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Does Oxytocin Impact the Psychotherapeutic Process? An Explorative Investigation of Internet-Based Cognitive-Behavioral Treatment for Posttraumatic Stress Disorder

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Keywords
Oxytocin · Therapeutic alliance · Cognitive behavioral therapy

Abstract
Background: Oxytocin might promote favorable psychotherapy outcomes by strengthening the therapeutic alliance. Its involvement in psychotherapeutic processes, especially regarding the therapeutic alliance, needs further investigation. ***Patients and Methods:*** Blood oxytocin of 35 male German Armed Forces service members who were seeking treatment for posttraumatic stress disorder (PTSD) was analyzed before the onset of a 5-week internet-based, trauma-focused psychotherapy. We investigated whether oxytocin influenced patients' ratings of the therapeutic alliance components "agreement on collaboration" and "emotional bond," assessed during and after treatment. We further explored oxytocin's impact on general change mechanisms of psychotherapy and on psychotherapy expectation and evaluation. ***Results:*** Oxytocin had no significant impact on early agreement on collaboration, which significantly predicted psychotherapy outcome. Early emotional bond was not predicted by oxytocin and was not predictive for psychotherapy outcome. Descriptive analyses showed that patients with higher pretreatment oxytocin concentrations provided higher ratings of general change mechanisms of psychotherapy. On a descriptive level, the associations between psychotherapy expectation and evaluation and oxytocin were mixed. ***Discussion and Conclusion:*** We found positive effects of higher pretreatment oxytocin concentrations in PTSD patients. This descriptive study is limited by its small sample size and needs replication in larger, independent samples. However, results indicate possible benefits of oxytocin on trauma-focused psychotherapy.

Beeinflusst Oxytocin den psychotherapeutischen Prozess? Eine explorative Untersuchung im Kontext einer internetbasierten kognitiv-verhaltenstherapeutischen Behandlung für die posttraumatische Belastungsstörung

Schlüsselwörter
Oxytocin · Therapeutische Allianz · Kognitive Verhaltenstherapie

Zusammenfassung
Hintergrund: Oxytocin könnte den Erfolg psychotherapeutischer Behandlungen erhöhen, indem es die therapeutische Allianz stärkt. Der Einfluss von Oxytocin auf den

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psychotherapeutischen Prozess, insbesondere die therapeutische Allianz, ist jedoch noch wenig erforscht. ***Patienten und Methoden:*** Im Blut von 35 Bundeswehrsoldaten, die eine fünfwöchige, internetbasierte, traumafokussierte Psychotherapie für die posttraumatische Belastungsstörung (PTBS) in Anspruch nahmen, wurde vor Behandlungsbeginn Oxytocin gemessen. Es wurde überprüft, ob Oxytocin die Bewertung der therapeutischen Allianz, speziell der Subkomponenten Zustimmung zur Zusammenarbeit und emotionale Bindung, die während und nach der Behandlung erfragt wurde, beeinflusste. Der Einfluss von Oxytocin auf weitere allgemeine Wirkfaktoren der Psychotherapie und die Psychotherapieerwartung und -bewertung wurde exploriert. ***Ergebnisse:*** Oxytocin hatte keinen signifikanten Einfluss auf die frühe Zustimmung zur Zusammenarbeit. Diese wiederum prädizierte die Symptomreduktion. Frühe emotionale Bindung wurde nicht von Oxytocin beeinflusst und prädizierte auch die Symptomreduktion nicht. Die Deskriptivstatistiken zeigten, dass die allgemeinen Wirkfaktoren der Psychotherapie von Patienten mit höheren Oxytocinkonzentrationen positiver eingeschätzt wurden. Die deskriptiven Zusammenhänge zwischen Psychotherapieerwartung und -bewertung und Oxytocin fielen unterschiedlich aus. ***Diskussionen und Schlussfolgerungen:*** Es wurden positive Effekte höherer Oxytocinkonzentrationen bei PTBS-Patienten beobachtet. Die Studie ist durch ihre kleine Stichprobengröße limitiert. Ihr Schwerpunkt lag auf deskriptiven Auswertungen und sie muss an größeren, unabhängigen Stichproben repliziert werden. Sie liefert jedoch erste Hinweise für einen positiven Nutzen von Oxytocin bei traumafokussierter Psychotherapie.

Theoretical Background

Research into the neurotransmitter and hormone oxytocin originated in biology. Recently, however, social neuroscience and clinical psychology have taken up this branch of research and identified oxytocin as a "social hormone." Pioneering studies have shown that the central nervous injection of synthetic oxytocin, which under natural conditions is released during pregnancy, childbirth, and lactation [Neumann et al., 1993], triggered nurturing behavior in rats [Pedersen and Prange, 1979], while the injection of an antagonist reduced it [Neumann et al., 1996]. Similarly, endogenous oxytocin concentrations in human fathers and mothers have been associated with parental behaviors such as nurturing, touching [Feldman et al., 2012], social engagement, affect synchrony, and positive communication with children [Feldman et al., 2011]. Oxytocin also increases interest in social interactions beyond the context of parent-child relationships: central nervous injection of an oxytocin antagonist reduced social exploration behavior in rats, whereas stress-induced social avoidance behavior was reduced by central nervous injection of oxytocin [Lukas et al., 2011]. Experimental studies in humans have shown that intranasal oxytocin administrations promoted trust [Kosfeld et al., 2005; Mikolajczak et al., 2010] and positive communication during a partnership conflict [Ditzen et al., 2009], to mention just two of many prominent examples that have been summarized in numerous reviews [Feldman, 2012; Donaldson and Young, 2008; MacDonald and MacDonald, 2010; Heinrichs et al., 2009].

However, it would be insufficient to call the effects of oxytocin exclusively "prosocial." For example, it was observed that patients with borderline personality disorder showed a lower level of trust after administration of intranasal oxytocin, compared to a placebo condition [Bartz et al., 2011a; Ebert et al., 2013]. This shows that findings from experimental studies of healthy people are not readily transferable to clinical populations.

The social salience hypothesis is an attempt to explain these opposite observations [Shamay-Tsoory and Abu-Akel, 2016]. It postulates that oxytocin increases the salience of social stimuli independently of their valence. Depending on individual traits and context, oxytocin fosters attention in relation to positive and negative social stimuli. Some relevant moderators have already been identified, including traumatic experiences in childhood and symptoms of mental disorders [Shamay-Tsoory and Abu-Akel, 2016; Olff et al., 2013]. But it is clear that more research is needed to precisely predict the social effects of intranasal oxytocin administration in specific clinical populations.

