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Oxytocin as a Biomarker of the Formation of Therapeutic Alliance in Psychotherapy and Counseling Psychology

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The therapeutic alliance is one of the most consistent predictors of therapeutic change, including symptom reduction and improvement in wellbeing and quality of life, across a variety of mental health interventions. Yet, little is known about its biological mechanisms. Oxytocin (OT) has been suggested as a biological mechanism by which bonds are formed and strengthened across species. This article is intended to demonstrate the potential of OT as a biomarker of therapeutic change in psychotherapy and counseling psychology, especially of the therapeutic alliance. We delineate three main potential paths of investigation based on the most recent research on OT in parent–child and romantic partner dyads. For each path, we provide a detailed explanation for whom, when, and how OT should be measured. Each path is illustrated using data collected in a randomized controlled trial of psychotherapy for major depressive disorder. These illustrations demonstrate the great potential of OT as a biomarker of (a) trait-like characteristics of the patients and the therapists, (b) the processes of therapeutic change, and (c) the dyadic synchrony between patients and their therapists. The potential clinical contribution of OT as a biomarker for each of these three paths is further demonstrated using a case study. Practical suggestions and directions for future research are discussed.

Public Significance Statement
The article highlights the promising potential of OT as a biomarker in psychotherapy research, through the most recent research on the role of OT in parent–child and romantic relationships, as well as through data from a randomized controlled trial of psychotherapy for major depressive disorder. The article provides practical suggestions on how this potential may be realized. Interdisciplinary studies integrating the two fields of inquiry, psychotherapy and OT research, can create new important knowledge that has the potential to make a substantial contribution to clinical practice and complement existing approaches for measuring the process of therapeutic change.

Keywords: oxytocin, biomarkers, alliance, therapeutic relationship, psychotherapy

The most consistent predictor of treatment success, across various types of therapeutic modalities and mental health interventions, is the therapeutic relationship formed between patients and their therapists (Barber, 2009; Crits-Christoph, Johnson, Connolly Gibbons, & Gallop, 2013; Flückiger, Del Re, Wampold, & Horvath, 2018; Totura, Fields, & Karver, 2018). The therapeutic relationship is commonly conceptualized as an attachment relationship, which may provide patients with a safe haven and a secure base for working through their difficulties. This relationship may also be therapeutic in itself, as part of the process of "earning" attachment security (Bowlby, 1988; Daniel, 2006; Mikulincer, Shaver, & Berant, 2013). Over the decades, many terms and definitions have been used to characterize the therapeutic relationship (Gelso, 2011). The most frequently used one is that of working alliance (Horvath, Del Re, Flückiger, & Symonds, 2011), commonly defined as the quality of the emotional bond between patients and their therapists, and their levels of agreement regarding the goals of the therapy and the tasks necessary to achieve them (Bordin, 1979; Hatcher & Barends, 2006). In a recent meta-analysis summarizing the findings from 295 studies and providing data on more than 30,000 patients, the alliance was found to be a significant and consistent predictor of treatment outcome (Flückiger et al., 2018).

Research on therapeutic alliance was instrumental in establishing the consistent association between early alliance and treatment outcome (Barber, 2009; Crits-Christoph et al., 2013). In recent

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years, studies began to examine more nuanced, clinically relevant questions to understand the essence of this association, with the aim of deriving evidence-based guidelines to inform clinical practice. Following contemporary theories of alliance that stress the important role of rupture resolution processes in the therapeutic alliance (Safran & Muran, 2000), studies in the last two decades focused on the dynamic nature of the alliance (Stiles & Goldsmith, 2010), and especially on rupture-resolution processes occurring in the alliance during the session (Eubanks, Muran, & Safran, 2018). Research on the dynamic nature of the alliance has shown the importance of disentangling the trait-like interpersonal characteristics of patients (their general ability to form satisfying relationships) from the state-like changes in alliance over the course of treatment, each theorized to play a distinct role (Zilcha-Mano, 2016, 2017). State-like changes in alliance may take the form of rupture and repair processes. Ruptures in the alliance, that is, deteriorations in its quality, generally belong to two categories: (a) withdrawal ruptures, in which patients move either away from the therapist and the treatment in a submissive fashion (e.g., providing laconic responses to questions asked by the therapist in an avoidant manner), or move toward the therapist, but in a way that denies an aspect of the patient's experience (e.g., when a patient appears overly compliant and submits to the therapist in an excessively deferential manner), and (b) confrontation ruptures, in which patients move against the therapist or the work of therapy and express anger (e.g., complaining about the therapist; Eubanks, Lubitz, Muran, & Safran, 2019; Safran & Muran, 2000). By systematically exploring, understanding, and resolving alliance ruptures, therapists can provide patients with a new constructive interpersonal experience that has the potential to modify their maladaptive interpersonal schemas (Safran & Muran, 1996, 2000) and may thereby contribute to adaptive changes in the trait-like alliance as well. A recent meta-analysis pointed out the important role of successful alliance rupture and repair in treatment efficacy (Eubanks et al., 2018).

The most commonly used method for assessing the alliance is based on patients' and therapists' self-report measures. Short and easy-to-use self-report measures are available, with strong psychometric properties (such as the Working Alliance Inventory [WAI], Hatcher & Barends, 2006; Horvath et al., 2011). The WAI contains items such as "My therapist and I trust one another," and "I believe my therapist likes me." Although self-report measures are inexpensive, simple, and quick, they have clear disadvantages, including the fact that they are limited to phenomena that the individual is aware of, able, and interested in reporting. Moreover, these measures are prone to ceiling effects, especially when answered by patients (Kivlighan & Shaughnessy, 1995). These disadvantages are especially critical in light of suggestions by contemporary theories that withdrawal ruptures may be easily missed. Indeed, empirical studies have reported that withdrawal ruptures often go undetected by both therapists and patients, and can have devastating effects on treatment outcomes (Eubanks et al., 2018, 2019; Muran, 2019).

To cope with the many disadvantages of self-report measures, comprehensive observer-based measures of alliance ruptures and repairs have developed. These behavioral coding systems yielded important new knowledge, which self-report questionnaires would have been unlikely to reveal. For example, withdrawal ruptures were found to be detected consistently only by coding systems, not by questionnaires (Eubanks et al., 2019). Coding systems are valuable tools in psychotherapy research, but they also have their disadvantages, such as the long training time required for coders to produce reliable and valid coding, and the fact that the coding process itself is time-consuming, which makes it impractical if one is interested in the process of change, session-by-session, over the entire course of treatment, for a large sample of patients. Therefore, to complement the coding systems and self-report questionnaires available for assessing the alliance, researchers may consider additional, less labor-intensive assessment approaches. Integrating a variety of assessment approaches may mitigate the disadvantages of each, and yield a comprehensive measure that is better able to capture the complexity and richness of the therapeutic encounter.

