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Brief Report

Oxytocin Reactivity to the Therapeutic Encounter as a Biomarker of Change in the Treatment of Depression

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Abstract

Objective: Depression affects millions worldwide, thus underscoring the urgent need to optimize health care practices. To better understand the processes involved in psychotherapy gains, studies have emphasized the need to complement subjective reports with objective measures, in particular biological markers. Oxytocin (OT) has been proposed as a potential biomarker in the treatment of depression given its involvement in depression-related psychological and physiological functions and the formation of close relationships. Here, we assessed whether OT reactivity to therapeutic encounters (absolute and/or directional reactivity) is linked to improvements in depressive symptoms from session to session during psychotherapy. *Method*: A total of 284 saliva samples were collected from 30 adult clients who underwent 16 sessions of manualized psychodynamic psychotherapy for depression in a university setting. Salivary OT was measured before and after five pre-selected sessions distributed evenly throughout the therapy. The Beck Depression Inventory-II (BDI-II) was administered at the beginning of each session. *Results*: Multi-level growth models indicated that clients exhibiting greater absolute OT reactivity showed greater improvement in depressive symptoms throughout treatment. Directional reactivity was not associated with depressive symptom change. In addition, clients with higher baseline OT levels displayed less change in depressive symptoms. *Conclusion*: These findings highlight reactivity of the OT system, in either direction, as an important feature of the treatment response. Consistent with recent models of the neurobiology of resilience, OT reactivity appears to serve as an important biomarker of psychotherapy gain in the treatment of depression.

***Public significance statement*:** This study highlights reactivity of the oxytocin system as an important biomarker of success in the treatment of depression.

Keywords: Depression, oxytocin, psychotherapy outcome, biomarkers, reactivity

Major depressive disorder (MDD) is a leading cause of disability worldwide and its deleterious effects on individuals, families and societies make the optimization of care practices for depression critical (World Health Organization, 2017). Despite the wide variety of effective psychological and pharmacological therapies for depression, the mechanisms underlying psychotherapy gains remain poorly understood (Cuijpers, 2018). To date, most studies on psychotherapy gains have relied on self-report measures to identify the underlying treatment processes (Crits-Christoph et al., 2013). Given the inherent shortcomings of these measures (Kazdin, 2008), a better understanding of the processes involved in psychotherapy gains could be substantially advanced by focusing on objective biological markers (Zilcha-Mano et al., 2020). A promising candidate is the neuropeptide oxytocin (OT), which is involved in a host of inter- and intra-personal processes that are disrupted in depression (Engel et al., 2019).

Research on the association between depressive symptoms and baseline OT levels in humans is inconclusive (Engel et al., 2019) with some studies reporting reduced (Apter-Levy et al., 2013; Frasch, 1995), others enhanced (Holt-Lunstad et al., 2011; Parker et al., 2010), and yet other similar (Cyranowski et al., 2008; Jobst et al., 2015) levels of OT in cases of MDD versus healthy controls. Indeed, a recent meta-analysis which found no systematic differences in endogenous OT concentrations between individuals with depression and healthy controls pointed to several limitations in existing studies, mainly reliance on cross-sectional data and one-point comparisons and a focus on levels rather than on the reactivity of the OT system (Engel et al., 2019). Hormonal reactivity is defined as the change from a person's baseline level as a response to an environmental stimulus (Khoury, 2015). Hormonal reactivity is an important marker of well-being and blunted hormonal reactivity was found to be associated with depression in other hormones such as cortisol and dehydroepiandrosterone (Apter-Levy et al., 2020; Feldman, Weller, Zagoory-Sharon & Levine, 2007; Pratt et al.,

2017). Furthermore, it has been suggested that OT reactivity may serve as a better indicator of depression than baseline levels (Engel et al., 2019; Feldman, 2020). While OT baseline levels tend to be stable within individuals over a period of months and even years (Feldman et al., 2007; Priel, Djalovski, Zagoory-Sharon & Feldman, 2019), people tend to differ in the way their oxytogergic system reacts in interpersonal contexts (Feldman, 2021). Since depressive symptoms typically change within individuals over time (Rottenberg, 2017), studies that aim to explore the reactivity of the OT system in relation to the dynamics of depressive symptomatology may contribute to further specifying the role of OT in depression (Engel et al., 2019).