If we transfer this branch of research into clinical psychology, it seems particularly interesting to study psychotherapy as a specific form of social interaction. The psychotherapeutic success is promoted by general change mechanisms [Grawe, 2004]. Previous studies have suggested that oxytocin in particular could promote the therapeutic alliance, one of the general mechanisms of change of psychotherapy. Specifically, it was postulated that intranasal oxytocin administration could contribute to an improvement of the therapeutic alliance and thus indirectly to an improvement of symptoms [Koch et al., 2014]. However, since psychopathology is known to be a moderator according to the social salience hypothesis, concerns were also raised about potentially harmful effects of such administrations [Hurlemann, 2017]. So far, a comprehensive review of the question of whether oxytocin actually has helpful or harmful effects in psychotherapeutic treatment remains to be performed. In this regard, two studies that evaluated the effects of intranasal oxytocin administration in patients with posttraumatic stress disorder (PTSD) are particularly noteworthy: in one study,

patients who received intranasal oxytocin instead of a placebo before undergoing a total of 10 weekly exposure therapy sessions reported lower PTSD symptoms and a more positive therapeutic alliance during therapy, although the effects were not statistically significant [Flanagan et al., 2018]. Another study examined the underlying biological mechanisms: compared to placebo, intranasal oxytocin administration in PTSD patients normalized the reduced reactivity to reward in the left anterior insula, part of the neural "salience network" that processes personally relevant information [Downar et al., 2002]. It was concluded that oxytocin could help PTSD patients to better perceive social support, which could bolster the therapeutic alliance [Nawijn et al., 2017].

The present study is intended to expand these preliminary findings by casting more light on the still open question of whether endogenous measurements that reflect the activity of the endogenous oxytocin system can also influence the psychotherapeutic process. Specifically, we examined the effect of endogenous oxytocin concentrations, measured before the start of psychotherapy, on psychotherapy process variables. We assumed a positive influence on the therapeutic alliance and explored the influence on general mechanisms of change of psychotherapy as well as on psychotherapy expectation and evaluation, which the subjects were asked about before, during, and after an internet-based cognitive-behavioral treatment (CBT) for PTSD.

Methods

Study Design

The present work is based on data from a randomized, waiting-list-controlled study, which evaluated the feasibility, acceptance, and effectiveness of a 5-week internet-based program of CBT for PTSD in German Armed Forces service members [Niemeyer et al., under review]. The study was preregistered in the Australian Clinical Trials Registry (ACTRN 12616000956404). After internal approval by the German Armed Forces, the study was authorized by the Ethics Committee of the Freie Universität Berlin (reference number: 85/2014; addendum: 116/2016). All study participants were thoroughly informed about the study goals, the study procedure, and the voluntary nature of participation, and were asked for written consent.

The patients were randomly assigned, by means of a computer-generated randomization list, to either the waiting list condition or the immediate treatment condition. Then the PTSD patients, either after an initial diagnostic examination and the subsequent 6-week passive waiting period (waiting list condition) or immediately after inclusion in the study (immediate treatment condition), underwent a diagnostic examination at the German Armed Forces Military Hospital Berlin (E1). Sociodemographic, psychological, behavioral, and biological data were collected. The blood test for measurement of oxytocin and the determination of the severity of the PTSD symptoms are particularly relevant to the aim of our study.

In the 5 weeks after E1, the patients completed the internet-based CBT, which consisted of 10 sessions (2 per week). The treatment was evaluated using internet-based psychological questionnaires that patients filled out before session 1 (E2), session 4 (E3), session 8 (E4), and after session 10 (E5). The psychotherapy process variables that were compiled before, during, and after treatment are particularly relevant for this study. Immediately after the end of the internet-based CBT (E6) and at a follow-up point 3 months later, the patients were invited to the German Armed Forces Military Hospital Berlin for further diagnostic examinations, which included assessing the severity of the PTSD symptoms.

Since the present study relates to the psychotherapeutic process, the examinations relevant to the overall study before the start of the waiting period and the follow-up examination were excluded from the analyses. All data records were used to investigate the effect of endogenous oxytocin concentrations before the beginning of treatment (E1) on psychotherapy process variables before, during, and after the internet-based CBT (from E2 to E5), regardless of whether the patients were assigned to the waiting list or immediate treatment condition.

Participants

Active and former German Armed Forces service members who wanted psychotherapeutic treatment for PTSD were eligible for the study. Exclusion criteria were acute psychosis, an acute manic episode, current substance abuse or substance dependency, current suicidal thoughts, a neurological disorder, an acute physical illness, simultaneous psychotherapeutic treatment, or irregular use of psychotropic drugs. The patients were recruited by advertisements in military magazines and on websites and forums for German Armed Forces service members. Leaflets and posters were also distributed in German Armed Forces health centers and German Armed Forces Military Hospitals. Finally, study staff and commanding officers distributed leaflets at follow-up seminars after deployments abroad, and the study was presented at conferences to German Armed Forces psychologists and psychiatrists.

Internet-Based Cognitive-Behavioral Treatment

The internet-based CBT consisted of 10 twice-weekly sessions. It is based on the protocols of *Interapy* [Lange et al., 2003] and *Integrative Testimonial Therapy* [Knaevelsrud et al., 2017] and was adapted to the military context. Each session consisted of a writing task that was performed by the patients. The text was then sent on a password-protected platform to one of two randomly assigned, licensed cognitive-behavioral therapists (H.N., S.Sch.). Both therapists had completed specific training for the internet-based CBT. The patients received written therapeutic feedback on their texts within one workday; it was based on a standardized treatment manual and was tailored to the specific situation of the patient. In the feedback, the patient's participation was recognized and positively reinforced, which was intended to promote patients' motivation. If the patients had difficulty with the content of a writing task, the feedback also contained further assistance. Patients received no separate feedback on sessions 2 and 5. For those, feedback was given after the following session for the previous two writing tasks.

Treatment was divided into three phases: biographical reconstruction (sessions 1 to 3), exposure (sessions 4 to 7), and cognitive restructuring (sessions 8 to 10). In the phase of the biographical reconstruction, the patients reflected on their previous life experiences from childhood to the time of the traumatic event. They described both positive and difficult experiences that they had successfully handled. Psychoeducational texts and support from the therapists then prepared the patients for the exposure sessions. In the four exposure texts, patients were asked to repeatedly describe the worst traumatic event they had experienced. They were instructed to write in the first person and the present tense, to put into writing the most painful aspects, emotions, and sensory impressions. The phase of cognitive restructuring, on the other hand,

aimed to give the patient a new perspective on the traumatic event. To achieve this, they were instructed to reflect on feelings such as guilt and shame, to question dysfunctional patterns in their thoughts and behaviors, to correct unrealistic assumptions, to consider possible positive consequences of the traumatic event, and to plan how they wanted to deal with such things in the future. A more detailed description of the treatment manual and a safety protocol in the event of crises can be found in Niemeyer et al. [under review].

