited one hundred patients with MDD through advertisements offering free treatment for depression. The protocol for collecting saliva samples was implemented after the trial had already

started, so fifty patients were not sampled. The data from the remaining fifty patients was used in this study. Inclusion criteria were (a) meeting MDD diagnostic criteria according to structured clinical interviews for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), scores above 14 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1967) at two evaluations occurring one week apart, and current MDD episode as measured by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998); (b) any medication taken by patients had to be dosage-stable for at least three months before entering the study, and patients had to be willing to maintain a stable dosage throughout treatment; (c) age between 18 and 65 years old; (d) Hebrew language fluency; and (e) provision of written informed consent. Exclusion criteria were (a) current or past risk of suicide or self-harm (HRSD suicide item >2); (b) current substance abuse disorder; (c) current or past diagnosis of schizophrenia or psychosis, bipolar disorder, or severe eating disorder requiring medical intervention; (d) history of organic mental or bodily disease; and (e) participating in psychotherapy at present or during the last three months. Patients were enrolled in 16-session manualized psychotherapy for MDD, as part of a randomized controlled trial (Zilcha-Mano et al., 2018; Zilcha-Mano et al., 2021). All fifty patients included in the study completed the 16-session manualized psychotherapy provided as a part of the RCT. The study was approved by the relevant Institutional Review Board, and informed consent was obtained from all participants involved in the study. Each patient received 16 50-minute-long therapeutic sessions that occurred at a fixed time and day of the week. The mean patient age was 31.50 (SD = 7.88), and 31 patients were women (62%). At intake, four patients were using anti-depressant medication throughout treatment, maintaining a stable dosage.

2.2. Therapists and Treatments

Seven therapists, all with formal training in psychodynamic treatment and at least five years of experience participated in the current study. Therapists received individual and group supervision both while training and during the active phase of the RCTs. Overall, therapists had an average age of 39.60 (SD = 5.87) and an average of 11.10 years of clinical experience (SD = 5.95). Six of the therapists were women (86%). Therapists provided 16, 50-minute-long sessions of short-term psychodynamic psychotherapy treatment.

2.3. Procedure and Measures

2.3.1. Salivary Cortisol

Patients and therapists were asked to refrain from eating, drinking (other than water), smoking, and having intimate contact with others (for example, hugging) for at least 30 min before the saliva sample procedure. A total of 800 saliva samples, collected from patients and their therapists, were used in the analyses. Samples were taken from patients and therapists at treatment sessions 4, 8, 12, and 16. At a fixed time of the day per dyad, two samples were collected in each treatment session, 30 min before therapy and immediately after session completion (pre-session and post-session). Participants were asked to place cotton swabs in their mouths, provided in Sarstedt Salivette® (Nümbrecht, Germany) containers, for 2 min. Participants were asked to report in an online questionnaire about possible factors that may affect cortisol levels at the time the sample was taken (e.g., medication use, alcohol or drug consumption, menstrual cycle phase, contraceptive use). Saliva samples were stored at − 20 oC until analysis. Samples were delivered in dry ice, under temperature control maintenance, to the daacro GmbH & Co. KG lab, University of Trier, Trier, Germany, where they were thawed, vortexed, and analyzed in duplicates to assure the reliability of results. Sample intra- and inter-assay coefficients of variance (CV) were calculated. Inter-assay CVs of less than 15% are generally acceptable (Hanneman et al., 2011). Our sample yielded mean inter-assay CVs of 6.8%.

2.3.2. Working Alliance Inventory

The therapeutic alliance was assessed using the self-report Working Alliance Inventory (WAI; Horvath and Greenberg, 1989; Tracey and Kokotovic, 1989). The WAI consists of 12 items rated on a 7-point Likert scale ranging from 1 (Never) to 7 (Always). WAI was answered at post-session by patients, (Immediately after patients provided post-session saliva samples), and a mean score was calculated for each session throughout treatment. The internal reliability range for the WAI throughout the treatment was .98–.95. For the analyses, WAI scores were used in congruence with cortisol sampling time points, at sessions 4, 8, 12, and 16.