Recent models on the neurobiology of resilience suggest that OT reactivity can serve as an indicator of individuals' ability to flexibly respond in interpersonal contexts, and as such constitutes a key marker of resilience and well-being (Feldman, 2020, 2021). Studies in the field of developmental psychology have shown that depressed mothers tend to have blunted OT reactivity, which mirrors the inflexibility of their oxytocinergic system (Apter-Levy et al., 2013). In addition, higher OT reactivity, as a response to interpersonal interaction, was found to be associated with higher resilience and well-being among children (Priel et al., 2019). There is some evidence suggesting that depression involves deficits in psychological flexibility (Rottenberg, 2017), such as rigidity of emotion regulation strategies (Joormann & Stanton, 2016) and inflexible responses in interpersonal contexts (Bonanno & Burton, 2013). Given the central role of OT in emotion regulation and bond formation (Feldman, 2012), the link between OT reactivity and responses to the treatment of depressive symptomatology merits further examination. The psychotherapeutic encounter, when considered as a laboratory for the formation and consolidation of close bonds, provides a particularly suitable context for research on the associations between OT reactivity and improvement in depressive symptoms.

OT has recently been proposed as a potential biomarker of therapeutic processes (MacDonald et al., 2013). To date, however, few studies have examined OT reactivity within the therapeutic relationship (Jobst et al., 2018; Zilcha-Mano et al., 2018, 2020). Pre-to-post session increases in OT levels were found to correlate with more frequent alliance ruptures (Zilcha-Mano et al., 2018) and reduced proximity-seeking with the therapist (Zilcha-Mano et al., 2020). Another study that explored the associations between OT reactivity and treatment outcomes in 16 depressed clients (Jobst et al., 2018) using a social exclusion manipulation found that in response to a social exclusion manipulation, most participants manifested a drop in OT levels. However, a faster return to a baseline level was positively associated with greater post-treatment improvement in depressive symptoms. However, OT was assessed only once, prior to the beginning of treatment, and reactivity was measured in a lab paradigm, rather than a therapy session. To the best of our knowledge, the extent to which clients' OT reactivity to the therapeutic encounter may be associated with the alleviation of depressive symptoms from session to session in the context of psychotherapy has not been examined.

Studies implementing hormonal reactivity designs have used various indices of reactivity (Engel et al., 2019; Khoury et al., 2015). Most have employed a difference score between baseline and post task levels (e.g., Baiao 2019; Bernhard 2018; Jobst et al., 2018; Zilcha-Mano et al., 2018). Other works that collected more than two samples of OT have tended to use the area under the curve (AUC; e.g., Cyranowski et al., 2008; Pratt et al, 2017; Ulmer-Yaniv et al., 2018). In the current study, we operationalized OT reactivity to the therapeutic encounter as the absolute percent change in OT from the beginning to the end of the session ($OTreactivity^{abs}$). The rationale for using this index of reactivity was based on (a) recent theoretical models that highlight the importance of reactivity of the OT system, regardless of the direction of the response (Feldman 2020, 2021), (b) studies showing that OT baseline levels tend to be stable within individuals over periods of months and even years

(Feldman, et al., 2007; Feldman, et al., 2013; Priel, 2019), whereas people tend to differ in the ways their oxytocinergic system reacts in interpersonal contexts (Feldman, 2021), (c) the literature which has provided inconclusive findings as to the direction of the associations between OT levels and depressive symptoms (e.g., Engel et al., 2019), and (d) recent studies that have used the absolute difference to assess reactivity in other hormones, such as cortisol (e.g., Ebrahimi et al., 2019).

Our main hypothesis was that clients who tended (on average) to exhibit greater OT reactivity to the therapeutic encounter in either direction ($OTreactivity^{abs}$), would exhibit greater improvement in depressive symptoms throughout treatment than clients presenting blunted OT responses.

To rule out a plausible rival hypothesis related to the importance of the directionality of the OT change, we also examined whether clients who tended (on average) to exhibit greater directional OT reactivity to the therapeutic encounter ($OTreactivity^{dir}$ – directional OT change), would exhibit greater improvement in depressive symptoms throughout treatment.