One potential approach to complement existing methods of measuring alliance is to focus on biological markers of the therapist-patient relationship. Many options may be relevant, but one of the most promising candidates is the neuropeptide oxytocin (OT), because of its unique role in bond formation and synchrony in close relationships (Schneiderman, Kanat-Maymon, Zagoory-Sharon, & Feldman, 2014). Measuring OT in relation to psychotherapy processes may deepen our understanding of the therapeutic process, enable new directions of research on the potential effects of psychotherapy on neurobiological systems, and help expand the definition of the therapeutic alliance to include a previously uncharted territory. In this context, it is important to note that many of the conceptual frameworks that consider the therapeutic alliance as the key "healing component" of therapy and the main vehicle for positive change compare its effects to those of the mother-infant attachment. However, there is little direct research to provide scientific evidence of such claims. Thus, demonstrating that a therapeutic process can affect the OT system in patient or therapist, or increase the "goodness of fit" between their OT production, particularly as it relates to better treatment outcomes and appears in sessions when the alliance is perceived to be tighter, may serve as proof of theoretical models suggesting that therapy reactivates the parent–child relationship, and similarly to it, can affect the brain, hormones, behavior, and mental life.

Brief Overview of the Relevant Literature on OT

Overview of OT Measurement as a Biomarker of Bond Formation and Maintenance in Interpersonal Relationships

OT is an evolutionarily early nonapeptide. In addition to its role in child birth uterus contraction and in lactation, it has the potential to regulate social behavior across mammalian species (Young, 2015). OT plays a well-established role in pair bond formation and maintenance, social interactions, intimate relationships, and the regulation of human social behavior (e.g., Carter, 1998; Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008; Heinrichs & Domes, 2008). The release of OT is stimulated by interpersonal cues, such as the touch of a significant person (Insel, 2010). OT has been found to be important in parent–child bonding, inducing attachment both on the side of the child (Feldman, Gordon, & Zagoory-Sharon, 2010; Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005) and of the parent (in humans: Feldman, Weller,

Zagoory-Sharon, & Levine, 2007; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a; in animals: Lukas, Bredewold, Neumann, & Veenema, 2010; Oreland, Gustafsson-Ericson, & Nylander, 2010; Veenema, Bredewold, & Neumann, 2007). Based on accumulating studies, it has been argued that OT serves as a specific biological mechanism by which bonds are formed and strengthened in various species (Algoe, Kurtz, & Grewen, 2017; Williams, Carter, & Insel, 1992).

OT may operate by increasing states of calmness, reducing stress and negative mood, and facilitating approach behaviors that are critical for bond formation and maintenance (Gordon et al., 2008). The anxiety-lowering effect of OT, mediated by modulation of the amygdala, of the hypothalamic (pituitary) adrenal axis, and of the cardiovascular system, may be important in motivating affiliative processes in humans and animals. When a safe situation involving another person is sensed, OT may be released, which then motivates approach and reciprocity (Merolla, Burnett, Pyle, Ahmadi, & Zak, 2013), as well as trust (Zak, Kurzban, & Matzner, 2005), empathy (Barraza & Zak, 2009; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2013), and compassion (Palgi, Klein, & Shamay-Tsoory, 2016).

Recently, it has been suggested that the oxytocinergic system plays a key role also in the interactive reciprocity and dyadic synchronized behavior characterizing the mother-infant relationship (Feldman, Magori-Cohen, Galili, Singer, & Louzoun, 2011), as well as in romantic relationships (Schneiderman, Zagoory-Sharon, Leckman, & Feldman, 2012). Studies demonstrate that OT improves interpersonal synchrony, that is, the ability of a pair to match and follow each other, and to focus attention while interacting (Arueti et al., 2013; Goldstein, Josef, Mayseless, Ayalon, & Shamay-Tsoory, 2019).

Notwithstanding the positive effects of OT, accumulating evidence demonstrates great inconsistency in its effect. For example, findings suggest mixed results regarding the effects of demographic variables, like age and gender (Hoge, Pollack, Kaufman, Zak, & Simon, 2008, vs. Weisman, Zagoory-Sharon, Schneiderman, Gordon, & Feldman, 2013), and of personality disorders (Lee, Ferris, Van de Kar, & Caccaro, 2009, vs. Bertsch, Schmidinger, Neumann, & Herpertz, 2013) on OT levels. Studies also reveal that OT effects are not always prosocial, suggesting, for example, an association between higher levels of OT and higher levels of attachment anxiety (Hurlemann & Scheele, 2016; Weisman et al., 2013). There is also evidence that in certain situations OT promotes aggressive tendencies toward the other, depending on the nature of the relationship between the observer and the target. For example, intranasal administration of OT was found to induce antisocial behaviors, including increased aggression following provocation (Ne'eman, Perach-Barzilay, Fischer-Shofty, Atias, & Shamay-Tsoory, 2016) and increased envy in competitive situations (Shamay-Tsoory et al., 2009).

Building on this conflicting evidence, Shamay-Tsoory and Abu-Akel (2016) have recently synthesized these seemingly disparate findings into the social salience hypothesis of OT, a theoretical framework that regards OT as a hormone that regulates the salience of internal and external social cues. According to the social salience hypothesis, the effects of OT are not uniform and may depend on contextual (external) cues as well as on interindividual tendencies (internal cues). The contextual factor (external cues) addresses the issue of the type of social interaction in which individuals are engaged. In positive cooperative situations, OT may increase attention to positive social cues, whereas in competitive settings it may increase the salience of cues of threat. The internal cue factor addresses the issue of individual differences. For example, in patients with a psychopathology that involves difficulties in social behavior, OT may regulate attention to threat signals more than in healthy individuals. The response of the OT system may also be strongly influenced by early emotional experiences that shaped the person's attachment orientation (Gordon, Martin, Feldman, & Leckman, 2011). For example, it has been shown that aversive early attachment experiences affect OT levels (Heim et al., 2009; Weisman, Zagoory-Sharon, & Feldman, 2012), so that individuals with secure attachment show higher levels of OT in response to stress than do individuals with anxious attachment orientation (Pierrehumbert, Torrisi, Ansermet, Borghini, & Halfon, 2012). Likewise, it was found that patients with aversive early attachment representations had a more negative response to intranasal OT than did those with more positive representations (Bartz, Zaki, Bolger, & Ochsner, 2011). Similarly, accumulating evidence points to sex-dependent effects of OT on behavior. For example, it has been shown that intranasal OT improves recognition of kinship relationship in women, and of competitive relationship in men (Fischer-Shofty, Levkovitz, & Shamay-Tsoory, 2012). These results suggest that hormonal and environmental influences together affect the OT system.

