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Oxytocin Synchrony Between Patients and Therapists as a Mechanism Underlying Effective Psychotherapy for Depression

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Objective: Oxytocin (OT) synchrony has been suggested as a key mechanism by which bonds are formed and strengthened in various species, including those between mother and infant and between romantic partners. It is unknown whether such biological synchrony also plays a role in psychotherapy efficacy, where it may underlie the adverse effect of social impairment on the efficacy of treatment of depression. ***Method:*** Five hundred eighty OT saliva samples were collected from 37 patient–therapist dyads on a fixed schedule over a 16-session ongoing randomized controlled trial for psychotherapy for depression. Biological synchrony was operationalized as the correlation between changes occurring repeatedly over treatment in patient and therapist OT levels pre- to postsession. ***Results:*** OT synchrony between patients and therapists was found to be associated with effective treatment. The findings support the proposed mediation model: (a) poorer social functioning at baseline predicted lower levels of patient–therapist synchrony in OT changes from pre- to postsession over the course of treatment; (b) lower levels of therapist–patient OT synchrony, in turn, predicted less reduction in depressive symptoms during treatment; and (c) based on quasi-Bayesian Monte Carlo simulations, the levels of therapist–patient synchrony significantly mediated the association between social impairment and reduction in depressive symptoms. Findings were replicated using robust inferential methods. ***Conclusions:*** The findings suggest that OT synchrony between patient and therapist may be a biological mechanism by which impaired interpersonal functioning undermines treatment outcome.

What is the public health significance of this article?
To our knowledge, this is the first study to focus on the biological synchrony between patients and their therapists during treatment sessions and to suggest that this synchrony is an important mechanism underlying the effects of impaired interpersonal functioning on treatment outcome. Patients with poorer social functioning at baseline were less biologically synchronized with their therapists during treatment sessions, and the poorer synchrony was associated with lower ability to benefit from treatment and to achieve symptoms reduction.

Keywords: psychotherapy, therapeutic alliance, depression, biological synchrony

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Despite effective psychotherapy and antidepressant treatments, about half the individuals suffering from major depressive disorder (MDD), the leading cause of disability worldwide (Friedrich, 2017), remain symptomatic and do not respond to treatment (Greer et al., 2010; Moussavi et al., 2007). Even those who respond remain at considerable risk of future relapse (Zantvoord et al., 2013). Over the decades, much effort has been invested in improving the efficacy of treatment for depression, but progress has been hindered by limited knowledge about the mechanisms that bring about therapeutic change (Cuijpers et al., 2019). Accumulating findings suggest that social functioning deficits, which are prevalent in MDD, may impair patients' ability to benefit from psychotherapy for MDD (Altenstein-Yamanaka et al., 2017; Frank et al., 2011).

The role of social deficits in the ability of patients to benefit from psychotherapy has been the focus of much research over the decades. The focus on social deficits and interpersonal factors as both pretreatment predictors (Bohart & Wade, 2013) and active in-treatment ingredients (Flückiger et al., 2018) is not surprising given the circumstances under which most treatments occur—between two individuals, a patient and therapist, working together with the aim of reducing the patients' symptoms and improving well-being and quality of life. Indeed, findings suggest that patients with more social deficits, as manifested in less secure at-

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tachment (Levy et al., 2018) and more interpersonal problems (Dinger et al., 2007), were found to have poorer treatment outcomes.

The literature has proposed several factors that may contribute to the adverse effect of social dysfunction on treatment efficacy. For example, in the case of individuals with more interpersonal impairments, benefit from gains in the therapeutic alliance were found to contribute less to improved treatment outcomes than in individuals with fewer such impairments (Falkenström et al., 2013; Gómez Penedo et al., 2019; Zilcha-Mano & Errázuriz, 2015). Another potential candidate for explaining the adverse effects of social deficits on treatment outcome is impairment in patient–therapist synchrony. Although many definitions of patient–therapist synchrony have been suggested (Delaherche et al., 2012), one common element in these definitions is the level of the therapist's attunement to the patient or the mutual temporal coordination in changes in a variety of modalities occurring in patients and therapists during treatment (Tschacher & Ramseyer, 2017). When the patient and therapist are showing changes in the same directions and relatively in the same amounts, they are said to be synchronized. Findings suggest that higher levels of patient–therapist synchrony are associated with better treatment outcome across modalities, including patient–therapist movement synchrony (Ramseyer & Tschacher, 2011) and acoustic synchrony (Reich et al., 2014). Although the level of synchrony between patients and therapists has attracted much empirical attention and is considered a critical ingredient in treatment success, little is known about its biological underpinning.

It can be suggested that dyads that include patients with better interpersonal abilities are more likely to be biologically synchronized and that such biological synchrony results in more effective work between patients and therapists and better treatment outcomes. As can be expected based on the neurobiology of human attachment (Feldman, 2017), patients with greater interpersonal impairment may transfer such impairment, together with the lack of adequate interpersonal skills for bond formation and maintenance, also to their relationship with their therapist, thereby failing to form the biologically synchronized interactions critical for treatment success. Thus, biological synchrony between patient and therapist may serve as a potential mechanism by which impaired interpersonal functioning undermines treatment outcome. To the best of our knowledge, no study to date has examined a potential role of biological synchrony between patients and therapists in mediating the effect of impaired interpersonal functioning on treatment outcome.

One promising potential biological mechanism underlying the effect of social functioning deficits on treatment outcome is the level of oxytocin (OT) synchrony between patient and therapist. OT is a nine-amino-acid cyclic neuropeptide produced in the paraventricular nucleus of the hypothalamus, known to play an important role in bond formation and synchrony in close relationships (Schneiderman et al., 2014; Shamay-Tsoory & Abu-Akel, 2016). It has been reported that OT generates antidepressant effects in animal models of depression (Matsuzaki et al., 2012) and is implicated in the pathophysiology of MDD, in animals (Amini-Khoei et al., 2017) and humans (McQuaid et al., 2014; though with considerable heterogeneity, Engel et al., 2019; Massey et al., 2016). Based on accumulating studies, it has been argued that OT serves as a biological mechanism by which bonds are formed and strengthened in various species (Algoe et al., 2017; Josef et al., 2019; Williams et al., 1992).