2.3.3. Hamilton Rating Scale for Depression

Patients' depression level (clinical outcome) throughout treatment was assessed using the Hamilton Rating Scale for Depression (Hamilton, 1967). Depression symptoms were assessed using 24 items, each ranked between 0 (Symptom not present) to either 2 or 4 (Symptom is causing distress and is present) on a Likert scale. HRSD scores range from 0 to 52. Scores of 19 and higher were indicative of severe depression, scores of 14–18 of moderate depression, scores of 13–8 of mild depression, and scores of 7 and below of normal symptoms or clinical remission (Anderson et al., 2010). We employed the first 17 items used for analysis because they constitute a gold standard for clinical trials for psychotherapies for depression (Cusin et al., 2010). HRSD was administered weekly, evaluators were advanced undergraduate, graduate, and PhD students in clinical psychology. All evaluators were extensively trained and were found to be reliable in the use of the HRSD, the reliability of the trained evaluators was evaluated weekly. HRSD Inter-judge reliability was .98 (Calculated as two-way mixed with absolute agreement; Shrout and Fleiss, 1979). For this analysis, HRSD score change slopes were calculated (separately for each patient) between intake and all treatment sessions, indicating the degree of change in depressive symptoms. Higher slope scores represent a steeper slope, indicative of greater HRSD score changes across treatment, associated with symptomatic improvement. Lower slope scores indicate a flatter slope, indicative of lesser HRSD score changes across treatment, associated with little symptomatic improvement.

2.4. Statistical Analysis Overview

2.4.1. Actor Partner Interdependence Model (APIM)

The data were hierarchically nested on three levels: assessments nested within patients and nested within therapists. To keep only within-dyad (patients and their therapists) and remove between-dyad effects, all cortisol measurements (pre-session and post-session) in the model were centered on each individual's mean. This also removes subject or therapist effects. As the data include multiple time points of assessment, we further examined whether post-session cortisol measurements have a trend in time (Curran and Bauer, 2011). The following trend models were evaluated: no trend in time, linear trend and linear in log of time. We examined a model with only a fixed intercept, a model with linear trend in session and a linear effect of the log of the session. We used the Bayesian Information Criterion (BIC) to determine the model with the best fit. The model found to have the best fit for post-session cortisol measurements was the one with no trend. This model was used in all analyses. To estimate the interdependence between patients' and therapists' changes in cortisol from pre- to post-sessions, the APIM was used (Kenny et al., 2006). The APIM allowed us to examine actor effects (i.e., the effects of the patient/-therapist pre-session cortisol on their own post-session cortisol levels), and partner effects (i.e., the effects of the patient/therapist pre-session cortisol on their partner's (patient/therapist) post-session cortisol levels), while controlling for the individuals' actor effect. Interdependence between the patient and therapist was indicated by the partner

effects.

2.4.2. Interdependence of Pre- to Post-session in Cortisol Levels

To examine whether patients' and therapists' changes in pre- to post-session in cortisol are interdependent, such that therapists' pre-session cortisol predicts subsequent patients' post-session cortisol and vice versa (Hypothesis a), we used the APIM as described below. The model included the patient's and therapist's post-session cortisol, predicted by the patient's and therapist's pre-session cortisol, controlling for the partner's pre-session cortisol levels. The final model was as follows:

$$PoC_{ij}=\beta_1 p_{ij}+\beta_2 t_{ij}+\beta_3 APC_{ij}\cdot p_{ij}+\beta_4 PPC_{ij}\cdot p_{ij}+\beta_5 APC_{ij}\cdot t_{ij}+\beta_6 PPC_{ij}\cdot t_{ij}+ e_{ij}$$

Where *PoCij:* Post-session cortisol for individual *i* with therapist *j*. p_{ij}: Indicator variable for the patient's role (patient: p_{ij}=1, therapist: p_{ij}=0). t_{ij}: Indicator for the therapist's role (=1-p_{ij}). APC_{ij}: Actor's pre-session cortisol for individual *i* in therapist *j*. PPC_{ij}: Partner's pre-session cortisol for individual *i* in therapist *j*. Error term e_{ij} is normally distributed with mean 0 and measurements are independent of each other.