Method

This study was approved by the local institutional review board, and all clients signed an informed consent form.

Participants. A total of 178 candidate participants were screened using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), as part of an ongoing study. Of this cohort, 64 individuals with BDI-II scores ≥17 were asked to come for an intake interview during which the Mini-International Neuropsychiatric Interview version 5.0 (MINI; Sheehan, 1998) was administered. The inclusion criteria were: (a) a primary diagnosis of MDD as indicated by MINI and (b) aged 18 to 67. The exclusion criteria were (a) active suicidality, (b) substance abuse or dependence, (c) current or past bipolar disorder, (d) presence of psychotic features, (e) past severe head injury, (f) pending legal proceedings, and (g) current pregnancy

or a medical condition warranting hormonal treatment. Thirty-five clients started treatment; two clients ceased to come to therapy before the 12th session and were considered dropouts. Three other clients opted to take psychiatric medication and were excluded from the analysis. The final cohort was composed of 30 (19 males) clients diagnosed with MDD, with a mean age of 34.63 (standard deviation [SD]=9.27; range: 21-59 years). Fourteen participants were single and 16 were married or in a permanent relationship, 23 had at least a bachelor's degree, and all but two were fully or partially employed. The clients' mean BDI-II score at intake was 22.5 (SD=7.75), indicating moderate depression levels (Beck et al., 1996).

Treatment and therapists. The clients underwent brief (16 session) supportive-expressive (SE) psychodynamic psychotherapy (Luborsky & Mark, 1991) adapted to the treatment of depression (Luborsky et al., 1995). The key treatment features included supportive techniques, such as affirmation and empathic validation, as well as expressive techniques such as interpretation and confrontation. SE therapy has been reported to be effective in the treatment of depression (Beck et al., 1996; Sheehan, 1998). The therapists were trained and supervised by senior clinicians with extensive expertise in SE therapy and received weekly individual and group supervision.

Nine therapists (5 females) participated in this study; 4 therapists treated 3-4 clients each, whereas the 5 remaining therapists treated 1-2 clients each. The therapists were advanced trainees in a university clinic with 3-7 years of experience.

Measures and procedure. Salivary OT was sampled before and after five pre-selected sessions, evenly distributed throughout the course of therapy (sessions 2, 5, 8, 11, and 14), for a total of 284 saliva samples (16 saliva samples were missing from the analysis as a result of insufficient saliva or clients arriving late to the session). Before these sessions, the clients were requested to abstain from eating for at least an hour before the therapy session and to avoid drinking or chewing gum at least half an hour before the sample collection.

Immediately before the sampling session, the clients filled out a questionnaire on their medical condition on that day. The collected samples were frozen at −20 °C.

The samples were subjected to three freeze-thaw cycles (−80 °C and 4 °C), and centrifuged at 1500 × g (4500 rpm) for 30 min to precipitate the mucus. The supernatant was collected and stored at −20 °C until assayed. Sensitivity was increased by concentrating the liquid samples by freeze-drying to yield a powder. The dry samples were reconstructed with an assay buffer immediately before the assay in one-fourth of the original volume. The OT concentration was measured as per the instructions provided by a commercial OT Enzyme-Linked Immunosorbent Assay (ELISA) kit. The intra-assay coefficients of the samples and controls were less than 12.9% and 24.1%, respectively.

$OTreactivity^{abs}$ was operationalized as the absolute change in OT percentage from the beginning to the end of the session. $OTreactivity^{dir}$ was operationalized as the increase in OT levels pre to post session Average $OTreactivity^{abs}$ and $OTreactivity^{dir}$across five sampling sessions was computed for each client.

Outcome measure. At the beginning of each session, the clients completed the BDI-II (Beck et al., 1996). The BDI reliability was moderate to good (within-client = 0.77, between-client = 0.80).

Data availability: The data are available on request from the corresponding author. The data are not publicly available because they contain information that could compromise participant confidentiality.