It has been suggested that the oxytocinergic system plays a key role in the interactive reciprocity and dyadic synchronized behavior characterizing the mother–infant relationship (Feldman et al., 2011), as well as in romantic relationships (Schneiderman et al., 2012). There have been some indications of biological synchrony in OT levels between parents and children and between romantic partners (Feldman et al., 2013; Feldman et al., 2010; Vittner et al., 2018), but this topic, currently of intense empirical interest, is still awaiting systematic evaluation. Such OT synchrony may be fundamental to effective treatment as well. In psychotherapy, OT synchrony can be defined as the association between patient and therapist changes in OT from pre- to postsession, so that when both therapist and patients are showing changes in the same direction (e.g., both show an increase in OT levels), they are referred to as expressing synchrony (Zilcha-Mano et al., 2020). Although OT synchrony is expected to manifest over time and to serve as the biological mechanism underlying relationship formation, it is not clear whether patients and therapist synchronize in their OT levels during effective psychotherapy. Promising findings suggest that OT may serve as a biomarker of the therapeutic relationship, as indicated based on behavioral coding systems and self-report questionnaires (Zilcha-Mano et al., 2018). However, to the best of our knowledge, no study to date has examined OT synchrony between patients and therapists. Similarly to beneficial effects of neuroendocrine synchrony in other interpersonal relationships (Priel et al., 2019; Ulmer-Yaniv et al., 2016), the neuroendocrine synchrony between patients and therapists is expected to result in more effective collaborative work between them.

The present study is the first to investigate the potential role of biological synchrony in the therapeutic relationship between patients and their therapists. We examined whether patients' and therapists' ability to synchronize on a biological level, as manifest in the association between changes in OT levels in patients and therapists following their interaction in therapy sessions (from pre- to postsession) over the course of treatment, is associated with more effective treatment. To further identify the role such potential biological synchrony may play in effective treatments, we proposed and examined a mediation model in which the patients' baseline levels of social impairment predict the extent to which they and their therapists are synchronized on a biological level, which in turn predicts the effectiveness of the treatment. We expect that (a) impaired social functioning at baseline predicts lower levels of patient–therapist biological synchrony; (b) lower levels of therapist–patient synchrony, in turn, predict less reduction in depressive symptoms during treatment; and (c) the levels of patient–therapist synchrony mediate the association between social impairment and reduction in depressive symptoms.

Method

Participants

The data of all patients enrolled in this ongoing randomized controlled trial (RCT) with the available OT assessments of patients and therapists, were included in the analyses. 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) at 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 must be stable for at least 3 months before the start of the study, and they must be willing to maintain stable dosage for the duration of treatment; (c) age between 18 and 60 years; (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.

A total of 580 OT samples, collected from 37 patient–therapist dyads were used in the analyses, so that for most dyads, four time points were collected (Sessions 4, 8, 12, and 16), with four samples collected at each time point (pre- and postsession samples of both patient and therapist). There were 2.02% observations missing (three dyads missed the last time point). Patients were enrolled in 16-session manualized psychotherapy for MDD, as part of an ongoing randomized control trial comparing supportive and supportive–expressive (SE) treatment (Zilcha-Mano et al., 2018). The mean age was 31.54 (SD = 9.63); 22 participants were female; 18 of the dyads were same sex (48.6%), and 19 were mixed (51.4%). Twenty-nine patients had a comorbid personality disorder. Twenty-five patients (67.6%) had a comorbid anxiety disorder, including generalized anxiety disorder (62.2%), social anxiety (32.4%), agoraphobia (21.6%), and panic disorder (2.7%). Of the patients, 10.8% had a posttraumatic stress disorder, and 5.4% obsessive–compulsive disorder. Patients' mean levels of the 17-item HRSD at intake was 21.41 (SD = 3.76). The study was approved by the relevant institutional review board, and all patients gave informed consent in writing before screening. Six treating psychotherapists, with a mean of 14.41 years of experience, participated in the study.

Treatments

Patients received 16 sessions (50-min per session) of SE treatment (Luborsky, 1984, 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 in a supportive-focused condition (including the use of supportive techniques, such as affirmation and empathic validation). For SE treatment, the Luborsky (1984, 1995) manualized treatment was used. The supportive condition includes all supportive techniques detailed in the manual used by Luborsky (1984, 1995), but it forbids the use of any expressive techniques, as detailed in Leibovich et al. (2018).