2.4.3. Moderation of Patient Alliance Ratings on Interdependence of Pre-session to Post-Session Cortisol

To examine whether the patient's alliance ratings moderated the partner effects of pre- to post-session changes in cortisol levels (Hypothesis b), we replicated the APIM model, adding the patient's alliance ratings as a moderator. The moderation effect was introduced into the model as an interaction between patient's post-session alliance ratings (WAI scores) to pre-session cortisol of patients and of therapists at post-session. The final model was as follows:

$$PoC_{ij}=\beta_1 p_{ij}+\beta_2 t_{ij}+\beta_3 APC_{ij}\cdot p_{ij}+\beta_4 PPC_{ij}\cdot p_{ij}+\beta_5 APC_{ij}\cdot t_{ij}+\beta_6 PPC_{ij}\cdot t_{ij}+\beta_7 WAI_{ij}+\beta_8 WAI_{ij}\cdot APC_{ij}\cdot p_{ij}+\beta_9 WAI_{ij}\cdot PPC_{ij}\cdot p_{ij}+\beta_{10} WAI_{ij}\cdot APC_{ij}\cdot t_{ij}+\beta_{11} WAI_{ij}\cdot PPC_{ij}\cdot t_{ij}+ e_{ij}$$

Where WAI_{ij}: Working Alliance Inventory (WAI) scores for individual *i* in therapist *j*.

2.4.4. Actor and Partner Effect Estimates Predicting Treatment Outcome

To examine whether cortisol interdependence is associated with clinical outcome, for each dyad, estimates for actor and partner effects were calculated, for patients and therapists separately. Then, in order to predict HRSD score slope, by using actor and partner effect estimates, we employed the following model:

$$HRSDsij=\beta 0 +\beta 1 \cdot t+\beta 2 \cdot p+\beta 3 \cdot AEij\cdot t+\beta 4 \cdot PEij\cdot t+\beta 5 \cdot AEij\cdot p+\beta 6 \cdot PEij\cdot p$$

Where *HRSDsij:* HRSD score slope for individual *i* with therapist *j*. p_{ij}: Indicator variable for the patient's role (patient: p_{ij}=1, therapist: p_{ij}=0). t_{ij}: Indicator for the therapist's role (=1-p_{ij}). AE_{ij}: Actor's effect estimate for individual *i* in therapist *j*. PE_{ij}: Partner's effect estimate for individual *i* in therapist *j*.

3. Results

3.1. Preliminary Analyses

3.1.1. Patient and Therapist Cortisol Descriptives

The mean patient cortisol change within session was − 2.95, with standard deviation (SD) of 5.42. The mean therapist cortisol change within session was − 0.79, with SD of 2.09.

3.1.2. Therapist Effect

To account for a possible therapist effect, we estimated the therapist's effect using a three-level hierarchical model, with sessions (observations), nested within patients, nested within therapists. The therapist's effect was not significant (b =.00, p = .99).

3.2. Interdependence of Pre-session Cortisol to Post-session Cortisol

All variables in the models were standardized (i.e., divided by their standard deviation) and therefore all reported coefficients are standardized. Results showed significant positive actor effects on subsequent changes in post-session cortisol for both patients (b =.22, SE =.05, p < .00) and therapists (b =.36, SE =.12, p < .00). In detail, both patients and therapists that experienced increased levels of pre-session cortisol (in relation to their mean levels of cortisol at pre-session), also experienced increased post-session cortisol levels (in relation to their mean cortisol levels). Furthermore, results showed significant partner effects for patients (b =.50, SE =.12, p < .00), but not for therapists (b = −.00, p = .87), on subsequent changes in post-session cortisol levels). In detail, the more patients experienced increased levels of pre-session cortisol (in relation to their mean pre-session cortisol levels), the more therapists also experienced increased levels of post-session cortisol (in relation to their mean post-session cortisol levels). Results are presented in Fig. 2.

3.3. Moderation of Patient Alliance Ratings on Interdependence of Pre-session to Post-Session Cortisol

A significant negative interaction was found between patients' alliance ratings and pre-session patient cortisol levels, on subsequent post-session therapist cortisol levels (b = −.40, SE =.11, p < .00). In other words, when patients reported a higher alliance rating, in the same session, the ability of the patient's pre-session cortisol levels to predict the therapist's subsequent post-session cortisol levels weakened.