Oxytocin

Measurement and Data Preparation

Oxytocin was measured in the blood of $n = 36$ patients ($n = 1$ patient completed the diagnostic examination, but did not show up for blood sampling), which was collected in 9.00-mL serum tubes (Sarstedt, Germany). After the blood was drawn, the tubes were gently swirled, then rested in the dark for 30 min to allow the blood to clot. The tubes were then centrifuged at 1,000 *g* for 10 min and the serum was pipetted into smaller 1.50-mL tubes (Eppendorf, Germany). These samples were stored in a freezer at −80 °C. At the end of the data collection, all samples were sent to the laboratory (RIAgnosis, Sinzing, Germany). They were extracted and analyzed using a highly sensitive and selective radioimmunoassay, as described by Landgraf et al. [1995] and Landgraf and Neumann [2004]. The intra-assay variability was <10%. All samples were analyzed using the same assay, eliminating inter-assay variability. The detection limit was between 0.1 and 0.5 pg/mL, depending on the age of the tracer. None of the samples were below the detection limit. There was no significant cross-reactivity with structurally related peptides, including the ring hexapeptides and the terminal tripeptides of oxytocin and vasopressin.

The distribution of the oxytocin concentrations was visually examined and statistically described ($n = 36$, M = 4.53, SD = 1.82, skewness = 3.05, kurtosis = 13.78). An outlier that was more than 3 SD above the M had to be removed. The remaining values were normally distributed ($n = 35$, M = 4.29, SD = 1.08, skewness = 0.12, kurtosis = −1.22) and were included in the statistical analyses.

Confounding Variables

Blood sampling was scheduled for 8 a.m. on the day of the examination. The exact time of the sampling was recorded and we were able to establish a high level of agreement with the protocol: in 88.57% of patients (31 samples), the blood was drawn exactly at 8 a.m. The deviations were 5, 10, and 15 min (2.86%, one sample each) and the time was not recorded for one sample and was therefore unknown. Patients were instructed not to drink anything except water, not to eat anything, not to consume caffeine, and not to smoke before the blood test. Compliance with these instructions was reported for 97.14% of the patients (34 samples) for drinking, 88.57% (31 samples) for food and caffeine consumption, and 71.42% (25 samples) for smoking. Age, body weight and height (Table 2), and leukocyte values were also recorded. The latter were within the normal range for 91.43% of the patients (32 samples) and for one sample each (2.86% each) they were too low, too high, or not available. Age ($r = 0.20$, $p = 0.24$), body mass index ($r = -0.01$, $p = 0.96$), and leukocyte values ($r = -0.06$, $p = 0.75$) were not significantly correlated with oxytocin.

Psychological Variables

The severity of PTSD symptoms was determined using the German translation of the Clinician-Administered PTSD Scale for DSM-5 [Weathers et al., 2018], a standardized interview.

The Scales for the Multiperspective Assessment of General Change Mechanisms in Psychotherapy (SACiP) [Mander et al., 2013], which comprise 21 items, were used to measure the therapeutic alliance. The subscale *Emotional Bond* (3 items) is based on the scale of the same name in the Working Alliance Inventory-Short Revised (WAI-SR) [Munder et al., 2010] and the subscale *Agreement on Collaboration* (6 items) combines the WAI-SR scales *Agreement on Goals* and *Agreement on Tasks*. Furthermore, the SACiP scales *Resource Activation* (3 items), *Clarification of Meaning* (3 items), *Problem Actuation* (3 items), and *Mastery* (3 items) were used. These were adapted from the Bern Post-Session Report for Patients and for Therapists [Flückinger et al., 2010] and pertain to the general change mechanisms of psychotherapy according to Grawe [2004]. The items of the SACiP can have values between 1 and 5, whereby higher values indicate a higher Emotional Bond, Agreement on Collaboration, Resource Activation, Clarification of Meaning, Problem Actuation, and Mastery. The SACiP was filled out at E3, E4, and E5, and thus during and after treatment.

The German version of the Patient Questionnaire on Therapy Expectation and Evaluation [Schulte, 2005] comprised a total of 11 items across the three subscales *Hope for Improvement* (4 items), *Fear of Change* (4 items), and *Suitability* (3 items). The items can have values between 1 and 5, whereby higher values indicate a higher Hope for Improvement, Fear of Change, and Suitability. This questionnaire was completed at E2, E3, E4, and E5, and thus before, during, and after treatment.

Statistical Analyses

The directed hypotheses that could be derived from the previous research related to the possible positive influence of oxytocin on the therapeutic alliance. Thus, inferential statistical tests were only performed for this variable, while the influence of oxytocin on the other psychotherapy process variables was only examined descriptively.

Since the therapeutic alliance in early phases of conventional face-to-face psychotherapy has proven to be particularly important for preventing termination of therapy and improving the symptoms of disorders [Horvath et al., 2011], and its predictive value in internet-based CBT is still disputed [Berger, 2017], we tested this relationship. Two linear regression analyses were performed for that purpose. Emotional Bond and Agreement on Collaboration, each assessed at E3, served as predictors, and the severity of the PTSD symptoms after the end of therapy served as a dependent variable. The severity of PTSD symptoms before the start of therapy was considered a control variable.

Since it has been explicitly stated that oxytocin may influence the therapeutic alliance [Koch et al., 2014], we conducted two additional linear regression analyses. In these, the oxytocin concentrations measured before the start of treatment served as predictors. Emotional Bond and Agreement on Collaboration, measured at E3, were examined as dependent variables. The patients' age was added as a control variable, because it differed between the two groups that were formed later on the basis of oxytocin concentrations.

The relationship between the independent and dependent variables examined in the regression analyses was further clarified by bivariate correlations. Partial correlations were also calculated, whereby the relationship between the independent and dependent variables was adjusted for the influence of the respective control variable of the regression. The α error level was set at 5% in each case.

Given the exploratory nature of the additional analyses, we only performed descriptive analyses of the influence of the oxytocin concentrations measured before the start of treatment on the later evaluations of the therapeutic alliance and on the other psychotherapy process variables. We compared the progression of the psychotherapy process variables of those patients with high and those with low oxytocin concentrations. The patients were assigned to the two groups based on a median split.

All analyses were performed with the program SPSS, version 25 (IBM).

Table 1. Number of patients and existing data

	E1	E2	S1	S2	S3	E3	S4	S5	S6	S7	E4	S8	S9	S10	E5	E6
			Biographical reconstruction				Exposure					Cognitive restructuring				
Participants	35	30	30	28	27	21	21	21	21	20	20	20	20	20	20	20
Low oxytocin	17	14	14	12	12	8	8	8	8	8	8	8	8	8	8	8
High oxytocin	18	16	16	16	15	13	13	13	13	12	12	12	12	12	12	12
Oxytocin	35															
Low oxytocin	17															
High oxytocin	18															
CAPS	35															20
Low oxytocin	17															8
High oxytocin	18															12
SACiP																
Emotional Bond						20					20				19	
Low oxytocin						7					8				7	
High oxytocin						13					12				12	
Agreement on Collaboration						20					20				19	
Low oxytocin						7					8				8	
High oxytocin						13					12				11	
Resource Activation						19					20				19	
Low oxytocin						7					8				8	
High oxytocin						12					12				11	
Motivational Clarification						20					20				20	
Low oxytocin						7					8				8	
High oxytocin						13					12				12	
Problem Actuation						18					20				20	
Low oxytocin						6					8				8	
High oxytocin						12					12				12	
Mastery						20					20				20	
Low oxytocin						7					8				8	
High oxytocin						13					12				12	
PATHEV																
Hope for Improvement		28				20					20				20	
Low oxytocin		12				7					8				8	
High oxytocin		16				13					12				12	
Fear of Change		28				20					20				20	
Low oxytocin		12				7					8				8	
High oxytocin		16				13					12				12	
Suitability		26				20					20				19	
Low oxytocin		10				7					8				8	
High oxytocin		16				13					12				11	