Procedure and Materials

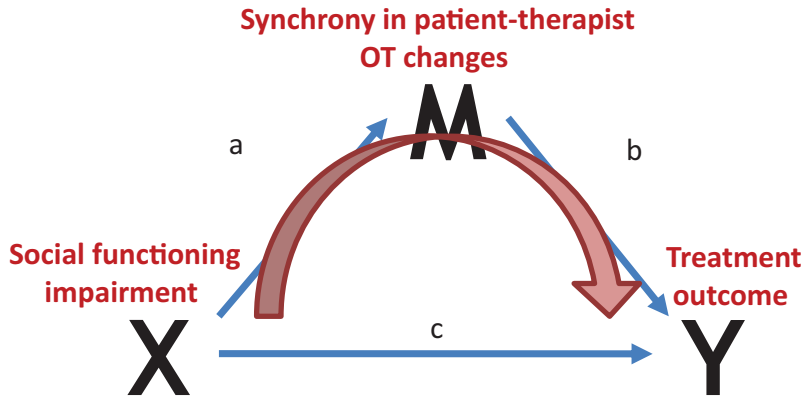
Salivary OT measures are increasingly becoming accepted in human endocrinology as potential biomarkers of behavior (Carter et al., 2007). They have been validated in various contexts and found to be interrelated with OT levels in plasma (Feldman, Gordon, et al., 2011). Therefore, in the present study, we used salivary OT measurements because they are minimally intrusive. OT levels in saliva were assessed at eight time points during the therapeutic process, before and after Sessions 4, 8, 12, and 16. To ensure the uniformity of collection parameters, participants were asked to refrain from 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 refrain from romantic or intimate touch for 30 min before arrival. Samples were collected by the evaluator assessing the weekly depression symptoms during the trial. Both the evaluator and the patient wore gloves during saliva collection. Saliva was obtained by chewing on a roll-shaped saliva collector for 2 min to stimulate salivation until it 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 batch. All samples were analyzed by the same company, RIAgnosis (RIA; Munich, Germany). The concentrations of salivary OT were quantified using radioimmunoassay (de Jong et al., 2015). For each sample, the saliva was evaporated (no extraction was used). Intra- and interassay variabilities of <10% were assessed; detection limit was 0.1 pg to 0.5 pg, depending on the age of the 125I-labeled tracer. The RIA analysis method does not use plates. To measure social functioning, the Social Role Functioning subscale (SR) of the Outcome Questionnaire (Lambert et al., 2004) was used. The SR contains five items assessing patient functioning at school, work, and leisure. It was found to show high validity and to be associated with related constructs such as functioning in the social role (including school, occupation, housework, and leisure domains), interpersonal problems, social anxiety, and social adjustment (de Jong et al., 2015). To quantify symptomatic change, we used a semistructured clinical interview, the HRSD, administered at baseline and before each session, over the 16 sessions of treatment.

Statistical Analysis

OT synchrony between patient and therapist was estimated repeatedly during treatment as a Fisher's Z transformation of the correlation between changes in OT during psychotherapy sessions using all available observations. For treatment outcome (HRSD), we used the changes from pretreatment to posttreatment in HRSD scores. One-sample permutation test (10,000 permutations) was applied to test the direction pattern of the OT synchrony.

We conducted a series of analyses to examine a mediation model in which baseline SR predicts the degree of synchrony between the changes in OT level of therapist and patient, which in turn predicts patient's symptom reduction (see Figure 1). We applied a linear regression-based analysis to test the proposed mediation model, using a quasi-Bayesian Monte Carlo method with 5,000 simulations, and White's heteroskedasticity-consistent estimator for the covariance matrix (Tingley et al., 2014; Zeileis, 2006). The outcome measure for the mediation analysis was the reduction in patient depressive symptoms as evaluated using the HRSD. We applied the following three models to test the proposed mediation model: (a) examining the ability of baseline SR to predict therapist–patient OT synchrony; (b) examining the association between OT synchrony and patient symptom reduction during treatment, conditioned on the effect of the baseline SR; and (c) examining the mediation effect, which was defined as a×b, with statistical inferences based on the approach described in the preceding text (Tingley et al., 2014; Zeileis, 2006). Marginal R^2 (R^2_m)

Figure 1
The Proposed Mediation Model



Note. According to the proposed mediation model (a) poorer social functioning at baseline predicts lower levels of therapist–patient synchrony; (b) lower levels of therapist–patient synchrony, in turn, predict less reduction in depressive symptoms as a result of treatment; and (c) the levels of therapist–patient synchrony mediate the association between social impairment and reduction in depressive symptoms. OT = oxytocin. See the online article for the color version of this figure.

statistics were provided as estimates of model effect sizes (Cohen, 1988).

The mediation analysis was based on the two regression models

$$OT\ synchrony_i = b_0 + b_1 \times baseline\ SR_i + e_i \quad (1)$$

and

$$\Delta HRSD_i = a_0 + a_1 \times baseline\ SR_i + a_2 \times OT\ synchrony_i + u_i, \quad (2)$$

where the errors e_i and u_i are assumed to be normally distributed around 0. The mediation of the synchrony (the indirect effect) is measured by $b_1 \times a_2$. The total effect of baseline SR on the change in HRSD is measured by $b_1 \times a_2 + a_1$ where a_1 is the direct effect.

Robust inferential methods are available that perform well with relatively small sample sizes (Ronchetti, 1990; Wilcox, 2011).We reanalyzed the data using robust regression (Pawitan, 2013) based on multivariate MM-estimators of the R package, MASS (Ripley, 2002). Generally, the procedure fits a weight to each observation using the Mahalanobis distance, so that the tail observations receive less weight. The significance of the estimated effects was calculated using a robust Wald test, and the mediation effect was tested based on the approach proposed by Zu and Yuan (2010), in which a bootstrap estimation of mediation effect was combined with a robust estimation routine

Results

Patient and therapist presessions OT levels and changes from pre- to postsessions throughout treatment showed stability over time at the sample level (see the online supplemental material).

OT Synchrony Between Patients and Therapists

OT synchrony showed no pattern of positive or negative direction ($M = -0.08$, $p = .49$), suggesting that at the sample level, there were no indications that patients and therapists were OT-synchronized.