Results

We used 3 level (session [S] nested within client [C], nested within therapists [T]) multi-level models (Hoffman, 2015) to examine the associations between OT reactivity and depressive symptoms. Specifically, to test the hypothesis that higher average absolute reactivity (or directional reactivity) $OTreactivity^{abs/dir}{}_{CT}$ to the therapeutic encounter would

be associated with greater improvement in depressive symptoms throughout treatment, we ran a series of moderated growth models. The equation is as follows:

$$BDI_{SCT} = \gamma_{000} + \gamma_{100} * Session_{SCT} + \gamma_{200} * OTreactivity^{abs/dir}{}_{CT} + \gamma_{300} * OTpre_{CT} + \gamma_{400} * Session_{SCT} * OTreactivity^{abs/dir}{}_{CT} + \gamma_{500} * Session_{SCT} * OTpre_{CT} + u_{00T} + r_{0CT} + e_{SCT}$$

where clients' BDI_{SCT} reports were the outcome, session number was the level-1 predictor, and average clients' $OTreactivity^{abs}{}_{CT}$ (or $OTreactivity^{dir}{}_{CT}$) was the level-2 moderator (grand mean centered). Since we were primarily interested in the effect of OT reactivity relative to baseline levels, average baseline levels ($OTpre_{CT}$; grand mean centered) were included as covariates. To account for between-client and between therapist variability, the intercept was treated as random both at level 2 (r_{0CT}) and at level 3 (u_{00T}). Treating the session slope as random effect did not improve the model fit ($\chi^2[4] = 4.23$, $p = .38$). A first-order autoregressive structure was imposed on the covariance matrix of the within-person residuals.

Table 1 presents the results. Supporting the key hypothesis, the findings indicated that clients who exhibited greater $OTreactivity^{abs}$ to the therapeutic encounter showed greater improvement in depressive symptoms across treatment. Figure 1 depicts OT reactivity and the change in depressive symptoms throughout treatment, in cases of good and poor outcomes drawn from the sample. The results also showed that there was no association between $OTreactivity^{dir}$ and change in depressive symptoms. Baseline OT levels interacted with session number in the $OTreactivity^{dir}$ model (and marginally significant in the

$OTreactivity^{abs}$ model), suggesting that higher OT levels at the beginning of a session were associated with reduced improvement in depressive symptoms throughout the treatment[1].

Discussion

This study responds to the recent call to examine biomarkers underpinning psychotherapy gains (Engel et al., 2019; Zilcha-Mano et al., 2020), by testing the associations between OT reactivity and improvement in depressive symptoms during the course of brief psychodynamic psychotherapy. The results suggested that individuals with MDD who showed greater absolute OT reactivity also exhibited larger improvement in depressive symptoms throughout treatment. No association was found between directional OT reactivity and change in depressive symptoms. These findings highlight the reactivity of the OT system, regardless of the direction of change, as an important biomarker of success in the treatment of depression and are consistent with recent models of resilience based on the neurobiology of affiliation, which proposes that the functionality of the OT system provides a biological substrate for resilience, where reactivity is theorized to be a key tenet of resilience (Feldman, 2020, 2021).

Decreased psychological flexibility appears to be one of the central features of depression (Rottenberg, 2017). Blunted OT reactivity may be a biomarker of such inflexibility, with effects cascading into psychological rigidity. The OT system is implicated

[1] We ran an additional session-level analysis to examine whether higher session-level absolute reactivity (or directional reactivity) would predict change in next session BDI. Clients' next session BDI reports were the outcome (while controlling for current session BDI), and clients' current session absolute reactivity (or directional reactivity) was the level-1 predictor (clients' mean centering of session reactivity assessments). Since our interest was in the effect of OT reactivity relative to baseline levels, baseline levels were included as covariates (clients' mean centering of pre-session assessments). We found no effects at the session level; in other words, neither absolute nor directional OT reactivity was associated with next session BDI. Baseline OT levels were also not associated with next session BDI.