The table shows the number of patients. Oxytocin was measured in the diagnostic examination (E)1. The German translation of the Clinician-Administered PTSD Scale for DSM-5 (CAPS) was used for E1 and E6. The German translation of the Patient Questionnaire on Therapy Expectation and Evaluation (PATHEV) was filled out for E2, E3, E4, and E5. The Scales for the Multiperspective Assessment of General Change Mechanisms in Psychotherapy (SACiP) were filled out for E3, E4, and E5. $n = 37$ patients completed the examination before treatment started, but the present study only applies to those $n = 35$ patients with valid oxytocin measurements. One patient's oxytocin measurement was lacking because the patient completed the test but did not provide blood, and one patient's score was excluded as an outlier. The patients were assigned to the groups with high or low oxytocin based on a median split. S, session.

Results

Patients

The number of patients and data at the examination time points are shown in Table 1. All study participants were male. An overview of the total number of patients included in the internet-based CBT and a list of the reasons why patients stopped participating in the study may be found in Niemeyer et al. [under review] and Engel et al. [under review]. A sample description of all patients

Table 2. Demographic, clinical, and endocrine profiles before treatment begin

	PTSD patients (n = 35)	Low oxytocin (n = 17)	High oxytocin (n = 18)	Comparison
Randomized allocated condition				
Waiting list (immediate treatment)	17 (18)	9 (8)	8 (10)	$\chi^2 = 0.25$ $p = 0.43$
Demographic information before the start of treatment				
Age[a]	37.91 (10.04)	34.00 (7.33)	41.39 (11.00)	$F_{(1,32)} = 5.17$ $p = 0.03$
BMI[a]	27.01 (3.16)	27.19 (3.85)	26.86 (2.62)	$F_{(1,30)} = 0.08$ $p = 0.77$
Number of cigarettes per day[a]	0.97 (1.14)	1.25 (1.18)	0.72 (1.07)	$F_{(1,32)} = 1.86$ $p = 0.18$
Number of deployments abroad[a]	2.85 (3.19)	3.12 (4.38)	2.61 (1.65)	$F_{(1,32)} = 0.21$ $p = 0.65$
Total number of days deployed abroad[a]	379.77 (386.90)	428.27 (521.41)	331.27 (182.10)	$F_{(1,28)} = 0.46$ $p = 0.52$
Dropout				
Dropouts, n (%)	15 (42.86)	9 (52.94)	6 (33.33)	$\chi^2 = 1.37$ $p = 0.24$
Therapy duration in days[a, b]	80.60 (31.21)	92.25 (38.13)	72.83 (24.34)	$F_{(1,18)} = 1.95$ $p = 0.18$
PTSD severity before beginning of treatment				
CAPS total value	33.60 (15.27)	36.06 (14.91)	31.28 (15.67)	$F_{(1,33)} = 0.85$ $p = 0.36$
Endocrine profile before beginning of treatment				
Oxytocin, pg/mL	4.29 (1.08)	3.34 (0.48)	5.18 (0.63)	$F_{(1,33)} = 92.88$ $p < 0.01$

The patients were assigned to the groups with high or low oxytocin based on a median split. [a] Due to missing values, this information was not available for all patients. [b] Refers only to the patients who completed the treatment. Unless otherwise noted, M (SD) are given. The comparisons were conducted with univariate ANOVAs or χ^2 tests. BMI, body mass index; PTSD, posttraumatic stress disorder; CAPS, German translation of the Clinician-Administered PTSD Scale for DSM-5.

and the two groups that were differentiated based on their oxytocin concentrations before the start of treatment is presented in Table 2.

As Table 2 shows, the patients with low oxytocin concentrations before the start of treatment were significantly younger than those with high oxytocin concentrations before the start of treatment. There were no group differences with regard to assignment to the group that was treated immediately, the waiting list condition, additional demographic variables, the severity of the PTSD symptoms, or termination of therapy.

The Therapeutic Alliance as a Predictor of Symptom Improvement

On average, the patients evaluated the therapeutic alliance as positive and their ratings continued to increase in the course of the internet-based CBT (Emotional Bond: M = 3.82, SD = 0.83 at E3; 4.02 ± 0.79 at E4; 4.23 ± 0.59 at E5; Agreement on Collaboration: 2.90 ± 0.99 at E3; 3.04 ± 1.02 at E4; 3.30 ± 1.01 at E5). Statistically controlling for the severity of the PTSD symptoms before the start of treatment did not reveal Emotional Bond as a significant predictor (β = –0.14, t = –1.05, p = 0.31). However, Agreement on Collaboration was a significant predictor of lower severity of PTSD symptoms after treatment (β = –0.27, t = –2.19, p = 0.04). Figure 1 illustrates the bivariate correlations between Emotional Bond and the severity of PTSD symptoms after treatment (r = –0.16, p = 0.52) and between Agreement on Collaboration and the PTSD symptoms after treatment (r = –0.44, p = 0.06). Controlling for the severity of symptoms before the start of treatment, the partial correlations were even more negative (Emotional Bond: r = –0.25, p = 0.31; Agreement on Collaboration: r = –0.48. p = 0.04).

Oxytocin as a Predictor of the Therapeutic Alliance

The oxytocin concentrations before the start of treatment did not signficantly predict Emotional Bond (β = 0.14, t = 0.61, p = 0.55). The effect of oxytocin on Agreement on Collaboration was also not statistically significant (β = 0.23, t = 0.99, p = 0.34). Also controlling for