The Proposed Mediation Model

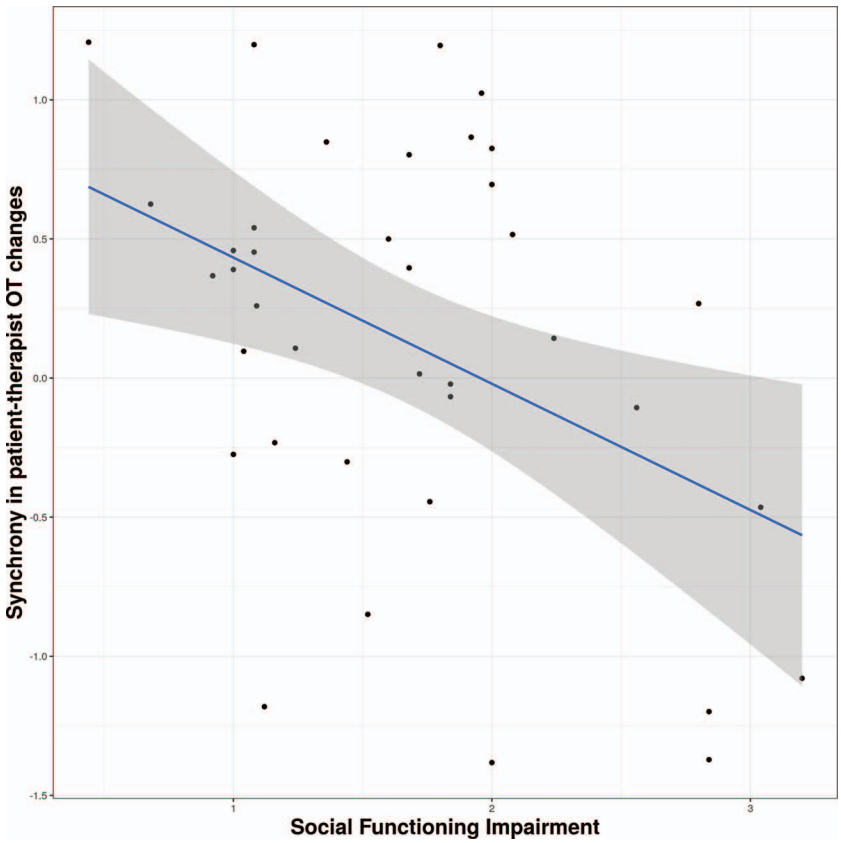
Higher baseline SR was associated with less patient–therapist OT synchrony (see Figure 2; B = −.45, 95% CI [−0.78, −0.13], $t[36] = -2.83$, $p = .008$, $R^2 = 0.18$). Adjusting for the baseline SR, higher OT synchrony was associated with better psychotherapy outcome (B = −4.41, 95% CI [−7.46, −1.35], $t[3] = 2.93$, $p = .006$, $R^2 = 0.21$; see Figure 3). Finally, OT synchrony mediated the effect of baseline SR on psychotherapy outcome (indirect effect = 2.01, 95% CI [0.37, 4.38], $p = .01$). Conditioning on the effect of OT synchrony, the baseline SR was no longer a significant predictor of treatment outcome (B = −2.91, 95% CI [−6.19, 0.37], $t[34] = -1.80$, $p = .08$). Findings were replicated using the robust inferential method, and OT synchrony remained a significant mediator of the effect of baseline SR on psychotherapy outcome (indirect effect = 2.03, 95% CI [0.162,4.58], $p = .02$; for more details, see the online supplemental material).

Post Hoc Sensitivity Analyses

To test the robustness of the findings reported in the current study, a series of post hoc models were tested (see the online supplemental material), showing that findings remained similar when (a) controlling for smoking status, use of medications, recreational drugs, sex of patient and therapist, same versus mixed sex dyads, and body mass index; (b) controlling for patient- and therapist-reported positive and negative affect, as reported after each session using the Positive and Negative Affect Schedule (Watson et al., 1988); (c) replacing change scores with postsession scores, while controlling for presession scores; (d) using only the first three assessments of OT to predict treatment outcome, with the aim of creating a temporal

Figure 2

The Association Between Baseline Impaired Social Functioning and Levels of Therapist–Patient Synchrony in OT Changes



Note. Gray area represents a 95% confidence interval for the regression line. OT = oxytocin. See the online article for the color version of this figure.

relationship between the predictor and outcome. Taken together, the findings based on the post hoc analyses support the ability of OT synchrony to significantly mediate the effect of baseline SR on treatment outcome.

Discussion

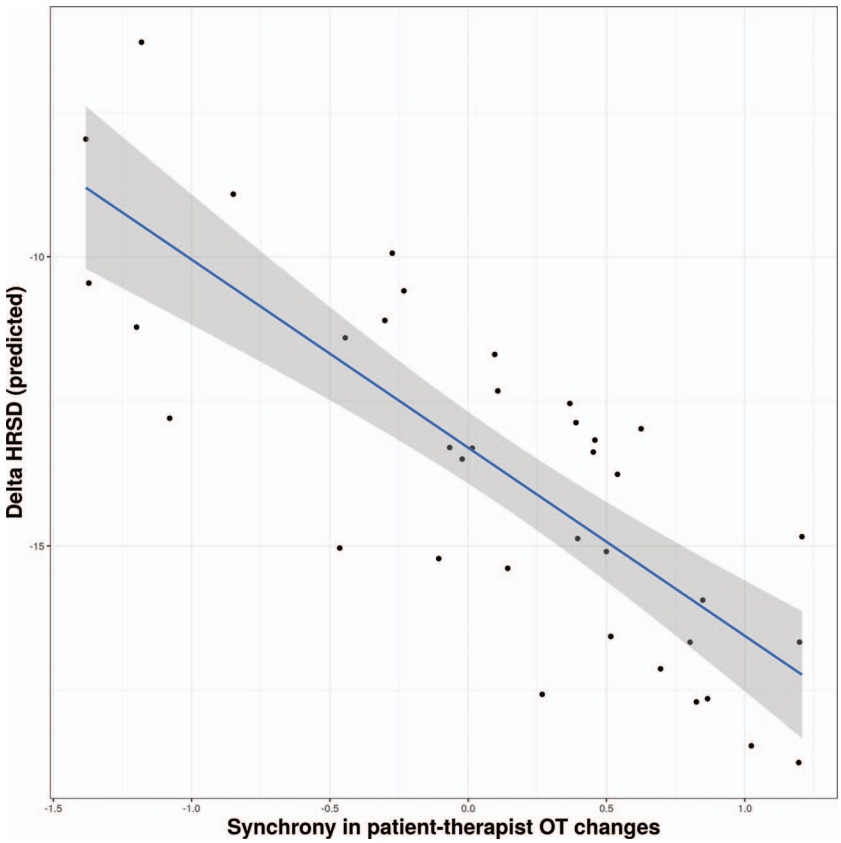
MDD is the leading cause of disability worldwide, but even with adequate doses of effective treatment, many patients fail to respond, especially those showing impaired social functioning (Cuijpers, 2017). The present findings suggest that patients and therapists tend to be more biologically synchronized in more effective treatments and that impairment in their level of synchrony is one of the biological mechanisms by which impaired social functioning undermines treatment outcome. The findings support the proposed mediation model, according to which poorer social role functioning before the start of therapy predicts lower levels of therapist–patient synchrony in OT changes over the course of treatment, which in turn predicts less reduction in depressive symptoms during treatment. To the best of our knowledge, this is the first study to show biological synchrony between patients and therapists as a biomarker of effective treatment, and to demonstrate its role as a mechanism underlying psychotherapy efficacy.