Taken together, individuals' gender and early attachment experiences appear to affect the development of the responsivity of the OT system. According to the social salience hypothesis, the OT system has a modulatory effect on attention and the assignment of salience to social stimuli. Therefore, the behavioral effects of OT are highly dependent on the degree to which social cues become salient and relevant based on the specific constellation of traits and characteristics that form the person's internal milieu. For example, individuals with an anxious attachment style may respond to therapeutic interactions with a relatively lower increase in endogenous OT than would individuals with a secure attachment style. For this reason, psychotherapy may affect individuals differently, based on the specific constellation of traits and other characteristics that form the person's profile. The evidence reported in the literature to date appears to support the social salience theory (e.g., Steinman, Duque-Wilckens, & Trainor, 2019; Tillman et al., 2018), but additional empirical evidence is needed to further corroborate or refute this theory.

Overview of OT Measurement as a Biomarker of Bond Formation and Maintenance in Psychotherapy

It has been suggested that the effects of comforting interactions with a therapist on outcome, and their role in regulating stress and inflammation, may be mediated in part by the release of OT (Brown & Brown, 2015). Although not measuring the process of change, some studies focused on baseline OT levels and used them as predictors of treatment outcome. For example, Jobst et al. (2018) investigated whether trait-like levels of baseline OT and context-specific changes in OT (changes in OT as a result of a social exclusion manipulation) as measured before the start of treatment predicted treatment outcome in a sample of 16 patients (nine women) with chronic depression, half with comorbid personality disorders. Consistent with the social salience hypothesis

of OT, findings suggest that both trait-like levels of OT (higher OT plasma levels at baseline) and state-like levels of OT (faster recovery following the social exclusion manipulation) correlated with greater changes in self-reported depressive symptoms, although not with the change in the clinician-based measure of depressive symptoms. The authors speculated that their findings may be the result of the ability of patients with higher baseline OT and greater capacity to normalize OT levels to form strong alliances that resulted in better patient-reported outcomes.

To our knowledge, only one study to date has examined empirically OT as a potential biomarker of alliance (Zilcha-Mano, Porat, Dolev, & Shamay-Tsoory, 2018). The study, based on 22 patients (14 women) diagnosed with major depressive disorder (MDD; 14 having comorbid personality disorders), found that patients' levels of OT increased significantly during psychotherapy sessions. After disentangling the state-like effects (the changes in OT an individual shows in a given session) from the trait-like ones (aggregated individual differences between patients in their tendency to show changes in OT), findings suggest that a larger increase in OT levels during sessions was associated with more instances of conflict and rupture in the alliance with the therapist. This was manifested in (a) greater increase in confrontation ruptures with the therapists and stronger efforts by therapists to resolve these ruptures, as coded by independent observers and (b) drops in the strength of the emotional bond between patients and therapists, as reported by patients. This study was the first to show that OT changes significantly during treatment sessions. Furthermore, the convergent findings of self-report and behavioral coding demonstrated that changes in OT during psychotherapy sessions captured important processes of ruptures in the formation of alliance with the therapist. These associations were found only after disentangling state-like and trait-like effects. To the best of our knowledge, no other study to date has used OT to measure the process of alliance formation in treatment, despite abundant empirical research on the importance of alliance for treatment success on one hand, and extensive research on OT as a biomarker for bond formation in interpersonal relationships on the other.

Practical Guidelines for Using OT as a Biomarker in Psychotherapy

In this section, we describe how OT may be assessed in psychotherapy research. Next, we outline several paths for using OT in psychotherapy and counseling research, and address practical issues relevant for each path, such as the timing of OT collection and measurement. We discuss three main paths: (a) OT as a stable trait-like characteristic of the individual (patient and therapist), which can be used to refer to individual differences in OT levels between patients and therapists (which may have the potential to function as moderators of treatment success), or to sustained change in OT levels, possibly as the result of treatment (the latter refers to OT as a potential biomarker of therapeutic outcome); (b) OT as a biomarker of the therapeutic process, measuring state-like changes in OT during a specific session or over the course of treatment, from one point of measurement to the next, which can be used to monitor the process of change during a therapeutic session or from one session to the next; and (c) dyadic OT, which refers to the goodness of fit and level of synchrony between patients and therapists, in both trait-like OT (as a biomarker of their baseline goodness of fit) and state-like OT (as a biomarker of the process of synchronization that develops between them in the course of treatment).

Peripheral OT Measurement

Given the lack of access to central measures of OT, investigators must measure endogenous peripheral OT in urine, saliva, or plasma. With the development of commercial OT–enzyme-linked immunosorbent assay (ELISA) kits, a commonly used analytical biochemistry assay, and the growing number of studies applying peripheral OT measurement that show comparable findings across labs, cultures, and methodologies, the validity of OT measures in plasma and saliva is becoming increasingly apparent. Initially, plasma OT measurement was the traditional method of assessment, but in the past decade the use of salivary OT measurement is becoming more widespread, following its validation vis-à-vis plasma OT measured at the same time (Feldman, Gordon, & Zagoory-Sharon, 2011). We believe that salivary OT is the more useful measure for psychotherapy research for a variety of reasons. It is relatively easier to collect from both therapist and patient, it does not require the presence of a stranger (physician or nurse), it is painless (pain may alter processes occurring before and during the session), and it can be collected repeatedly across the session and over multiple sessions from both patient and therapist.

The appeal of urinary OT has recently declined for several reasons, including the fact that levels generally do not correlate with those found in plasma or saliva (which are interrelated, see Feldman et al., 2011). Urinary OT is thought to reflect a somewhat different process, and OT concentration in urine reflects levels collected over a much longer period. In psychotherapy, although any assessment of a physiological biomarker may be perceived as an intrusion, salivary measures are the least intrusive and least resembling a medical examination, compared to the collection of plasma or urine samples.