in cellular, molecular, and network assembly-level reactivity, and dynamically integrates the brain and periphery, as well as cross-talk with the stress, reward, and immune systems (Grinevich et al., 2016). The reactivity of this ancient system is thought to be involved in the formation of maternal-infant bonds and pair-bonding in mammals, leading to growth in social competencies, empathy, well-being, and resilience (Feldman et al., 2016). Thus, individuals suffering from depression who have blunted OT reactivity may experience difficulties in responding to the therapeutic encounter or allowing change to occur. A blunted OT response throughout the session may be a biological marker of greater rigidity and the difficulty to react to an interpersonal interaction, leading to a lesser inclination to benefit from treatment. The current findings are consistent with studies suggesting that the reactivity of the OT system plays a role in depression (Pratt et al., 2015), and those from a longitudinal study on the effects of maternal MDD showed that offspring of depressed mothers with greater reactivity of the OT system were more resilient and exhibited less psychopathology (Priel et al., 2019). Our findings are also consistent with a recent study indicating that OT reactivity to interaction between adults depends on the quality of their exchange, particularly the degree of reciprocity, attunement, and empathy expressed during the session (Djalovski Zagoory-Sharon, Kinreich & Feldman, 2021).

The findings are not only consistent with a study showing that OT reactivity is associated with positive outcomes in the treatment of depression (Jobst et al., 2018), but also extend previous research by detailing the associations between OT reactivity measured in multiple sessions across treatment and the session-to-session changes in depressive symptoms.

The findings also indicate that higher OT levels at the beginning of a session predicted less improvement in depressive symptoms. This is consistent with research showing associations between higher baseline OT before the start of treatment and elevated symptoms

(Zilcha-Mano et al., 2020). Higher baseline OT may be associated with increased attachment anxiety, which may limit the benefits of the therapeutic relationship (Weisman et al., 2013). In the current study we focused on between-person differences in OT reactivity and its association with change in depressive symptoms throughout treatment. In addition, depression levels were only measured at the beginning of each session. Given that OT reactivity is a rapid biological reaction, the outcome measures need to be obtained immediately before and after the biological response (Bernhard et al., 2018). Future studies would benefit from measuring depression levels at both the beginning and at the end of the session to examine whether OT reactivity within a session results in a change in depressive symptoms pre to post session. Furthermore, given the current consensus that the effects of OT are person- and context-dependent (Shamay-Tsoory & Abu-Akel, 2016), future studies could conduct a more detailed investigation of specific clients' or therapists' trait-like as well as state-like characteristics that may influence the association between OT reactivity and symptomatic change. Since OT is released in response to stressful situations that trigger affiliative needs (Taylor et al., 2006), it would be worthwhile to examine whether stress levels at the beginning of a session influence the association between OT and treatment outcome. Alternatively, given the association between OT and behavioral synchrony in dyads across multiple relationships (Feldman, 2012), future studies could examine whether the association between OT reactivity and treatment outcome is mediated by client-therapist synchrony.

This study has a number of limitations, including its small sample size and the measurement of peripheral OT. Whereas salivary measures are well-validated in relation to plasma level, genetic variability, and brain activity (Massey et al., 2016; Weisman et al., 2012), the associations between peripheral and central activity of the OT system remain poorly understood (Valstad et al., 2017). Despite these limitations, this study constitutes an important step forward by incorporating OT measurements into the therapeutic context and

highlighting the importance of OT reactivity as a key biomarker in the treatment of depression.

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Table 1.

Multi-level models predicting change in BDI over treatment by OT indices

	OT reactivity absolute model			OT reactivity directional model		
	Est.	*CI*	*p*	*Est.*	*CI*	*p*
Intercept	18.755	[14.36, 23.15]	<0.001	18.821	[14.61, 23.03]	<0.001
Session	-0.508	[-0.64, -0.38]	<0.001	-0.509	[-0.64, -0.38]	<0.001
OT_Pre	-0.002	[-0.09, 0.08]	0.959	-0.024	[-0.10, 0.05]	0.534
OT_Reactivity	8.124	[-6.82, 23.07]	0.269	-5.104	[-15.09, 4.88]	0.297
Session X OT_Pre	0.004	[0.00, 0.01]	0.070	0.005	[0.00, 0.01]	0.008
Session X OT_Reactivity	-0.718	[-1.34, -0.10]	0.024	-0.212	[-0.69, 0.26]	0.381

Note. OT = Oxytocin.