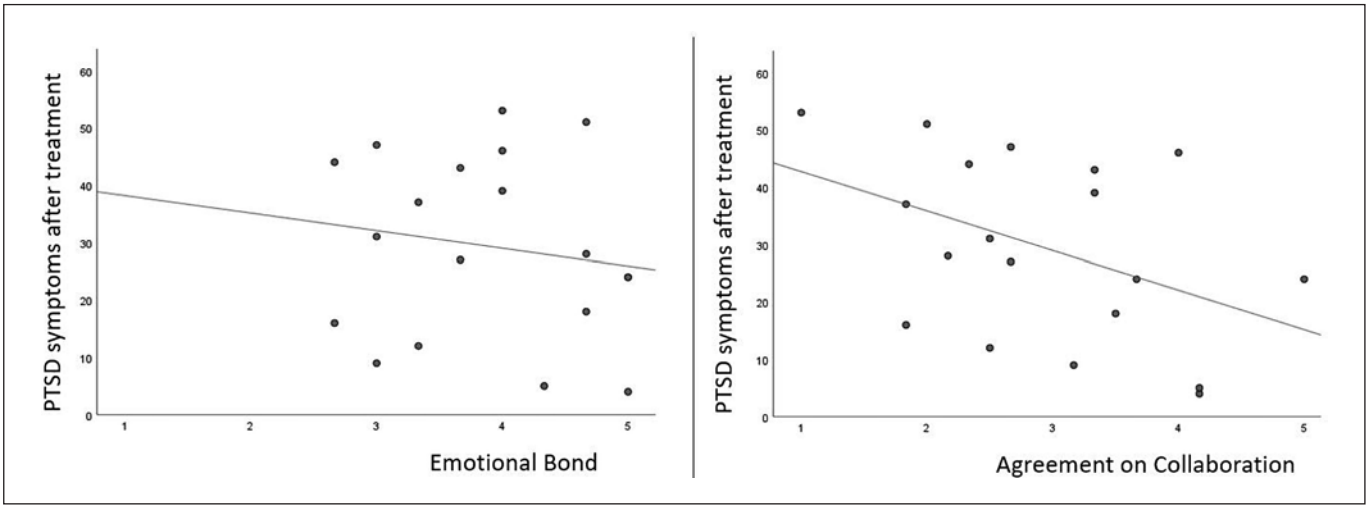

Fig. 1. The bivariate relationship between the two components of the therapeutic alliance (Emotional Bond: $r = -0.16$, $p = 0.52$ and Agreement on Collaboration: $r = -0.44$, $p = 0.06$), measured during the examination (E)3, and the symptoms of posttraumatic stress disorder (PTSD) after treatment (E6).

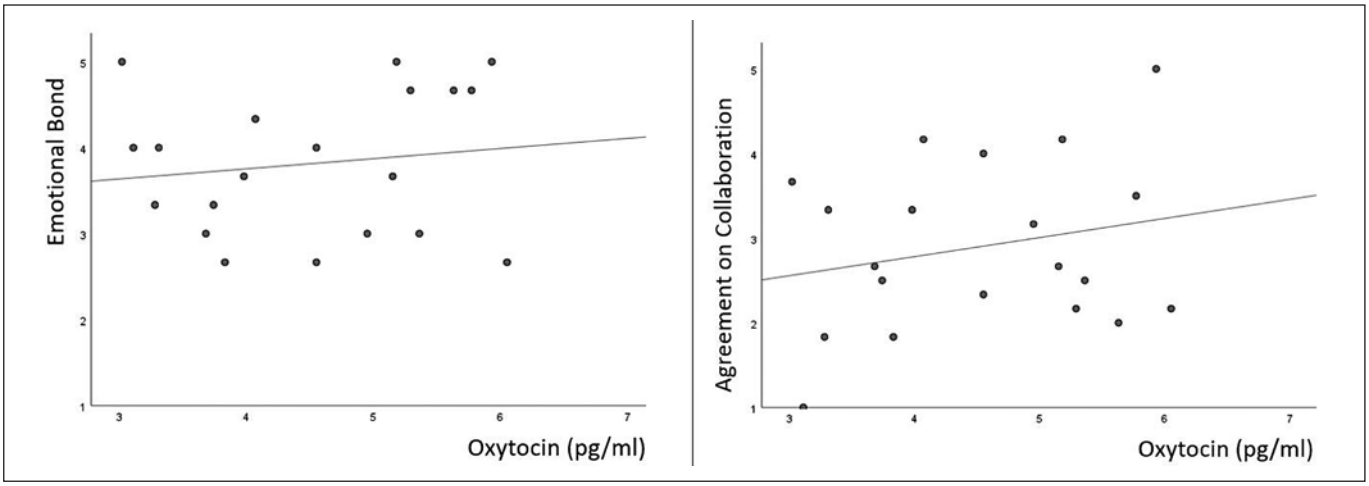

Fig. 2. The bivariate relationship between oxytocin concentrations, measured before the start of treatment in the diagnostic examination (E)1, and the two components of the therapeutic alliance (Emotional Bond: $r = 0.14$, $p = 0.55$ and Agreement on Collaboration: $r = 0.23$, $p = 0.34$), measured at E3.

the age of the patients, neither predictor was significant (Emotional Bond: $\beta = 0.12$, $t = 0.51$, $p = 0.62$; Agreement on Collaboration: $\beta = 0.09$, $t = 0.37$. $p = 0.72$). The bivariate correlations between oxytocin and Emotional Bond ($r = 0.14$, $p = 0.55$) and between oxytocin and Agreement on Collaboration ($r = 0.23$, $p = 0.34$) are shown in Figure 2. Controlling for age, the partial correlations turned out to be less positive (Emotional Bond: $r = 0.13$, $p = 0.62$; Agreement on Collaboration: $r = 0.09$, $p = 0.72$).

The effect of oxytocin on evaluation of the therapeutic relationship, which was queried at later time points, is shown in Figure 3. In accordance with the results of the regression analyses, the descriptive analyses showed that patients with high oxytocin concentrations before the start of treatment reported higher Emotional Bond during treatment (high oxytocin: M = 3.92, SD = 0.84 at E3; 4.11 ± 0.81 at E4; 4.33 ± 0.62 at E5; low oxytocin: 3.62 ± 0.72 at E3; 3.87 ± 0.69 at E4; 4.05 ± 0.42 at E5) and Agreement on Collaboration (high oxytocin: 3.17 ± 0.92 at E3; 3.24 ± 0.96 at E4; 3.53 ± 1.00 at E5; low oxytocin: 2.40 ± 0.86 at E3; 2.75 ± 0.98 at E4; 2.98 ± 0.87 at E5).

The Influence of Oxytocin on General Change Mechanisms of Psychotherapy

Figure 4 illustrates the influence of oxytocin concentrations before the start of treatment on the general change mechanisms of psychotherapy, namely Resource