How Should OT Samples Be Collected and Stored?

There are two methods of collecting saliva samples: by oral swab or by passive drool. The most common synthetic swabs in current use are manufactured by Sarsted and Salimetrics. To the best of our knowledge, these methods of collection do not affect OT levels, as measured with the ELISA assay. After collection, samples should be kept ice-chilled for up to 1 h, before storing at −20 °C. Within a few weeks, samples should be centrifuged and aliquoted (freeze dried). Freeze drying, which removes water, is typically used to preserve perishable materials and extend their shelf life. After freezing the material, pressure is reduced and the material is heated to allow the frozen water to sublimate. In the case of OT measurements, this technique concentrates and stabilizes the sample to extend the storage period to up to 10 years. The liquid samples are stored at −80 °C. To concentrate the samples by a factor of 4, the liquid samples are lyophilized and kept at −20 °C until assayed by the OT-enzyme immunoassay (EIA) kit (for more information, see Feldman et al., 2011; Priel, Djalovski, Zagoory-Sharon, & Feldman, 2019; Ulmer-Yaniv et al., 2018).

Main Paths and Practical Considerations for Implementing OT in Psychotherapy Research

Using salivary assessment, it is possible to focus on baseline trait-like levels of OT, state-like changes in OT, and the goodness of fit between patient and therapist. Consistent with the biobehavioral synchrony conceptual model on the neurobiology of affiliation (Feldman, 2012, 2015, 2016, 2017), we suggest that all these processes affect patient and therapist behaviors, and in turn are affected by them. Therefore, it would be beneficial to assess actual (observed) and reported behavior of patients and therapists during the session as a correlate of the OT measures. As in the case of any measure implemented in the design of psychotherapy and counseling research, the decisions which measures to include, and how and when to measure them must be consistent with the researcher's theory and conceptual framing of the questions. It must also be feasible and tailored to leveraging the unique characteristics of the clinic. OT measurement should be carried out in a culturally sensitive way, respecting diverse opinions, values, and attitudes of each individual. By adopting a sensitive approach (Castonguay & Muran, 2017), we achieved a positive experience, with most of our patients and therapists reacting with curiosity and interest.

Baseline OT levels in patient and therapist.

Open paths for investigation. It has been shown that baseline OT, measured in both plasma and saliva, is individually stable over a period of months and even years in mothers, fathers, infants, and children (Feldman et al., 2007; Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013; Priel et al., 2019; Schneiderman et al., 2012). Yet, it should be noted that individual stability of measured OT in parents raising small children, partners starting a romantic relationship, or in any other respondents over particular periods across the life span, has not been sufficiently researched. Still, baseline OT may be considered a biomarker of certain personality traits related to social-affiliative functioning, such as affiliative tendency, empathy, social fitness, social engagement, or reciprocal relational style. The fact that OT may be individually stable may raise a host of questions relevant for psychotherapy research, and provide new approaches to their measurement. Do therapists with higher baseline OT tend to display more sensitive and empathic behavior (as do parents, lovers, or close friends; Feldman et al., 2007, 2011; Feldman, Gordon, et al., 2013; Schneiderman et al., 2012) toward their patients and pay more attention (consistent with the social salience hypothesis mentioned above) to subtle nonverbal cues that bear on their patients' inner mental state or level of involvement in the therapy? Are therapists with higher baseline OT generally better therapists than are those with lower baseline OT? Is treatment outcome for patients of therapists with higher OT better than that of patients of therapists with lower OT? If yes, are these improved outcomes manifest in all patients or only in those with specific disorders (e.g., anxiety disorders, but not conduct disorders)?

Similar questions can be raised for patients' baseline OT levels. Do those with higher baseline levels have a better prognosis, so that patients with a higher baseline OT achieve more satisfactory outcome at the end of treatment, show lower dropout rates, report greater satisfaction with the process and the therapist, and display faster symptom recovery? Are there interaction effects of patients' OT levels and the type of disorder in predicting treatment pace or outcome, so that baseline levels can predict the course of therapy for some patients but not for others?

Practical considerations. We recommend that, when possible, baseline levels be determined on the basis of more than a single assessment. At least two samples should be taken for calculating baseline levels, and those should be collected before the beginning of treatment, to ascertain that they are not affected by the process itself. Few studies have tested the diurnal cycle of OT directly. One of these studies indicated that OT levels peak at 2 a.m., and unlike cortisol, do not decline in the afternoon. In repeated assessments across the same day, we noted that in the morning hours there are fluctuations in OT levels and these stabilize in the afternoon hours (Weisman et al., 2012). The afternoon hours (3–7 p.m.) are therefore thought to be a good time for sample collection, when individual variability does not interfere with sharp diurnal changes. An effort should be made to collect all samples in a study within the same time period of the day. Furthermore, because OT has been implicated in processes of hunger and satiety (Olszewski, Klockars, & Levine, 2016), its levels are strongly influenced by food intake. Therefore, it is recommended not to measure OT right after a meal, and we usually require patients to refrain from eating 1 hr before measurement. Regarding the study of individuals with food insecurities in clinical settings, special sensitivity should be exercised because little is known about their OT levels.

Baseline measures are more robust when they are based on several measures of OT taken at the same visit. In longitudinal studies of OT in relation to psychopathology or in research linking OT with brain patterns, conducted in the Feldman lab, OT was typically collected three or more times during a single home or lab visit. The area under the curve (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) was used to establish the baseline OT measure. This measure was then used in comparison with parent and child behavior, psychiatric symptoms, other hormones including cortisol or secretory immunoglobulin A, and brain activation patterns (Levy et al., 2016; Pratt, Zeev-Wolf, Goldstein, Feldman, & Feldman, 2019; Priel et al., 2019; Ulmer-Yaniv et al., 2018).

Baseline levels of OT can be assessed at home or in the lab before the therapeutic session. The former is more advisable because it may reduce the risk of being affected by the expectancy of the treatment, although the latter may have the advantage of greater standardization across participants. When researchers are interested in OT as a measure of stable changes following treatment, it is possible to measure OT before and after treatment, and again several weeks or months after termination of treatment, to check whether levels dropped, stayed the same, or increased after the treatment ended, and whether these patterns are associated with stable therapeutic gains.