The current findings suggest that only when the treatment was effective were the patient and therapist biologically synchronized in OT changes occurring during treatment sessions. This finding is consistent with the social salience hypothesis (Shamay-Tsoory & Abu-Akel, 2016), stressing the importance of contextual factors for changes in OT levels. Because only a few studies to date have found evidence of OT synchrony in any interpersonal relationship and even fewer have found an association between such synchrony and the outcome of the interaction, the current findings contribute to the general literature on OT in interpersonal relationships. Moreover, the present study is the first to demonstrate longitudinal OT synchrony in human relations.

The current findings are consistent with previous reports suggesting synchrony in OT levels between partners involved in attuned and effective attachment interactions. For example, coupling of parent and infant's heart rhythms (Feldman & Eidelman, 2007; Feldman, Magori-Cohen, et al., 2011) and coordinated release of OT (Feldman, Gordon, et al., 2011) were evident during episodes of social synchrony in gaze and affect. Similarly, there is evidence to suggest that during naturalistic interactions, romantic partners are coordinated in their gaze and affect patterns (Anders et al., 2011) and exhibit an increase in OT levels that correlates

Figure 3

The Association Between Levels of Therapist–Patient Synchrony in OT Changes and HRSD Changes



Note. Gray area represents a 95% confidence interval for the regression line. OT = oxytocin; HRSD = Hamilton Rating Scale for Depression. See the online article for the color version of this figure.

with the degree of their social synchrony (Schneiderman et al., 2012). Therefore, it can be suggested that increased functionality of the OT system is a neurobiological mechanism by which attachment enhances brain-to-brain synchrony.

The current findings shed new light on the role of OT in attuned interpersonal relationships. Until now, research was based on rigorous laboratory studies with limited ecological validity (e.g., undergraduate students interacting in a lab for a short time around a given task) or had strong ecological validity but were based on less controlled laboratory designs (e.g., couples and parent–child dyads whose relationships are generally unfolding outside of the lab, starting and ending irrespective of the research). The current findings demonstrate the role of OT synchrony in relationships that are formed in the lab and are restricted to the lab alone and at the same time are genuine. The findings are consistent with the neurobiology of human attachment conceptualized by Feldman (2017), which suggests that synchronous biological and behavioral processes established as part of the mother–infant bond are transferred to meaningful relationships throughout the individual's life, and play an important, potentially reparatory role. The current findings may also provide biological evidence for the long-standing claim that the patient–therapist relationship has a shared biological basis with mother–infant attachment (Winnicott, 1971).

The most important limitation of the present study is the small sample size. Note, however, that the findings were replicated by applying an analytical approach based on robust statistics to reduce the risk of artifacts in a small sample. An additional limitation is that social functioning was measured using a subscale of a self-report measure. Future studies should use full self-report measures, as reported by the individual or a significant other, as well as less explicit measures of social functioning. Similarly, although the assessment of HRSD is considered the gold standard for assessing depression severity in randomized controlled trials, it also has shortcomings (Bagby et al., 2004). Future studies with larger samples should use moderated-mediation models to investigate the roles of individual differences in patient and therapist characteristics (Shamay-Tsoory & Abu-Akel, 2016) as potential moderators of the mediation effect of OT synchrony. Such studies should also measure OT before and after each session of treatment, to enable a systematic examination of whether improvement in OT synchrony precedes improvement in symptom severity. Future studies should also evaluate how different operationalization of synchrony

(Delaherche et al., 2012) may affect the type of knowledge obtained regarding the role of OT synchrony in treatment. Finally, because it is an ongoing trial and the information regarding treatment condition is held by a third party, and therefore it is not available to the investigators until the end of the trial, we were not able to control for it in the current study. Future studies should examine whether the same findings emerge in different types of treatments, and especially treatments that focus on producing changes in the alliance (Safran & Muran, 2000).

This is the first study to investigate the existence of OT synchrony between patient and therapists and to demonstrate the potential role of OT synchrony as a biomarker of effective therapeutic processes. If replicated in future studies with larger samples, the findings may have important clinical implications. Based on the current findings, it may be suggested that higher social functioning in patients with MDD is an asset that can provide them with the capability of forming a more reciprocal and stronger therapeutic relationship with their therapists, which is characterized by high level of hormonal synchrony. By contrast, patients with impaired social functioning are less likely to form synchrony in their therapeutic relationship with their therapists, which may lower their chances of benefitting from treatment. Thus, interventions to enhance biological synchrony between patients and therapists may be of great importance for patients who are screened at baseline as having impaired social functioning. Such potential interventions may include training for therapists on the formation of synchronized relationships, feedback to therapists on their level of biological synchrony based on OT changes (endocrine fit feedback), and administration of intranasal OT to the patient (Flanagan et al., 2018; MacDonald et al., 2013) or to both patient and therapist.