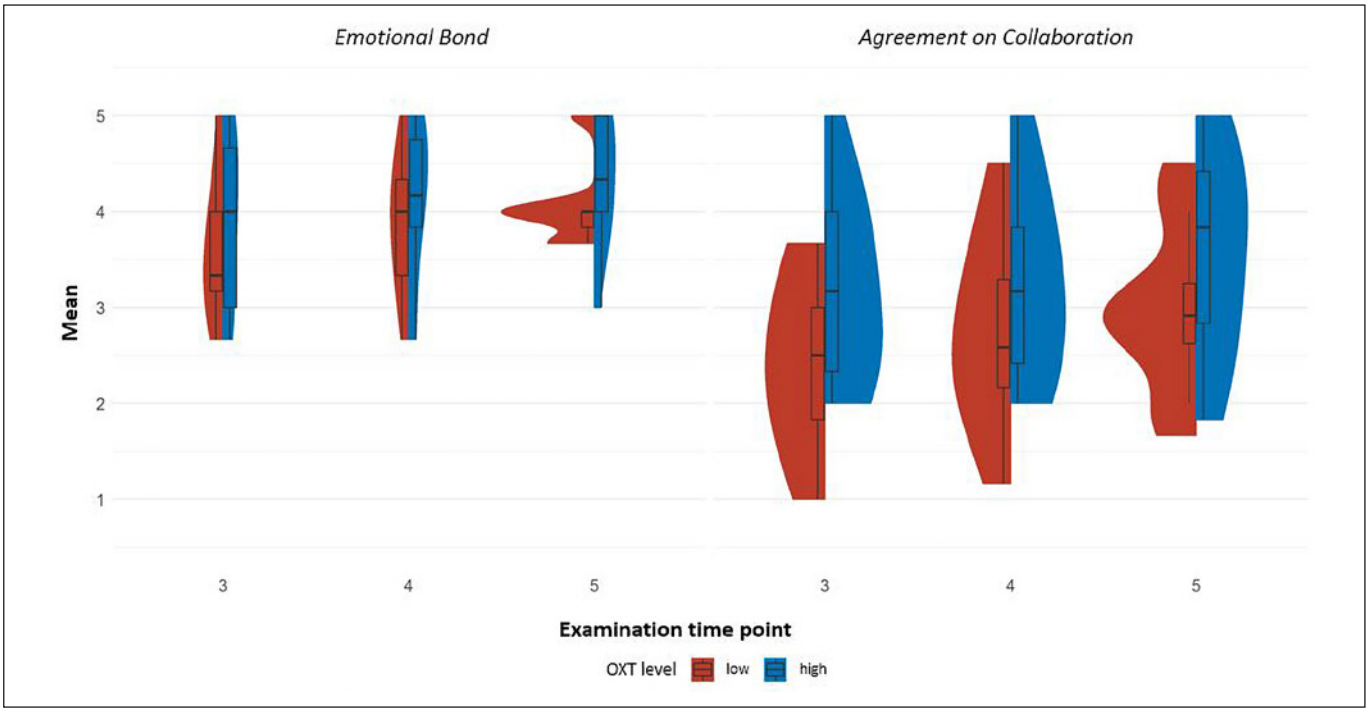

Fig. 3. Evaluations of the therapeutic alliance (Emotional Bond and Agreement on Collaboration), measured during and after treatment at the examination time points (E)3, E4, and E5, as a function of the oxytocin (OXT) level before the start of treatment (E1). The patients were assigned to the groups with high or low OXT based on a median split.

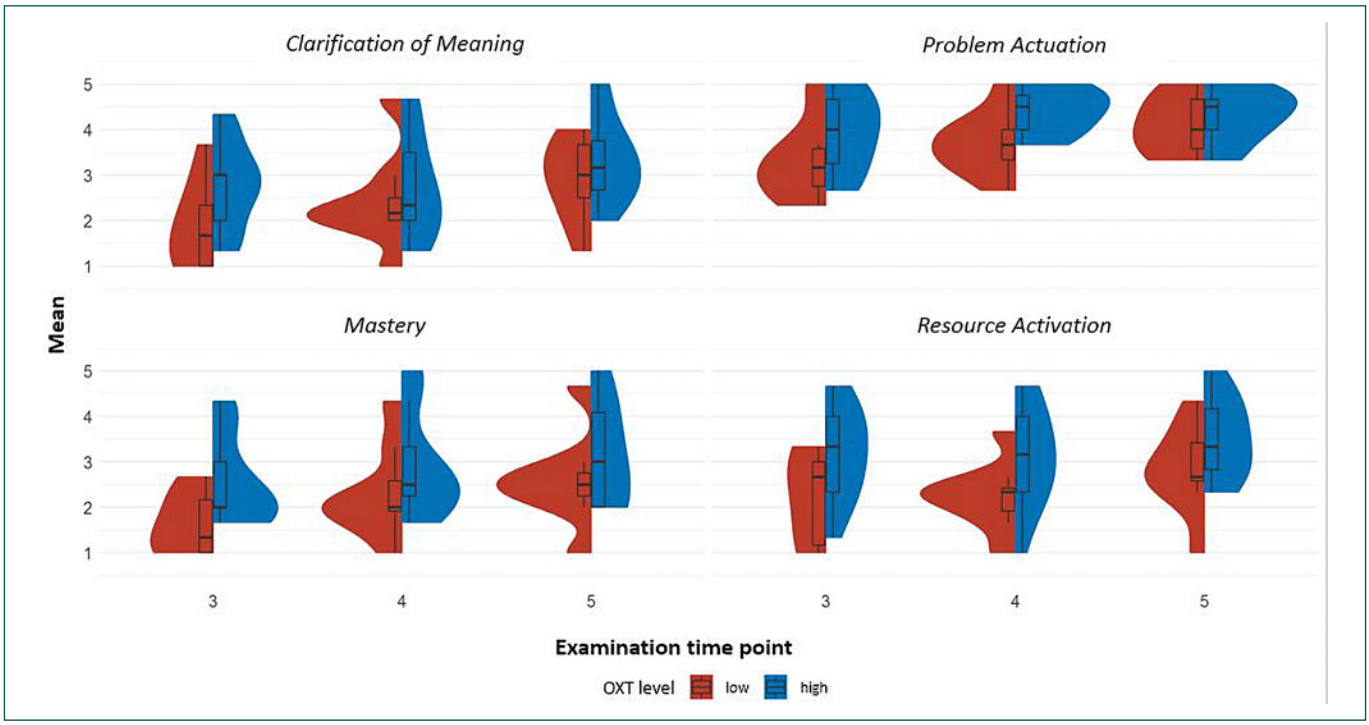

Fig. 4. General change mechanisms (Resource Activation, Clarification of Meaning, Problem Actuation, and Mastery), measured during and after treatment at the examination time points (E)3, E4, and E5, as a function of the oxytocin (OXT) level before the start of treatment (E1). The patients were assigned to the groups with high or low oxytocin based on a median split.