Illustration using actual data. To demonstrate the potential of trait-like OT measurement, we use data collected at the University of Haifa Psychotherapy Research Lab as part of a randomized controlled trial of supportive-expressive treatment for MDD (for more details, see Zilcha-Mano, Dolev, Leibovich, & Barber, 2018). In this study, only one measurement of OT was collected, before the start of treatment, and it is referred to here as a trait-like OT. Patients were instructed to refrain from eating and drinking (other than water) for 1 hr before OT measurement, and to rinse their mouth 10 min before saliva collection. They were also asked to refrain from romantic or intimate touch for 1 hr before OT

measurement. Based on saliva samples of 40 individuals (M_{age} = 30.22, 14 women) diagnosed with MDD at pretreatment, a significant correlation was found between higher trait-like OT and more interpersonal problems and lower satisfaction with the quality of intimate relationships (measured using the Outcome Questionnaire, Interpersonal Relationship subscale, Lambert, Vermeersch, & Brown, 2004), $r = .41$, $p = .008$. Future studies using several measures of baseline OT are needed to support the validity of this finding, with respect to both the direction and the magnitude of the effect.

Change in OT levels in patient and therapist.

Open paths for investigation. OT is a system that responds to intense social and affiliative experiences. In infancy, following a session of tactile contact between mothers (affectionate touch) or fathers (stimulatory touch) and their 4- to 6-month-old infants, OT levels significantly increased in both parents (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010) and infants (Feldman et al., 2010). The increase was observed only when the interactions were synchronous and reciprocal, and when the parent provided high levels of touching. However, by the time a child reached the preschool stage, typical face-to-face interactions in the home environment, or merely being in the presence of the parent at home, did not increase children's OT level, although it normalized the low OT levels of preschoolers with high-functioning autism spectrum disorder (Feldman, Golan, Hirschler-Guttenberg, & Ostfeld-Etzion, 2014). Modulations in OT at later stages of development require stronger stimuli, such as exposure to stressful paradigms (Seltzer, Ziegler, & Pollak, 2010) or intranasal administration (Weisman et al., 2012). It is intriguing to examine whether a successful therapy session, in which both patient and therapist feel that their alliance strengthened and progress has been made, is also associated with OT increase. In parallel, it would be instructive to examine whether sessions marked by negative feelings, a sense of being misunderstood, or being "stuck" correlate with a decrease in OT from its baseline levels. It would be of interest also to test whether such links between successful sessions and increase in OT, if found, appear early or later in the therapy, are observed for some patients and not for others, and whether they can predict sessions with sudden gains in the therapy.

When interpreting the direction of the effect of state-like levels of OT, it is crucial to take into account the context. State-like levels of OT are, by definition, context-specific. According to the social salience hypothesis, which was developed based on findings about the role of OT in interpersonal relations, the effects of OT are not uniform but rather depend on contextual cues. In positive cooperative situations, OT may be associated with positive social cues, whereas in competitive settings, it may be associated with cues of threat. Because baseline levels of OT were found to be stable across months and even years, the fluctuations around them (the state-like changes in OT) are likely to be related to contextual circumstances.

Practical considerations. Changes in OT levels may be measured at various time intervals and frequencies. When feasible, we recommend measuring Time (T)1 at baseline (at least 10 min after arrival and before the beginning of the session), T2 immediately following the session, and T3 15 min thereafter, for recovery. Change in OT levels may be computed from T1 to T2, reflecting levels accumulated during the session; from T1 to T3, reflecting what has been retained; and from T1 to the average of T2 and T3. Such change can be correlated with variables related to the process occurring within a given session, or to broader parameters such as the type of psychopathology or personality variables. Change can also be measured across the entire therapy. One may wish to examine OT levels at the beginning, middle, and end of therapy. Alternatively, it is possible to measure at several successive sessions, for instance in the main phase of the therapy, to assess the trajectory of OT change and whether levels increase, decrease, or stay unchanged across the sessions. The frequency at which sessions should be sampled depends on the rate of change that is expected in the therapeutic construct of interest. As far as alliance is concerned, a session-by-session assessment has been found to be ideal when self-report measures were used, and may be recommended for OT as well. OT state-like measures can be collected from the patient, the therapist, or both, depending on the research question.

Illustration using actual data. To demonstrate the potential in OT change measurement, we use data collected at the University of Haifa Psychotherapy Research Lab as part of the same randomized controlled trial of psychotherapy for MDD mentioned earlier (Zilcha-Mano, Dolev, et al., 2018). A total of 128 saliva samples were collected from 16 patients diagnosed with MDD, undergoing manualized supportive expressive treatment. The mean age was 29.41 years (SD = 6.67; nine were women). Samples were collected before and after treatment Sessions 2, 4, 8, and 16. Multilevel hierarchically nested analyses suggest that greater within-patient increase in OT was associated with impairment in the process of attachment formation, as evident in reduced seeking of proximity to the therapist, measured using an adaptation of the attachment formation questionnaire (Fraley & Davis, 1997) to assess relationship with the therapist ($\beta = -0.18$), $t(35) = -2.70$, $p = .01$. In this example, changes in OT signal that a meaningful process has occurred and should receive attention in treatment. The direction of the effect (meaningful corrective experience vs. a rupture in alliance formation) should be evaluated by taking into account the context, which is generally important in psychotherapy research, but even more so when using biological measures.

Hormonal synchrony: Goodness of fit between patient and therapist OT.

Open paths for investigation. Another path of investigation is that of the goodness of fit between patients and therapists in OT. Neuroendocrine synchrony or hormonal attunement or "fit" refers to the degree of correlation in levels of hormones between affiliated partners. Such hormonal synchrony in OT levels has been repeatedly shown between parents and children, and between romantic partners, as measured in plasma, saliva, and urine (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013; Feldman, Golan, et al., 2014; Feldman, Gordon, Influs, et al., 2013; Feldman et al., 2010; Gordon et al., 2010a,2010b; Pratt et al., 2015; Ulmer-Yaniv et al., 2018). Several important insights emerge from this body of research. First, generally, OT synchrony is found between parent and child, but the link is mediated by sensitive, empathic, and synchronous parenting, so that in cases of more synchronous relationships the endocrine fit is greater. Because such findings are correlational and not causal, the reverse interpretation can also be true: Parents may provide more sensitive parenting to children who are more biologically similar to them. Thus, differentiating trait-like levels of similarity (suggesting which dyads are bound to succeed) and state-like levels of similarity (progression toward

more synchronized interactions) is of great importance, especially when studying relationships from their starting point, as in the case of the therapeutic dyad. Second, the degree of endocrine synchrony in OT levels and the social behavior of mother and child influence each other reciprocally. Finally, endocrine synchrony and more socially engaged and reciprocal relationship between mother and child mediate the effects of stressful early life conditions, such as chronic exposure to war-related trauma or to maternal depression, on the development of the child's symptomatology (e.g., Priel et al., 2019; Ulmer-Yaniv et al., 2018). The goodness of fit in OT levels between affiliated partners is therefore considered to be an asset that can provide a resilience buffer to children who are growing up under conditions of chronic early stress.