References

Algoe, S. B., Kurtz, L. E., & Grewen, K. (2017). Oxytocin and social bonds: The role of oxytocin in perceptions of romantic partners' bonding behavior. *Psychological Science*, *28*(12), 1763–1772. https://doi.org/10.1177/0956797617716922

Altenstein-Yamanaka, D., Zimmermann, J., Krieger, T., Dörig, N., & grosse Holtforth, M. (2017). Self-reported interpersonal problems and impact messages as perceived by significant others are differentially associated with the process and outcome of depression therapy. *Journal of Counseling Psychology*, *64*(4), 410–423. https://doi.org/10.1037/cou0000221

Amini-Khoei, H., Mohammadi-Asl, A., Amiri, S., Hosseini, M. J., Momeny, M., Hassanipour, M., Rastegar, M., Haj-Mirzaian, A., Sanjarimoghaddam, H., Mehr, S. E., & Dehpour, A. R. (2017). Oxytocin mitigated the depressive-like behaviors of maternal separation stress through modulating mitochondrial function and neuroinflammation. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *76*, 169–178. https://doi.org/10.1016/j.pnpbp.2017.02.022

Anders, S., Heinzle, J., Weiskopf, N., Ethofer, T., & Haynes, J. D. (2011). Flow of affective information between communicating brains. *NeuroImage*, *54*(1), 439–446. https://doi.org/10.1016/j.neuroimage.2010.07.004

Bagby, R. M., Ryder, A. G., Schuller, D. R., & Marshall, M. B. (2004). The Hamilton Depression Rating Scale: Has the gold standard become a lead weight? *American Journal of Psychiatry*, *161*(12), 2163–2177. https://doi-org.ezprimo1.idc.ac.il/10.1176/appi.ajp.161.12.2163

Bohart, A. C., & Wade, A. G. (2013). The client in psychotherapy. In M. Lamber (Ed.), *Bergin and Garfield's handbook of psychotherapy and behavior change* (Vol. 6, pp. 219–257). John Wiley & Sons.

Carter, C. S., Pournajafi-Nazarloo, H., Kramer, K. M., Ziegler, T. E., White-Traut, R., Bello, D., & Schwertz, D. (2007). Behavioral associations and potential as a salivary biomarker. *Oral-Based Diagnostics*, *1098*(1), 312–322. https://doi.org/10.1196/annals.1384.006

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Lawrence Erlbaum.

Cuijpers, P. (2017). Four decades of outcome research on psychotherapies for adult depression: An overview of a series of meta-analyses. *Canadian Psychology*, *58*(1), 7–19. https://doi.org/10.1037/cap0000096

Cuijpers, P., Reijnders, M., & Huibers, M. J. (2019). The role of common factors in psychotherapy outcomes. *Annual Review of Clinical Psychology*, *15*, 207–231. https://doi.org/10.1146/annurev-clinpsy-050718-095424

de Jong, T. R., Menon, R., Bludau, A., Grund, T., Biermeier, V., Klampfl, S. M., Jurek, B., Bosch, O. J., Hellhammer, J., & Neumann, I. D. (2015). Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. *Psychoneuroendocrinology*, *62*, 381–388. https://doi.org/10.1016/j.psyneuen.2015.08.027

Delaherche, E., Chetouani, M., Mahdhaoui, A., Saint-Georges, C., Viaux, S., & Cohen, D. (2012). Interpersonal synchrony: A survey of evaluation methods across disciplines. *IEEE Transactions on Affective Computing*, *3*(3), 349–365. https://doi.org/10.1109/T-AFFC.2012.12

Dinger, U., Strack, M., Leichsenring, F., & Henning, S. (2007). Influences of patients' and therapists' interpersonal problems and therapeutic alliance on outcome in psychotherapy. *Psychotherapy Research*, *17*(2), 148–159. https://doi.org/10.1080/10503300600865393

Engel, S., Laufer, S., Knaevelsrud, C., & Schumacher, S. (2019). The endogenous oxytocin system in depressive disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *101*, 138–149. https://doi.org/10.1016/j.psyneuen.2018.11.011

Falkenström, F., Granström, F., & Holmqvist, R. (2013). Therapeutic alliance predicts symptomatic improvement session by session. *Journal of Counseling Psychology*, *60*(3), 317–328. https://doi.org/10.1037/a0032258

Feldman, R. (2017). The neurobiology of human attachments. *Trends in Cognitive Sciences*, *21*(2), 80–99. https://doi.org/10.1016/j.tics.2016.11.007

Feldman, R., & Eidelman, A. I. (2007). Maternal postpartum behavior and the emergence of infant–mother and infant–father synchrony in preterm and full-term infants: The role of neonatal vagal tone. *Developmental Psychobiology*, *49*(3), 290–302. https://doi.org/10.1002/dev.20220

Feldman, R., Gordon, I., Influs, M., Gutbir, T., & Ebstein, R. P. (2013). Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity. *Neuropsychopharmacology*, *38*(7), 1154–1162. https://doi.org/10.1038/npp.2013.22

Feldman, R., Gordon, I., & Zagoory-Sharon, O. (2010). The cross-generation transmission of oxytocin in humans. *Hormones and Behavior*, *58*(4), 696–676. https://doi.org/10.1016/j.yhbeh.2010.06.005

Feldman, R., Gordon, I., & Zagoory-Sharon, O. (2011). Maternal and paternal plasma, salivary, and urinary oxytocin and parent–infant synchrony: Considering stress and affiliation components of human bonding. *Developmental Science*, *14*(4), 752–761. https://doi.org/10.1111/j.1467-7687.2010.01021.x