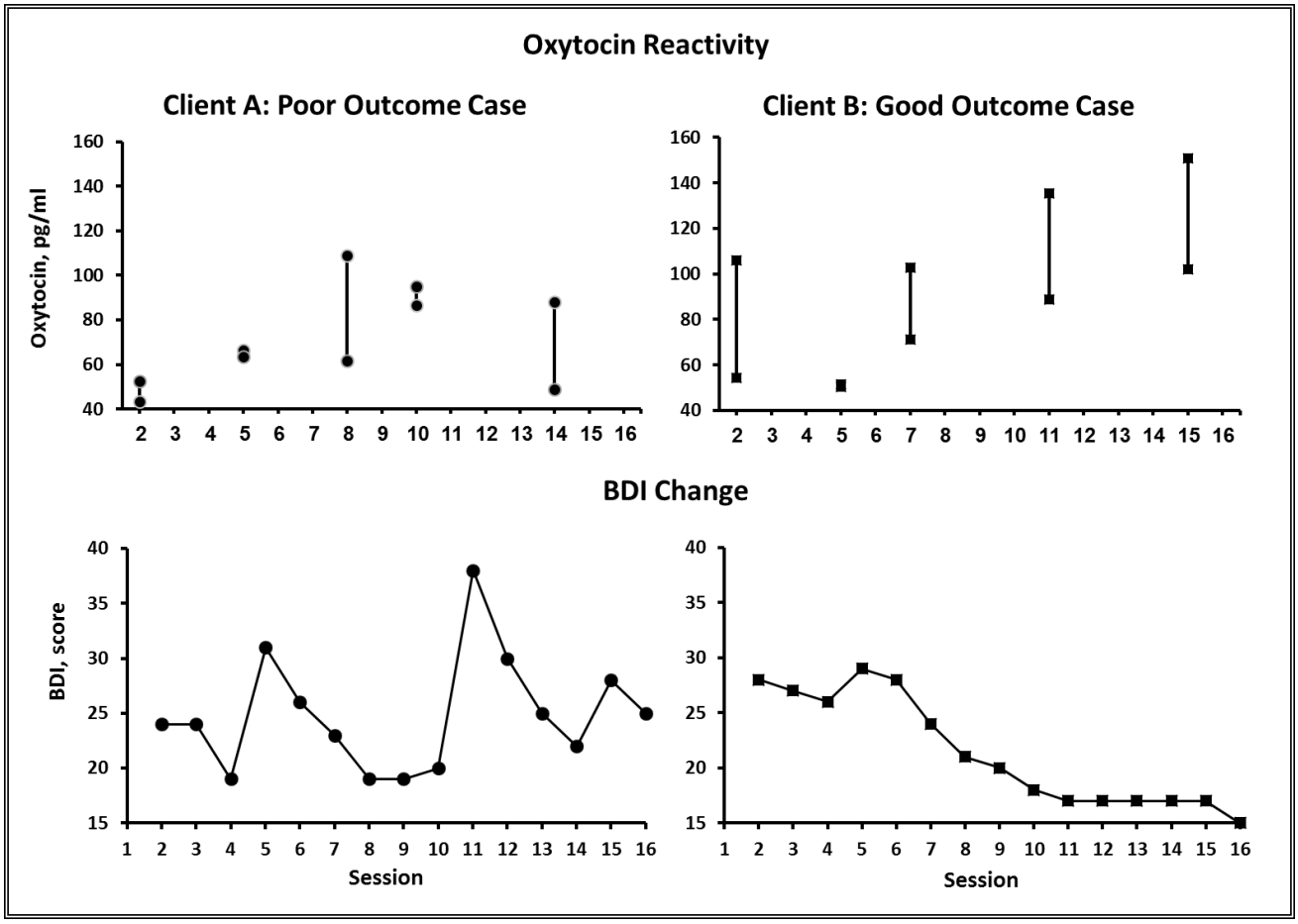

Figure Legends

Fig. 1. Illustration of within session OT absolute reactivity in five pre-selected sessions throughout treatment (upper panels) and change in depressive symptoms throughout treatment (lower panels), in a poor outcome case (client A, left panels) and a good outcome case (client B, right panels) drawn from our sample.; OT = Oxytocin; BDI = Beck Depression Inventory.