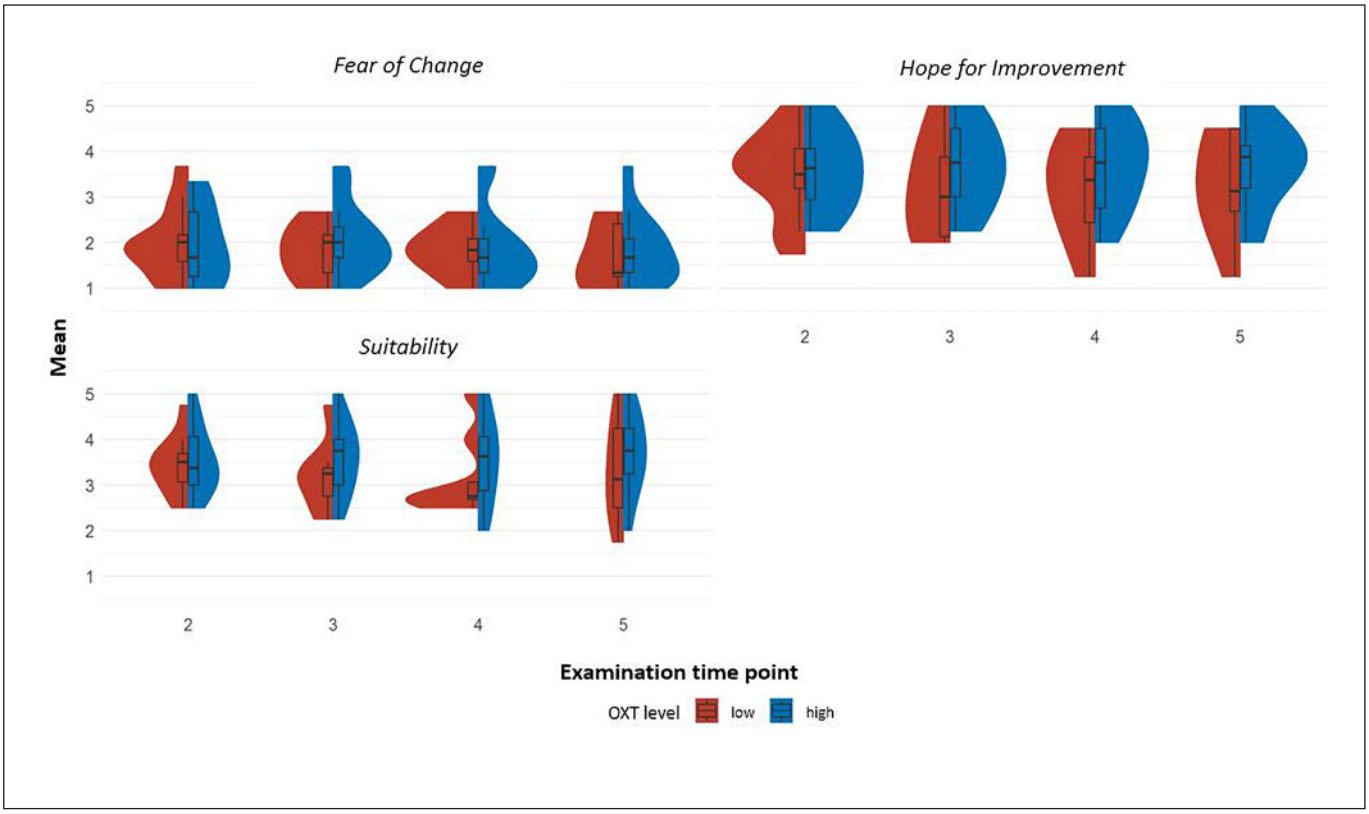

Fig. 5. Psychotherapy expectation and evaluation (Hope for Improvement, Fear of Change, and Suitability), measured before, during, and after treatment at the examination time points (E)2, E3, E4, and E5, as a function of the oxytocin (OXT) level before the start of treatment (E1). The patients were assigned to the groups with high or low oxytocin based on a median split.

Activation, Clarification of Meaning, Problem Actuation, and Mastery. The figure shows that the levels of the general change mechanisms increased in the course of the internet-based CBT. It also shows that patients with high oxytocin concentrations reported higher Resource Activation prior to treatment (high oxytocin: M = 3.19, SD = 0.96 at E3; 3.14 ± 1.04 at E4; 3.52 ± 0.82 E5; low oxytocin: 2.19 ± 0.96 at E3; 2.25 ± 0.72 at E4; 2.83 ± 0.93 at E5), as well as higher Clarification of Meaning (high oxytocin: 2.77 ± 0.95 at E3; 2.78 ± 1.20 at E4; 3.36 ± 0.92 at E5; low oxytocin: 1.86 ± 0.94 at E3; 2.42 ± 1.00 at E4; 2.92 ± 0.85 at E5), higher Problem Actuation (high oxytocin: 3.92 ± 0.82 at E3; 4.42 ± 0.47 at E4; 4.31 ± 0.55 at E5; low oxytocin: 3.33 ± 0.86 at E3; 3.71 ± 0.65 at E4; 4.08 ± 0.60 at E5), and a higher level of Mastery (high oxytocin: 2.56 ± 0.93 at E3; 2.97 ± 1.12 at E4; 3.11 ± 1.10 at E5; low oxytocin: 1.62 ± 0.65 at E3; 2.33 ± 0.97 at E4; 2.58 ± 0.97 at E5).

The Influence of Oxytocin on Psychotherapy Expectation and Evaluation

Figure 5 shows the influence of the oxytocin concentrations before the start of treatment on psychotherapy expectation and evaluation, especially on the variables Hope for Improvement, Fear of Change, and Suitability. The visualizations show that patients with high oxytocin concentrations before the start of treatment evaluated the Hope for Improvement (high oxytocin: M = 3.58, SD = 0.85 at E2; 3.65 ± 0.88 at E3; 3.71 ± 0.93 at E4; 3.67 ± 0.89 at E5; low oxytocin: 3.48 ± 0.93 at E2; 3.14 ± 1.07 at E3; 3.16 ± 1.02 at E4; 3.28 ± 1.09 at E5) and Suitability (high oxytocin: 3.55 ± 0.69 at E2; 3.60 ± 0.75 at E3; 3.54 ± 0.95 at E4; 3.66 ± 0.88 at E5; low oxytocin: 3.45 ± 0.61 at E2; 3.21 ± 0.75 at E3; 3.12 ± 0.84 at E4; 3.31 ± 1.03 at E5) during treatment as higher and Fear of Change at E2 as lower (high oxytocin: 1.94 ± 0.82; low oxytocin: 2.00 ± 0.76). However, Fear of Change at the later measurement points was reported as higher by this group (high oxytocin: 2.08 ± 0.75 at E3; 1.92 ± 0.87 at E4; 1.83 ± 0.75 at E5; low oxytocin: 1.81 ± 0.56 at E3; 1.83 ± 0.50 at E4; 1.71 ± 0.68 at E5).

Discussion

Summary of Results

In the present study, the influence of endogenous oxytocin concentrations that were measured in the blood of

$n = 35$ German Armed Forces service members before the start of a trauma-focused, internet-based CBT was explored for variables that reflect the psychotherapeutic process. Oxytocin was positively but not significantly correlated with Agreement on Collaboration, a component of the therapeutic alliance, in the early stages of therapy. Agreement on Collaboration, in turn, predicted significant improvements in symptoms. The second component of the therapeutic alliance, Emotional Bond, was positively but not significantly influenced by oxytocin and, in turn, did not significantly predict symptom improvements. Descriptive analyses showed that oxytocin had a positive influence on the other general effects of psychotherapy, namely Resource Activation, Clarification of Meaning, Problem Actuation, and Mastery. Furthermore, patients with higher concentrations of oxytocin before treatment reported higher Hope for Improvement, Fear of Change, and Suitability.