Feldman, R., Magori-Cohen, R., Galili, G., Singer, M., & Louzoun, Y. (2011). Mother and infant coordinate heart rhythms through episodes of interaction synchrony. *Infant Behavior and Development*, *34*(4), 569–577. https://doi.org/10.1016/j.infbeh.2011.06.008

Flanagan, J. C., Sippel, L. M., Wahlquist, A., Moran-Santa Maria, M. M., & Back, S. E. (2018). Augmenting prolonged exposure therapy for PTSD with intranasal oxytocin: A randomized, placebo-controlled pilot trial. *Journal of Psychiatric Research*, *98*, 64–69. https://doi.org/10.1016/j.jpsychires.2017.12.014

Flückiger, C., Del Re, A. C., Wampold, B. E., & Horvath, A. O. (2018). The alliance in adult psychotherapy: A meta-analytic synthesis. *Psychotherapy: Theory, Research, & Practice*, *55*(4), 316–340. https://doi.org/10.1037/pst0000172

Frank, E., Cassano, G. B., Rucci, P., Thompson, W. K., Kraemer, H. C., Fagiolini, A., Maggi, L., Kupfer, D. J., Shear, M. K., Houck, P. R., Calugi, S., Grochocinski, V. J., Scocco, P., Buttenfield, J., & Forgione, R. N. (2011). Predictors and moderators of time to remission of major depression with interpersonal psychotherapy and SSRI pharmacotherapy. *Psychological Medicine*, *41*(1), 151–162. https://doi.org/10.1017/S0033291710000553

Friedrich, M. J. (2017). Depression is the leading cause of disability around the world. *Journal of the American Medical Association*, *317*(15), 1517–1517. https://doi.org/10.1001/jama.2017.3826

Gómez Penedo, J. M., Babl, A., Krieger, T., Heinonen, E., Flückiger, C., & grosse Holtforth, M. (2019). Interpersonal agency as predictor of the within-patient alliance effects on depression severity. *Journal of Consulting and Clinical Psychology*, *88*(4), 338–349. https://doi.org/10.1037/ccp0000475

Greer, T. L., Kurian, B. T., & Trivedi, M. H. (2010). Defining and measuring functional recovery from depression. *CNS Drugs*, *24*(4), 267–284. https://doi.org/10.2165/11530230-000000000-00000

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *The British Journal of Social and Clinical Psychology*, *6*(4), 278–296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

Josef, L., Goldstein, P., Mayseless, N., Ayalon, L., & Shamay-Tsoory, S. G. (2019). The oxytocinergic system mediates synchronized interpersonal movement during dance. *Scientific Reports*, *9*(1), 1894–1902. https://doi.org/10.1038/s41598-018-37141-1

Lambert, M. J., Vermeersch, D. A., & Brown, G. J. (2004). *Administration and scoring manual for the OQ-30.2*. American Professional Credentialing Services.

Leibovich, L., Nof, A., Auerbach-Barber, S., & Zilcha-Mano, S. (2018). practical clinical suggestion for strengthening the alliance based on a supportive–expressive framework. *Psychotherapy: Theory, Research, & Practice*, *55*(3), 231–240. https://doi.org/10.1037/pst0000195

Levy, K. N., Kivity, Y., Johnson, B. N., & Gooch, C. V. (2018). Adult attachment as a predictor and moderator of psychotherapy outcome: A meta-analysis. *Journal of Clinical Psychology*, *74*(11), 1996–2013. https://doi.org/10.1002/jclp.22685

Luborsky, L. (1984). *The principles of psychoanalytic psychotherapy*. Basic Books.

Luborsky, L. (1995). Supportive–expressive dynamic psychotherapy of depression: A time-limited version. In J. P. Barber & P. Crits-Christoph (Eds.), *Dynamic therapies for psychiatric disorders* (pp. 41–83). Basic Books.

MacDonald, K., MacDonald, T. M., Brüne, M., Lamb, K., Wilson, M. P., Golshan, S., & Feifel, D. (2013). Oxytocin and psychotherapy: A pilot study of its physiological, behavioral, and subjective effects in males with depression. *Psychoneuroendocrinology*, *38*(12), 2831–2843. https://doi.org/10.1016/j.psyneuen.2013.05.014

Massey, S. H., Backes, K. A., & Schuette, S. A. (2016). Plasma oxytocin concentration and depressive symptoms: A review of current evidence and directions for future research. *Depression and Anxiety*, *33*(4), 316–322. https://doi.org/10.1002/da.22467

Matsuzaki, M., Matsushita, H., Tomizawa, K., & Matsui, H. (2012). Oxytocin: A therapeutic target for mental disorders. *The Journal of Physiological Sciences*, *62*(6), 441–444. https://doi.org/10.1007/s12576-012-0232-9

McQuaid, R. J., McInnis, O. A., Abizaid, A., & Anisman, H. (2014). Making room for oxytocin in understanding depression. *Neuroscience and Biobehavioral Reviews*, *45*, 305–322. https://doi.org/10.1016/j.neubiorev.2014.07.005

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: Results from the World Health Surveys. *Lancet*, *370*(9590), 851–858. https://doi.org/10.1016/S0140-6736(07)61415-9

Pawitan, Y. (2013). *All likelihood: Statistical modelling and inference using likelihood*. Oxford University Press.