3.4. Coefficients of Partner Effect for Different WAI Levels

We further investigated the partner effects in relation to different levels of the WAI, aiming to discern the impact of WAI scores on the interdependence between patients' pre-session to therapists' subsequent post-session cortisol levels. For patients reporting higher reported WAI scores (e.g. one SD above the mean), the effect of the patient's partner effect was estimated to be 2.41 (SE = 0.78). For patients with lower reported WAI scores (e.g., one SD below the mean), the effect of patients' partner effect was estimated to be 3.19 (SE = 0.56). The point estimates were calculated as the sum of the coefficients of pre-session cortisol (2.8) and its interaction with the WAI score (0.39). Their standard errors were estimated based on the respective standard errors of these coefficients and their covariance.

3.5. Power Analysis

To assess the reliability of our study's findings on cortisol interdependence during psychotherapy sessions, a post-hoc power analysis was

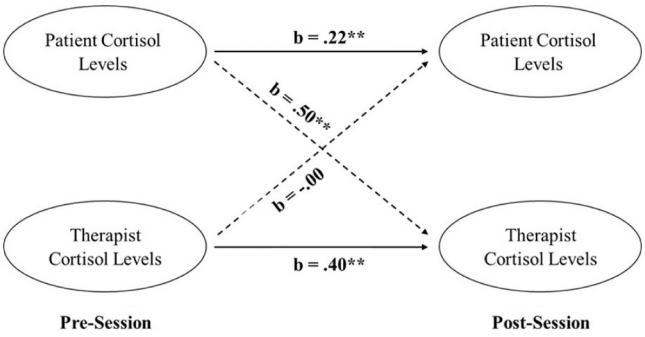

Fig. 2. *Interdependence of Cortisol Levels of Patients and Therapists Between Pre- to Post-sessions. Note.* Actor (continuous lines) and partner (dashed lines) associations between patients' and therapists' changes in cortisol levels from pre- to post-sessions. * * p < 0.001.

conducted using effect sizes and standard errors from actor and partner effects. The analysis revealed adequate sensitivity, with a power of 0.99 for patients and 0.99 for therapists in detecting the observed effects of increased pre-session cortisol on subsequent post-session levels. However, power for therapist-specific partner effects was comparatively lower at 0.48, emphasizing the need for careful interpretation of therapist-related outcomes.

3.6. Actor and Partner Effect Estimates Predicting Treatment Outcome

A significant negative effect was found between patients' actor effect estimates, on predicting HRSD score slopes (b = −8,98, SE = 2.66, p < .00). In other words, the stronger the auto-regressive effect of patients on the pre- to post session cortisol levels, the less symptomatic changes they experience throughout treatment. Furthermore, a significant positive effect was found between patients' partner effect estimates, on predicting HRSD score slopes (b = 18.56, SE = 8.12, p = .02). In other words, the stronger the predictive effect of patient pre session cortisol on post session therapist cortisol levels, the more symptomatic changes patients experience throughout treatment. No significant effects were found for therapist actor (b = −.00, p = .64), or partner (b =.00, p = .88) effects on predicting patient HRSD score slopes.

3.7. Sensitivity Analyses

3.7.1. Age and Gender Covariates

Studies conducted on cortisol change with age and between genders point to possible differences in cortisol secretion by age and gender (Almeida et al., 2009). We controlled for patient age and gender in all models. All results (patient and therapist actor effects, and patient partner effect) remained significant, and no significant effect was found for either age (b =.00, p = .42) or patient gender (b = −.00, p = .11) in the first model, and no significant effect was found for age (b =.00, p = .38) or patient gender (b =.00, p = .11) in the second model.

3.7.2. BMI Scores Covariate

Studies point to role of obesity and lipid cells in the production of cortisol (Schorr et al., 2015). We controlled for BMI scores in all models. All results (patient and therapist actor effects, and patient partner effect) remained significant, and no significant effect was found for BMI in the first (b =.00, p = .98) or the second (b =.00, p = .99) models.

3.7.3. Moderation of Time on Interdependence of Pre-session to Post-Session Cortisol

To test whether there is any evidence of cortisol independence development throughout treatment, we used time (session number) as a potential moderator. No significant interactions were found between patients' session numbers and pre-session patient cortisol levels, on subsequent post-session patient cortisol levels (b = −.01, SE =.00, p = .08), and between therapist pre-session cortisol levels, on subsequent post-session therapist cortisol levels (b =.00, SE =.01, p = .73). Similarly, No significant interactions were found between patient's pre-session cortisol levels, on subsequent post-session therapist cortisol levels (b =.01, SE =.01, p = .48), and between pre-session therapist cortisol levels, on subsequent post-session patient cortisol levels (b =.00, SE =.00, p = .70).