Applying these findings to the therapeutic context, it is reasonable to assume that greater similarity in baseline OT levels between patient and therapist leads to greater understanding, a more reciprocal and stronger treatment alliance, and more positive outcome. Yet, no study to date has tested these assumptions. Such findings, if confirmed, would have important implications for the "neurobiology of human attachment" conceptual framework (Feldman, 2017), which suggests that biological and behavioral synchronous processes established within the mother-infant bond are transferred to meaningful relationships throughout the individual's life and play an important, potentially reparatory, role. Such findings may also provide biological evidence for the longstanding claim that the patient–therapist relationship mirrors at many levels the mother–infant attachment.

Research questions related to OT synchrony between therapist and patient are many and important. In addition to whether greater endocrine fit results in more successful therapy, it is important to test whether the effect of hormonal attunement is disorder-specific; it is possible that for some disorders, greater fit promotes therapeutic gains, whereas for others it may be irrelevant or even hinder the therapeutic process. Another set of questions has to do with whether in the course of a successful therapy, OT levels of patient and therapist become more tightly coupled. Still another set of questions can zoom in on sessions in which both parties felt that an important breakthrough was achieved and mutual understanding was at its peak, and check whether these sessions were marked also by tighter coupling of patient and therapist OT. Such sessions can be compared with other sessions of the same dyad that were defined by the participants as "mediocre" and as "unsuccessful." Finally, it is possible to examine whether therapists and patients with greater hormonal synchrony reach positive outcomes faster, make greater therapeutic gains, and whether these gains tend to persist longer over time.

Practical considerations. When researchers are interested in the fit between patients' and therapists' baseline OT, the practical considerations mentioned above for baseline OT should be followed. When researchers are interested in the fit between patients' and therapists' OT change across the course of treatment, the practical considerations mentioned above for state-like OT should be followed. Studies focusing on patient-therapist synchrony should consult the abundant literature on dyadic data analyses on the approach that best fits their data analysis.

Illustration using actual data. To demonstrate the potential of exploring the level of patient–therapist synchrony in state-like OT measurement, we use the data of a single case of a woman in her early thirties, from the randomized controlled trial mentioned above (Zilcha-Mano, Dolev, et al., 2018). This case was chosen because it showed a high Pearson correlation between the patient's and therapist's state-like OT. Figure 1 shows that the correlation between the patient's and the therapist's changes in OT from presession to postsession over the course of treatment (Sessions 4, 8, 12, and 16) was very high ($r = .85$). The case had a good outcome, showing a dramatic reduction in symptom severity, from a score of 27 on the Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960) at baseline to a score of 8 at termination.

A Clinical Demonstration of the Usefulness of OT as a Biomarker in Psychotherapy

Dan, a student in his early 30s, sought treatment for depression that has persisted for several years. Dan received supportive–expressive psychotherapy at the University of Haifa Psychotherapy Research Lab, where he was diagnosed with MDD. At intake, Dan reported feelings of futility of life and an oppressive sense of loneliness. He also reported that he had never been able to maintain good and stable interpersonal relationships with anyone. He was highly interested in having a romantic partner, but has never had a stable and meaningful relationship. The interpersonal difficulties he described were also reflected in the questionnaires he completed at intake. For example, on the Inventory of Interpersonal Problems, he reported a relatively high levels of distress in interpersonal relationships (a score of 43 on the overall Inventory of Interpersonal Problems–34, Alden, Wiggins, & Pincus, 1990; Horowitz, Rosenberg, Baer, Ureño, & Villaseñor, 1988). The Experiences in Close Relationships Scale (Brennan, Clark, & Shaver, 1998) showed clear signs of avoidant attachment (a score of 4.56). The general profile that emerged from all the questionnaires was one of distancing and difficulty with intimacy in close relationships. Dan's OT levels were measured at intake and before and after Sessions 4, 8, 12, and 16. The therapist's OT levels were measured at the same sessions (except for the intake meeting). Both patient and therapist completed alliance questionnaires after each therapy session. Sessions 4 and 8 were coded for ruptures and repairs (Eubanks et al., 2019). To learn about trait-like OT changes, we focused on OT levels of the patient before each therapy session. To learn about state-like OT contextual changes

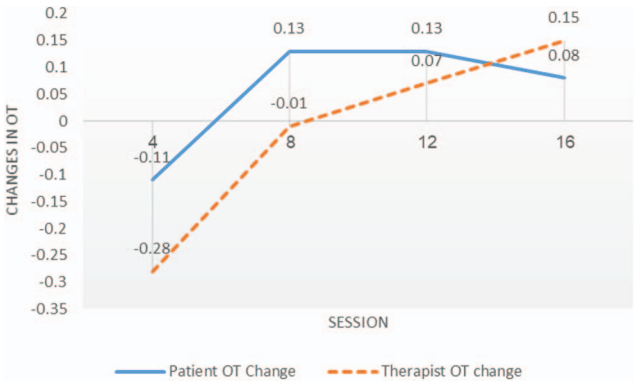

Figure 1. Patient's and therapist's changes in oxytocin (OT) from pre- to postsession over the course of treatment (Sessions 4, 8, 12, and 16). See the online article for the color version of this figure.

within the session, we focused on changes from presession to the end of the session, both in the patient and in the therapist.

Regarding state-like OT, as shown in Figure 2, Session 4 was characterized by ruptures in the therapeutic alliance. Evidence of ruptures was noticeable on all three measures: self-report, behavioral coding, and changes in OT from pre- to postsession, both in the patient and in the therapist. As evidenced by the coding, the session was characterized by both withdrawal and confrontation ruptures, with both therapist and patient reporting the ruptures in the self-report questionnaires. The withdrawal ruptures were manifest in silences, a sense that the patient did not know what to say, distancing himself from the therapist, and changing the subject of the conversation to another topic when discussing issues that were emotionally charged for him. The confrontation ruptures were manifest in pressure on the therapist to provide a solution for the patient's condition, a sense that the treatment was not working for him, and complaints that the treatment was not progressing at the pace he would have liked.

