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**Oxytocin as a Neurobiological Marker of Ruptures in the Working Alliance**

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Although the effects of change in oxytocin (OT; a 9-amino acid cyclic neuropeptide produced in the paraventricular nucleus of the hypothalamus) during social and intimate interactions are well established, little is known about OT function during psychotherapy sessions. Based on the recent literature on OT in interpersonal interactions, demonstrating increased levels during close interpersonal contact and exposure to emotionally loaded stimuli [1], OT levels are expected to increase during psychotherapy sessions. Based on contemporary theories and research on the overarching role of OT in regulating social cues of rewarding and conflictual/aggressive experiences [2], OT levels are expected to show an even greater increase during sessions that include salient interpersonal interactions, as in the case of major gains or ruptures in the working alliance with the therapists. In the present work we focused on major ruptures in the working relationship, as their importance has been repeatedly argued in the theoretical literature and demonstrated empirically [3, 4]. We expected OT levels to show greater increases during sessions that include ruptures in the alliance, as assessed by (a) drops in the strength of the patient-rated alliance and (b) external behavioral coding of alliance ruptures.

Study setting and participants are described in detail elsewhere [5, and at clinicaltrials.gov identifier: NCT02728557]. Patients diagnosed with major depressive disorder ( $n = 22$ ) were randomized to one of two 16-session manualized short-term psychodynamic treatments, supportive-expressive or supportive, as part of an ongoing randomized control trial. The mean age was 30.22 years ( $SD = 7.30$ ), and 14 participants were female. Twelve had a comorbid personality disorder. The patients' mean score on the 17-item Hamilton Rating Scale [6] at intake was 21.40 ( $SD = 3.92$ ). The study was approved by the Institutional Review Board, and all patients gave informed consent in writing before screening. The treating psychotherapists had a mean of 10.94 years of experience.

A total of 172 saliva samples were collected, before and after treatment sessions 4, 8, 12, and 16. The concentrations of salivary OT were quantified by radioimmunoassay. Although the physiological role of OT in saliva and its link with plasma OT is not entirely clear, studies have repeatedly documented detectable concentrations of OT in saliva associated with increased intimacy and affiliation [7]. 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. Following each session, patients rated the alliance with their therapists using the Working Alliance Inventory [8], in which we focused on the bond subscale to assess the strength of the emotional bond. All sessions were videotaped. The Rupture Resolution Rating System [9] was used to code 2 types of ruptures: confrontational (patients express anger toward the therapist or discontent) and withdrawal (patients avoid expressing dissatisfaction or some other aspect of their experience with the therapists). Using the Rupture Resolution Rating System, coders also coded the therapists' attempts to repair the ruptures resorting to various resolution strategies. Each session was coded by 2 trained independent coders, showing high reliability between them ( $ICC_{2,1}$ : confrontation = 0.90, withdrawal = 0.95, resolution = 0.94).

The data were hierarchically nested (assessments within patients); thus, we used the SAS PROC MIXED procedure for multilevel modeling and added the patient as a random effect. First, to examine whether OT increased significantly during therapy sessions, we estimated the means of OT changes from pre- to postsession assessment using multilevel analyses, predicting changes in OT with an intercept only. Second, we examined the associations between changes in OT and patient-rated bond, as well as observer-rated rupture and resolution episodes across treatment, controlling for the fixed effect of time. Because it has been demonstrated that the salience effect of OT depends on baseline individual differences [2], we used centering to disentangle differences in the tendency to show changes in OT across experiences from within-patient processes.

Findings show that the levels of OT increased significantly during psychotherapy sessions, with an estimated mean change of 0.82 ( $SD = 1.01$ ,  $t_{21} = 5.01$ ,  $p < 0.0001$ ). Table 1 shows that a larger increase in OT levels during the sessions was associated with more instances of conflict and rupture in the alliance with the therapist, as manifested in (a) greater increases in confrontation ruptures

**Table 1.** Slope estimates for the ability of OT changes over the course of treatment to predict alliance formation with the therapist

Measure	Slope estimate	SE	t value	p
Self-report measure				
Emotional bond with the therapist	-0.25	0.07	-3.13	0.002
Behavioral coding				
Confrontational ruptures	0.79	0.24	3.26	0.007
Withdrawal ruptures	0.006	0.22	0.03	0.97
Therapist efforts to resolve ruptures	0.64	0.18	3.43	0.005

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 is the first to show that OT changes significantly during treatment sessions. The convergent findings of self-report and behavioral coding demonstrate that changes in OT during psychotherapy sessions capture important processes of alliance ruptures in the formation of alliance with the therapist. These findings are consistent with the literature on the role of OT in close interpersonal relationships. Given the small sample size, caution should be exercised when interpreting the findings, and future studies with larger samples should control for type of treatment and patient gender, focus on major gains in the alliance and their effect on OT changes, and test OT in the plasma. This is the first study to demonstrate a neurobiological mechanism underlying changes in the therapeutic alliance, which is the most investigated construct in psychotherapy research and the one most consistently associated with treatment outcome.

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