3.7.4. Session timing Covariate

We inspected the session timing in our sample, based on the diurnal pattern to Cortisol (Upton et al., 2023). In this study, therapy sessions were conducted between 8:00 (AM) and 21:00 (PM). The mean session time was 13:30 (PM), with standard deviation of 3.7. Session time varied randomly, with all therapists meeting patients in different times of the day (no therapist was limited to a certain period of time-of-day in this study). Based on existing literature and our sample size, we divided session timing into three periods: Morning (8:00–12:00, n = 17), Noon (12:00–17:00, n = 19) and Afternoon (17:00–21:00, n = 14). We controlled session timing as a covariate in our Interdependence models. All findings remained significant, and no significant effect was found for session timing (b =.00, SD =.11, p = .99).

4. Discussion

The present study aimed to explore cortisol interdependence between patients and therapists in psychotherapy for MDD, to investigate whether the working alliance between them moderates this interdependence, and to test whether cortisol interdependence associates with treatment outcome. Aligning with research investigating cortisol interdependence in romantic partners or parent-child relationships, evidence was found for cortisol interdependence between patients and therapists. Specifically, while both patients and therapists predicted their own cortisol levels from pre- to post-session (actor effects), patients' pre-session cortisol levels also predicted their therapist's subsequent post-session cortisol levels (partner effect). Thus, when patients experienced higher (than usual) cortisol levels at pre-session, so did their therapists at post-session, this may be understood as therapist responsiveness (Fig. 1). This partner effect was more robust in dyads with lower relationship quality, as indicated by poorer patient alliance ratings. Furthermore, the patient's partner effect was associated with better treatment outcomes, as indicated by increased HRSD score slopes.

Regarding the study's first hypothesis, this study's findings partially support our hypothesis. Specifically, findings show auto-regulation effects of cortisol levels from pre- to post-session for patients and therapists (actor effects). However, interdependence was found only for patient cortisol levels, but not for therapists (partner effect). This finding aligns with studies showing that cortisol interdependence may occur in a one-way manner, such as for parents predicting their children's cortisol levels (or vice-versa) or for only one partner in a romantic relationship (Bernard et al., 2017; Bader et al., 2021). For example, Bader et al. (2021) found that 1-year-old infants' cortisol levels predicted their parents' subsequent cortisol levels preceding the strange situation procedure, but not the other way around. Similarly, Bernard et al. (2017) found that only mothers' cortisol levels predicted their 1-year-old infants' subsequent cortisol levels preceding a naturalistic laboratory stressor. Furthermore, similar findings are shown in studies investigating interdependence on other modalities of arousal in psychotherapy. For example, a study by Wieder and Wiltshire (2020) found that, in the setting of CBT in-vivo exposure, therapists' vocally-encoded emotional arousal levels predicted shifts in patients' vocally-coded emotional arousal levels, but not the other way around. In this study, the significance of the patient's partner effect, in contrast to the non-significance of the therapist's impact, suggests implications for how therapists respond to patients arriving for therapy sessions. This dynamic may have a positive outcome, with therapists reacting constructively to the emotional charge that patients bring, offering regulation. Conversely, it could have a detrimental effect, where the patient's emotional state becomes contagious, potentially down-regulating both the patient and the therapist. The finding of a partner-effect on therapists' post-session cortisol levels prompts an exploration of whether the patient's experience is transmitted to the therapist for regulation, or if the therapist is instead affected, potentially experiencing further distress. The framework for this exploration may lie in the Emotional Suppression Theory (Gross and Levenson, 1993), indicating that in emotional contexts, the use of suppression strategies may intensify unwanted experiences and embodied arousal (Gross and Levenson, 1997; Wegner and Zanakos, 1994; Hofmann et al., 2009).