Priel, A., Djalovski, A., Zagoory-Sharon, O., & Feldman, R. (2019). Maternal depression increases child susceptibility to psychopathology across the first decade of life; Oxytocin and synchrony as markers of resilience. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *60*(1), 30–42. https://doi.org/10.1111/jcpp.12880

Ramseyer, F., & Tschacher, W. (2011). Nonverbal synchrony in psychotherapy: Coordinated body movement reflects relationship quality and outcome. *Journal of Consulting and Clinical Psychology*, *79*(3), 284–295. https://doi.org/10.1037/a0023419

Reich, C. M., Berman, J. S., Dale, R., & Levitt, H. M. (2014). Vocal synchrony in psychotherapy. *Journal of Social and Clinical Psychology*, *33*(5), 481–494. https://doi.org/10.1521/jscp.2014.33.5.481

Ripley, B. D. (2002). *Modern applied statistics with S*. Springer. https://doi-org.ezprimo1.idc.ac.il/10.1046/j.1467-9884.2003.t01-19-00383_22.x

Ronchetti, E. (1990). Small sample asymptotics: A review with applications to robust statistics. *Computational Statistics & Data Analysis*, *10*(3), 207–223. https://doi.org/10.1016/0167-9473(90)90002-Y

Safran, J. D., & Muran, J. C. (2000). *Negotiating the therapeutic alliance: A relational treatment guide*. Guilford Press.

Schneiderman, I., Kanat-Maymon, Y., Zagoory-Sharon, O., & Feldman, R. (2014). Mutual influences between partners' hormones shape conflict dialog and relationship duration at the initiation of romantic love. *Social Neuroscience*, *9*(4), 337–351. https://doi.org/10.1080/17470919.2014.893925

Schneiderman, I., Zagoory-Sharon, O., Leckman, J. F., & Feldman, R. (2012). Oxytocin during the initial stages of romantic attachment: Relations to couples' interactive reciprocity. *Psychoneuroendocrinology*, *37*(8), 1277–1285. https://doi.org/10.1016/j.psyneuen.2011.12.021

Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological Psychiatry*, *79*(3), 194–202. https://doi.org/10.1016/j.biopsych.2015.07.020

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for *DSM–IV* and ICD-10. *The Journal of Clinical Psychiatry*, *59*(Suppl. 20), 22–33. https://pubmed.ncbi.nlm.nih.gov/9881538/

Tingley, D., Yamamoto, T., Hirose, K., Keele, L., & Imai, K. (2014). Mediation: R package for causal mediation analysis. *Journal of Statistical Software*, *59*(5), 1–38. https://doi.org/10.18637/jss.v059.i05

Tschacher, W., & Ramseyer, F. (2017). Nonverbal synchrony. In A. Wenzel (Ed.), *The SAGE encyclopedia of abnormal and clinical psychology* (pp. 2298). SAGE. https://doi.org/10.4135/9781483365817.n202

Ulmer-Yaniv, A., Avitsur, R., Kanat-Maymon, Y., Schneiderman, I., Zagoory-Sharon, O., & Feldman, R. (2016). Affiliation, reward, and immune biomarkers coalesce to support social synchrony during periods of bond formation in humans. *Brain, Behavior, and Immunity*, *56*, 130–139. https://doi.org/10.1016/j.bbi.2016.02.017

Vittner, D., McGrath, J., Robinson, J., Lawhon, G., Cusson, R., Eisenfeld, L., Walsh, S., Young, E., & Cong, X. (2018). Increase in oxytocin from skin-to-skin contact enhances development of parent–infant relationship. *Biological Research for Nursing*, *20*(1), 54–62. https://doi.org/10.1177/1099800417735633

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS

scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.1037/0022-3514.54.6.1063

Wilcox, R. R. (2011). *Introduction to robust estimation and hypothesis testing*. Academic Press.

Williams, J. R., Carter, C. S., & Insel, T. (1992). Partner preference development in female prairie voles is facilitated by mating or the central infusion of oxytocin. *Oxytocin in Maternal, Sexual, and Social Behaviors*, *652*, 487–489. https://doi.org/10.1111/j.1749-6632.1992.tb34393.x

Winnicott, D. (1971). *Playing and reality*. Basic Books.

Zantvoord, J. B., Diehle, J., & Lindauer, R. J. (2013). Using neurobiological measures to predict and assess treatment outcome of psychotherapy in posttraumatic stress disorder: Systematic review. *Psychotherapy and Psychosomatics*, *82*(3), 142–151. https://doi.org/10.1159/000343258

Zeileis, A. (2006). *Object-oriented computation of sandwich estimators* (Report No. 37). Vienna University of Economics and Business. https://epub.wu.ac.at/1644/

Zilcha-Mano, S., Dolev, T., Leibovich, L., & Barber, J. (2018). Identifying the most suitable treatment for depression based on patients' attachment: Study protocol for a randomized controlled trial of supportive–expressive vs. supportive treatments. *BMC Psychiatry*, *18*(1), 362–371. https://doi.org/10.1186/s12888-018-1934-1

Zilcha-Mano, S., & Errázuriz, P. (2015). One size does not fit all: Examining heterogeneity and identifying moderators of the alliance–outcome association. *Journal of Counseling Psychology*, *62*(4), 579–591. https://doi.org/10.1037/cou0000103

Zilcha-Mano, S., Porat, Y., Dolev, T., & Shamay-Tsoory, S. (2018). Oxytocin as a neurobiological marker of ruptures in the working alliance. *Psychotherapy and Psychosomatics*, *87*(2), 126–127. https://doi.org/10.1159/000487190

Zilcha-Mano, S., Shamay-Tsoory, S., Dolev-Amit, T., Zagoory-Sharon, O., & Feldman, R. (2020). Oxytocin as a biomarker of the formation of therapeutic alliance in psychotherapy and counseling psychology. *Journal of Counseling Psychology*, *67*(4), 523–535. https://doi.org/10.1037/cou0000386

Zu, J., & Yuan, K. H. (2010). Local influence and robust procedures for mediation analysis. *Multivariate Behavioral Research*, *45*(1), 1–44. https://doi.org/10.1080/00273170903504695

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