Regarding the state-like OT during Session 8, as can be seen in Figure 2, it is clear that there is no agreement between the measures. The patient showed a large increase in OT levels during the session, but the therapist showed a smaller increase. Both patient and therapist reported high levels of alliance. Coding suggests that the meeting was characterized by high levels of withdrawal ruptures. The disagreement between the measures regarding withdrawal ruptures is consistent with the theoretical literature. Although these ruptures are manifest in great personal distress for the patient (as indicated by the large increase in the patient OT levels), they are often missed by the therapist (as indicated by the slight change in the therapist OT levels following the session). Withdrawal ruptures are often not revealed in the self-report of the therapist, who is usually unaware of them, or of the patient, who often has difficulty reporting them (because of lack of awareness or because of difficulty admitting the occurrence of the rupture). In this session, the withdrawal ruptures were manifest in frequent changes of subject at moments of discussing topics that were emotionally charged and difficult for the patient. At these times, the patient tended to withdraw into distant and abstract talk about his difficulties ("People naturally want to stay away from each other, and then everyone remains alone with himself"). This case illustrates that for a rich understanding of the complexities and clinical nuances of the therapeutic relationship, it is important to take into account the context and integrate various approaches to measuring the therapeutic relationship.

Regarding changes in trait-like OT during treatment, it is noticeable that with improvement in the patient's condition, as manifest in symptom reduction (a reduction of 10 points on the Hamilton Rating Scale for Depression), in his ability to establish more secure attachment (a 2-point reduction on the avoidance subscale of the Experience in Close Relationship Scale, Brennan et al., 1998), and in his ability to form a stronger alliance with the therapist (an increase of almost one point on the average score of the WAI), there was also a rise in the levels of OT before the therapy sessions. This positive development may reflect the patient's overall improvement over the course of the treatment in his ability to form meaningful relationships, or improvement over the course of treatment in anticipation of the therapy sessions. Because OT was not measured in the patient's home but in the lab, close to the therapy session, it is not possible to distinguish between the two interpretations of the findings.

This clinical example illustrates the potential of OT as a biomarker of processes that take place in the state-like alliance during each therapy session. The change in OT from pre- to postsession reflected processes of in-session rupture and repair in the alliance, and was sensitive not only to confrontation ruptures but also to ones of withdrawal. As such, OT demonstrated its potential to provide information that could not be derived from self-report questionnaires. This example also illustrates the potential of OT as biomarker for changes in the patient following the therapeutic process, which are more trait-like and stable, such as improvement in the ability to form satisfying

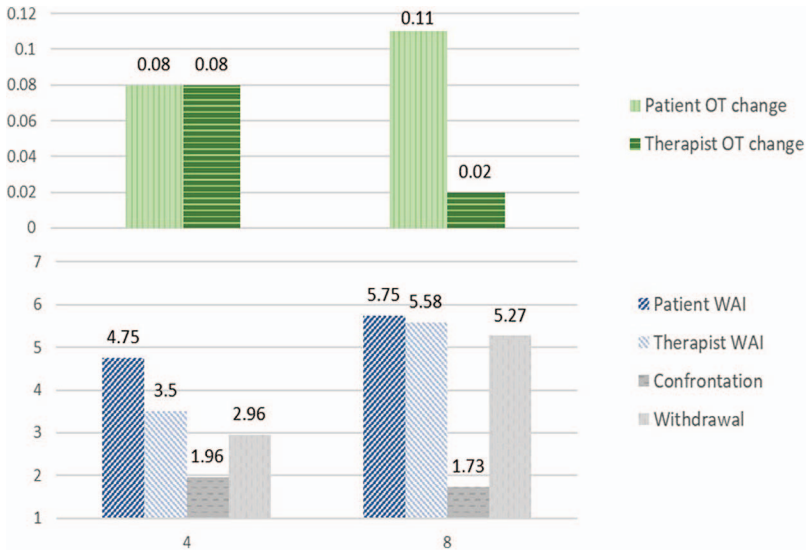

Figure 2. Patient's and therapist's changes in oxytocin (OT) from pre- to postsession, self-report Working Alliance Inventory (WAI), and rupture behavioral coding (withdrawal and confrontation). The rupture coding underwent transformation to fit the WAI. See the online article for the color version of this figure.

relationships with others. Note that the relationships suggested in this case study between OT levels and ruptures should be investigated in a large sample, taking into account that according to the social salience hypothesis (Shamay-Tsoory & Abu-Akel, 2016), these associations may depend on external contextual social cues (e.g., competitive/aggressive vs. cooperative/accepting environment), and on individual baseline differences.

Open Questions and Directions for Future Research

This article is intended to serve as a sourcebook for future research investigating OT as a potential biomarker for processes occurring as part of the therapeutic encounter, with the aim of detecting neural signatures of therapeutic processes, especially those related to the therapeutic relationship. Biologically based markers have the potential to complement other commonly used assessments, such as self-report and coding systems, to reach a high level of accuracy through the convergence of distinct approaches to measure the same broad phenomenon. Research on OT as a biomarker in psychotherapy and counseling is still in its early stages of development, and there are more open questions than answers regarding the utility and the characteristics of OT in different treatment conditions and patients populations. Studies are needed to assess stable trait-like OT levels and investigate their ability to serve as predictors or moderators of treatment outcome (indicating what works for patients with distinct trait-like OT levels), and as biomarkers of stable achievements in treatment (answering the question whether treatment efficacy can be detected based on lasting OT levels). Studies are also needed to detect state-like contextual changes in OT in the course of individual sessions, and to investigate their ability to serve as biomarkers of the process of change within session, such as processes of rupture and repair.

The potential clinical implications of OT as a biomarker in psychotherapy research is enormous, but its actual merit awaits systematic research. If studies support the role of OT as a biomarker for trait-like characteristics, predicting differential response to distinct treatments, OT may serve to improve the ability to identify the optimal treatment for each individual, and even to match patients with therapists according to their trait-like OT goodness of fit. If studies support the role of OT as a biomarker for state-like changes during psychotherapy sessions, it will be possible to explore the benefits of using OT changes as a feedback to therapists. The literature on the efficacy of feedback to therapists on their patients' progress in treatment, based on patient-reported symptom severity, has shown promising findings (Lambert, 2013). Yet, feedback to therapists based on patients' reported alliance may not be effective (Errázuriz & Zilcha-Mano, 2018). A critical shortcoming of existing trials providing feedback to therapists on the alliance is their exclusive dependence on patient self-reports, which may reveal confrontational ruptures that the therapist is already aware of, but not withdrawal ruptures, about which the therapist needs the feedback to gain awareness. Future studies may investigate whether the efficacy of feedback to the therapists can be enhanced by monitoring state-like changes in OT during each session.