Regarding the study's second hypothesis, this study's findings support one of the competing hypotheses for the direction of interdependence when considering the moderating effect of relationship quality. Specifically, findings show that relationship quality (patient-rated) moderated cortisol interdependence between patients and therapists, so the poorer the relationship, the more the patient's pre-session cortisol

levels predicted their therapist's subsequent post-session cortisol levels. This finding implies that a diminished sense of meaning in how the patient views the patient-therapist relationship, corresponds to a greater influence on their cortisol levels in the subsequent post-session period. This finding is in line with studies conducted in developmental psychology and interpersonal fields, showing that cortisol interdependence occurs mainly in lower-quality relationships or interpersonal contexts (Williams et al., 2013; Borelli et al., 2019; Hibel et al., 2019; Meyer and Sledge, 2020). In detail, Williams et al. (2013) showed that in families with less affective responsiveness, mothers and their children were more interdependent in their cortisol diurnal slopes. Similarly, Borelli et al. (2019) found that mothers showing less sensitivity during a stressful task with their children tended to show more cortisol interdependence with them before the performance of the task. Hibel et al. (2019) found that in mother-child dyads where the children were maltreated, both mothers and their children's cortisol levels predicted each other's subsequent cortisol levels. Among studies included in a systematic review (Meyer and Sledge, 2020), ten studies focused on the quality of the relationship as a potential moderator. These studies show evidence of a negative association between the relationship quality of romantic partners and cortisol interdependence. This means, when the relationship quality was lower, as manifested in less marital satisfaction (Saxbe and Repetti, 2010) or partner support (Liu et al., 2013), or worse communication and conflict resolution (Seiter et al., 2019), partners were more interdependent in their diurnal cortisol levels. For example, Doerr et al. (2018) sampled the cortisol levels of partners over five days. Partners were asked to report, among other measures, about their engagement and relationship satisfaction with each other. Results indicated that when couples reported being more engaged between samples, their cortisol interdependence became weaker (Doerr et al., 2018). Conversely, this finding is not in line with studies conducted in psychotherapy settings, showing that arousal interdependence, as measured by other modalities (for example, acoustic pitch, Imel et al., 2014), occurs mainly in higher-quality relationships. A possible explanation could be that cortisol interdependence shows different patterns than other patterns of interdependence found in psychotherapy, which warrants further research.

Regarding the study's third hypothesis, a negative association was found between patients' cortisol auto-regulation effects and fewer symptomatic changes, while stronger predictive effects of patient pre-session cortisol on therapist post-session cortisol correlated with more symptomatic changes. Therapeutic efficacy may be linked to the patients' self-directedness, which may be reflected in consistent arousal levels, influencing cortisol concentrations throughout treatment. One plausible explanation, aligning with our conceptual model, is that patients heavily rely on auto-regulation effects. This reliance may indicate a persistence in maladaptive regulation patterns that characterize the patient's pre-treatment state. In contrast, effective treatments typically involve patients being influenced by the therapist's responsiveness, facilitating changes in their established patterns (Kramer and Stiles, 2015; Watson et al., 2020; Wieder and Wiltshire, 2020). In accordance with this conceptual framework, the present findings suggest that individuals maintaining auto-regulation patterns exhibit poorer treatment outcomes.

If replicated in future studies, findings may shed more light on how patient and therapist arousal, as manifested in cortisol, may be affected by the strength of their alliance. In the context of a stronger alliance, when patients experience increased pre-session arousal levels, as manifested by higher-than-usual cortisol levels, the emotional lability that could occur between patient and therapist may be more regulated (Lindqvist et al., 2023; Rober, 2023), thus having less impact on the therapist's subsequent cortisol levels. In contrast, in the context of a weaker alliance, when patients experience increased pre-session arousal levels, as manifested by higher-than-usual cortisol levels, the emotional lability that could occur between patient and therapist may be less regulated, resulting in a stronger impact on the therapist's subsequent post-session cortisol levels. Possibly, a stronger alliance may provide therapists with more resources for emotional regulation, allowing them to be less influenced by the patients' increased cortisol levels.

Consistent with the post-hoc explanation, the contagious effect of arousal on interpersonal interactions within relationships is well documented. Studies have highlighted the contagious nature of arousal, which manifests as increased cortisol levels between individuals, often found within aversive situations (for instance, the context of negative affect; Papp et al., 2009; Meyer and Sledge, 2020). As mentioned, this phenomenon exists mainly within relationships with poorer ratings, resulting in heightened cortisol levels. Conversely, individuals in happier, more satisfactory, relationships tend to exhibit lower cortisol levels (Saxbe and Repetti, 2010; Liu et al., 2013; Meyer and Sledge, 2020). Therefore, one possible explanation for the current findings could be that when patients arrive at therapy with heightened arousal levels, a better alliance between patients and therapists may provide a better environment for emotion regulation during the session, resulting in the therapist arriving at the end of the session better regulated and being more effective for their patients. This regulation may manifest in lower arousal and subsequent cortisol levels, which aligns with existing findings supporting increased cortisol levels and worse treatment outcomes in MDD (Fischer et al., 2017). For example, Papp et al. (2013) suggested that in higher-quality relationships, a partner's presence often plays a regulatory role for the other. Such interpersonal dynamics were linked to specific contexts of interactions or different states in relationships (Butler, 2011; Butler and Randall, 2013). The possible contribution of these findings is the integration of this understanding into the clinical training of therapists. By underscoring often unnoticed processes, the research may contribute to raising therapists' awareness of internal processes occurring within the patient, that may not necessarily mirror the therapist's physiological responses. This heightened awareness enables therapists to use their own emotions as a guiding compass, enhancing therapeutic efficiency and fostering a stronger alliance with their patients.

While this is the first study to find evidence of cortisol interdependence between patients and therapists, it also has limitations. First, the present sample was relatively modest, potentially limiting the generalizability of current findings. Second, in order not to interrupt therapy sessions, we only sampled saliva at pre- and post-sessions. Therefore, the ability to pinpoint mutual cortisol changes to specific factors occurring during sessions is limited. It should be noted, however, that cortisol in saliva has a low temporal resolution and often carries a roughly 30-minute delay from peak secretion to its peak in saliva; hence, even with more sampling points, it would be difficult to pinpoint specific within-session events using this measure. Third, in the absence of a control group not undergoing psychotherapy, our ability to exclusively attribute cortisol changes to therapy sessions is limited. Future research incorporating a well-matched control group is needed to clarify the specific impact of psychotherapy on cortisol dynamics. Last, saliva samples were not sampled at each session, which may limit the temporal precision of the results. Future research could explore the dynamics of cortisol interdependence over time by incorporating a larger sample of patients and therapists, accompanied by a more extensive array of cortisol measurements. This approach will contribute significantly to understanding the formation and development of cortisol interdependence.

4.1. Conclusions

The novelty of these findings lies in the exploration of cortisol interdependence in a psychotherapy for MDD setting. In this novel setting of exploring cortisol interdependence, this study found results in line with existing literature, showing interdependence in cortisol levels between patients and therapists. Specifically, patients' pre-session cortisol levels predicted therapists' subsequent post-session cortisol levels. The findings also support the importance of relationship factors in moderating cortisol interdependence by indicating that cortisol

interdependence between patients and therapists is more robust the more alliance ratings are poorer. Future studies can shed more light on how pre-session arousal levels, measured in cortisol levels, could manifest in the therapeutic processes occurring during therapy sessions. Furthermore, future studies may consider employing multimodal features, which encompass cortisol with other various arousal indices, which may offer a more expansive and holistic perspective. This approach takes into account the distinct contributions of each modality, potentially leading to a more comprehensive understanding of the interdependent dynamics at play. The findings of this study may aid in shedding more light on processes that may otherwise go unnoticed within therapy. Applying this knowledge into clinical training of therapists may benefit clinical training and raise therapists' awareness about internal processes occurring within the patient that do not directly correspond with similar physiological processes within the therapist. In turn, therapists will be able to pay more attention to their feelings (or the absence of them) as a guiding compass for the patient's experience in therapy sessions, possibly to be more efficient in therapy, which may lead to form a stronger therapeutic alliance.

Ethical approval

The study was conducted using data retrieved from a RCT, according to the guidelines of the Declaration of Helsinki. The University of Haifa ethical committee approved the execution of the study (Approval Number: 118/15, Date: 10 October 2015).

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Informed Consent from participants

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Levi Eyal: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Peysachov Galit:** Conceptualization, Methodology, Writing – review & editing. **Admon Roee:** Conceptualization, Methodology, Writing – review & editing. **Zilcha-Mano Sigal:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

None.

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