In addition to peripheral measurements, studies on OT and psychotherapy may use intranasal administration and assess how and on what factors therapeutic processes differ when patient, therapist, or both are under the influence of OT. OT may serve as a therapeutic agent in itself, by administration of intranasal OT to the patient (Herpertz & Bertsch, 2015; Lischke, Herpertz, Berger, Domes, & Gamer, 2017; Sippel, Allington, et al., 2017), or as a therapeutic catalyst or augmentation agent, when administered either to patients (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018; Macdonald, et al., 2013) or to both patient and therapist, to augment other established treatments. It has been suggested that administrating intranasal OT immediately before a psychotherapy session may boost the effect of the session by improving the alliance. OT may optimize also the processing of emotionally relevant stimuli by modulating activity and connectivity patterns in (para)limbic and prefrontal brain regions (Bethlehem, van Honk, Auyeung, & Baron-Cohen, 2013; Wigton et al., 2015). At the same time, it has also been suggested that OT may have a counterproductive effect by intensifying aggressive behavior (Shamay-Tsoory & Abu-Akel, 2016). The genetics and epigenetics of OT may be another area of inquiry in psychotherapy research. Allelic variability on the OT receptor gene (*OXTR*) in genotypes linked with attachment, empathy, social cognition, or theory of mind abilities (Feldman, Monakhov, Pratt, & Ebstein, 2016) may be used to predict treatment outcomes or goodness of fit between patient and therapist. Finally, methylation changes in *OXTR* following therapy may be used to indicate a successful or unsuccessful process. When applying such genetic measures in clinical settings, cultural sensitivity should be exercised both in collecting the samples (Ofstedal & Weir, 2011) and in interpreting the results (Kim et al., 2011). Issues of trust in the therapeutic setting should also be taken into account.

This article focused mainly on the interpersonal role of OT and its potential associations with the therapeutic alliance, based on the theoretical frameworks of the working alliance and attachment theory. OT should also be investigated based on other theoretical frameworks, such as that of the real relationship (Gelso, Kivlighan, & Markin, 2018), and those that may not be exclusively interpersonal but are essential to the therapeutic processes, such as emotion regulation (Labuschagne et al., 2012). Although we focused in this article on OT, there are other biomarkers that have been shown to be linked with the OT system and may be relevant for the therapeutic process, particularly those showing hormonal attunement between mother and child, which are amenable to sensitive and synchronous parenting. These include hormones implicated in the stress response, such as cortisol, salivary alpha amylase, or dehydroepiandrosterone (Feldman, Singer, & Zagoory, 2010; Feldman, Vengrober, Eidelman-Rothman, & Zagoory-Sharon, 2013; Pratt et al., 2017); affiliation-related hormones, such as vasopressin or beta endorphin (Apter-Levi, Zagoory-Sharon, & Feldman, 2014; Ulmer-Yaniv et al., 2016); sex hormones, such as testosterone (Gordon, Pratt, Bergunde, Zagoory-Sharon, & Feldman, 2017; Weisman, Zagoory-Sharon, & Feldman, 2014); and markers of the immune system, such as secretory immunoglobulin A (Ulmer-Yaniv et al., 2018; Yirmiya, Djalovski, Motsan, Zagoory-Sharon, & Feldman, 2018). Because the OT system provides a neuroendocrine milieu for the activity of hormones implicated in the bonding process (Feldman, 2016), psychotherapy research may benefit from integrating OT assessment with other attachment-related neuroendocrine systems.

Although we regard OT measurement as a promising arena for future psychotherapy and counseling research, its promise should be considered together with the challenges inherent in the implementation of hormonal measures in psychotherapy research. Measuring hormones requires time, effort, and funds. The integration of OT measurement in psychotherapy research is still in its infancy, and inconsistent findings still await systematic evaluation. Although the ability of OT to detect meaningful processes appears promising, the

context needs to be taken into account to verify the direction of the effect (positive vs. negative). Much still needs to be discovered regarding potential moderators and confounders that need to be taken into account. Little is known as yet about all the parameters that should be considered when tailoring the OT measurement to a given clinical setting. An additional limitation in implementing OT measurement in psychotherapy and counseling settings has to do with the fact that the time of the day may affect the measures, especially when the time of the session is not fixed and when there are changes in the timing of a given session. Note also that estimating the exact timing of the OT effect is challenging because OT serves a dual role, both as a central neurotransmitter/neuromodulator and as a peripheral hormone. Some of the OT synthesized in the paraventricular nuclei/supraoptic nuclei is transported by axons and released in target brain areas, where its acts as a neurotransmitter. But release from the neuron cells also creates less directed diffusion effects in brain areas that contain OT receptors. Another pathway of the OT effect is that of axonal transport to the hypophyseal bloodstream, where it enters the peripheral bloodstream for its hormonal action (MacDonald & MacDonald, 2010). When OT is measured only before and after the session, rather than throughout the session, it is possible to measure only the processes that can be captured at the end of the session and that are not limited to a momentary effect only. Finally, in addition to the systematic research that is needed, methodological developments are also required before OT can be implemented to assist in clinical practice. Much development has occurred in the last several years in OT measurement. The traditional method of assessing OT levels was plasma OT measurement. But in the past decade, the use of salivary OT measurement has become widespread. With the development of commercial OT-ELISA kits, a commonly used analytical biochemistry assay, the assessment of OT has become much easier than it was only several years ago. We expect the process of OT measurement development to continue in the coming years.

The present article highlighted the promising potential of OT as a biomarker in psychotherapy research based on previous literature from other fields of inquiry as well as on analyses of data collected in a randomized controlled trial for MDD and provided practical suggestions on how this potential may be realized. We believe that interdisciplinary studies integrating the two fields of inquiry, psychotherapy and OT research, can create new important knowledge that has the potential to make a profound contribution to clinical practice. The present article was written as a collaborative work between researchers in neuroscience and psychotherapy research, based on friendship, mutual curiosity, and interest in forming a shared language. We hope it may be of help for future collaborative work around the world.

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