Interpretation of the Results

The positive evaluations of the therapeutic alliance in the internet-based CBT examined here are in line with previous findings on the therapeutic alliance for internet-based treatments [Berger, 2017; Sucala et al., 2012]. Previous research on internet-based CBT has provided mixed findings regarding the relationship between the therapeutic alliance and symptom improvements [Berger, 2017]. Our study could help explain this heterogeneity, since we analyzed two components of the therapeutic alliance differentially. The Emotional Bond in the early treatment phase could not predict any symptom changes, but Agreement on Collaboration in the early treatment phase predicted reduced severity of the PTSD symptoms after the treatment was completed. It was previously conjectured that a ceiling effect, based on uniformly high ratings of Emotional Bond and, associated with it, a lack of variance in the predictor variable, was responsible for the fact that no relationship between the therapeutic alliance and symptom improvements was discovered in internet-based treatments [Berger, 2017]. Our results, however, contradict this assumption. Although the Emotional Bond was rated as high on average, the variance indicators nevertheless showed sufficient inter-individual variability. Our results indicate that the process-oriented component of the therapeutic alliance, that is, the Agreement on Collaboration, is more relevant for Internet-based treatments than the more emotion-oriented component, the Emotional Bond.

The influence of oxytocin on evaluations of the therapeutic alliance in the early treatment phase was statistically verified. The inferential and descriptive statistics consistently showed that oxytocin did not significantly influence the Emotional Bond. The correlation between oxytocin and Agreement on Collaboration was also not significant, but was higher at first. However, the strength of this relationship was reduced by the additional consideration of age.

We also explored the influence of oxytocin on the later evaluations of the therapeutic alliance, on other general change mechanisms of psychotherapy, and on psychotherapy expectation and evaluation. The general change mechanisms of psychotherapy were rated as more positive by patients with high oxytocin concentrations before the start of treatment than by patients with low oxytocin concentrations before the start of treatment. Regarding psychotherapy expectation and evaluation, patients with high concentrations of oxytocin before treatment reported higher Hope for Improvement and Suitability across all treatment phases and lower Fear of Change in the early treatment phase. However, this group reported higher Fear of Change in the later treatment phases. It also cannot be ruled out that the group differences are at least partially due to response tendency biases.

According to the social salience hypothesis, it is assumed that oxytocin increases the salience of social stimuli and thus, depending on individual characteristics, achieves either pro- or antisocial effects [Shamay-Tsoory and Abu-Akel, 2016]. Based on studies of borderline personality disorder [Bartz et al., 2011a; Ebert et al., 2013] psychopathology was previously discussed as a moderator that explained the harmful effects of oxytocin in clinical populations [Bartz et al., 2011b; Olff et al., 2013; Shamay-Tsoory and Abu-Akel, 2016]. In the present study with PTSD patients, however, prosocial effects of oxytocin were described at the descriptive level. This suggests that specific symptoms, such as chronic interpersonal insecurities [Bartz et al., 2011a], regulate the effects of oxytocin rather than generally increased vulnerability due to psychological problems.

Limitations

The most important limitation of the present study was the limited possibility of reaching statistical conclusions. This was due to the small sample size and our decision to avoid a large number of statistical tests by not using hypothesis-validating statistical procedures for most psychotherapy process variables. An a priori power analysis we performed to estimate the number of patients we needed in order to evaluate the effectiveness of internet-based CBT, resulted in a sample size of $n = 100$ [Niemeyer et al., under review]. Any additional analysis, such as the role of biological markers in treatment, would have required an even larger number of patients to reach statistically valid conclusions. Problems with recruitment and dropouts, which had been previously reported in military samples [Hoge et al., 2014], resulted in a significantly reduced sample size compared to our goal. That was the

reason for our decision to reduce the number of inferential statistical tests to a minimum and instead focus on descriptive evaluations. Our evaluations should therefore be regarded as exploratory and our results, which can be viewed as preparatory work for further studies, must be confirmed in larger, independent samples.

Another limitation concerns the meaningfulness of endogenous oxytocin concentrations. On the one hand, their measurement is presented as an important noninvasive tool to study interactions between the oxytocin system and psychological processes [Crockford et al., 2014]. On the other hand, psychological processes are controlled by the central nervous system, whereby peripheral oxytocin concentrations only reflect the central nervous availability of oxytocin under specific conditions, such as after acute stress or intranasal administration [Valstad et al., 2016]. Furthermore, endogenous oxytocin concentrations are not stable over time and are susceptible to the influence of confounding variables. In the present sample, the oxytocin concentrations before the start of treatment and immediately after treatment were not correlated ($r = 0.04$, $p = 0.89$) [see Engel et al., under review]. This makes it clear that the group differences in the later therapy phases, which have a longer time interval to the oxytocin measurements, should especially be interpreted with caution. The use of psychotropic drugs should be mentioned as a possible relevant confounding variable. Although this was intraindividually stable in the present study, it could vary interindividually.

It should also be noted that the patients with lower oxytocin concentrations were younger than those with higher oxytocin concentrations. The reduction in the relationship between oxytocin and the variables of the therapeutic alliance at the beginning of treatment, after taking age into account, suggests that age differences could also be relevant for the group differences.

The psychotherapeutic treatment that we studied was delivered through a specific medium: the internet. It has been well demonstrated that internet-based CBT effectively reduces PTSD symptoms, with effect sizes that are comparable to those of conventional face-to-face psychotherapy [Kuester et al., 2016]. However, internet-based CBT has some specific characteristics, particularly with regard to the social interaction between patient and therapist. So far, little research has been done on the mechanisms underlying symptom improvements in internet-based CBT; however, there are indications that these differ in part from the mechanisms of action in face-to-face psychotherapy [Andersson et al., 2014]. The predictive value of the therapeutic alliance for symptom improvement in internet-based CBT is still disputed [Berger, 2017], whereas the therapeutic alliance of face-to-face psychotherapy has been established as a general change mechanism [Horvath et al., 2011]. Although internet-based CBT represents an interesting context to investigate the influence of oxytocin on psychotherapy process variables, it remains unclear to what extent the results are also applicable to face-to-face psychotherapy.

Conclusion

The present study provides evidence that endogenous oxytocin concentrations have prosocial effects in PTSD patients. This was shown in positive evaluations of the therapeutic alliance and other general psychotherapeutic mechanisms of change, which were compiled in the context of an internet-based CBT program. It is necessary to validate these results in a larger, independent sample using inferential statistics and to confirm them outside the specific context of internet-based CBT.

It has been debated whether stimulation of the endogenous oxytocin system by intranasal administration of synthetic oxytocin [van IJzendoorn et al., 2012] might be contraindicated in clinical populations [Hurlemann, 2017]. In our study, however, at least with regard to endogenous oxytocin concentrations, evidence of possible positive effects was found. Future studies could examine a possible therapeutic benefit of oxytocin nasal sprays for the effectiveness of trauma-focused psychotherapy. The therapeutic alliance is particularly important in the early treatment phase, in order to keep patients in treatment and to stimulate symptom improvement [Horvath et al., 2011]. Therefore, future studies could specifically investigate whether trauma-focused psychotherapy could be promoted by stimulating the oxytocin system in the early treatment phase.

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Statement of Ethics

After internal approval by the Bundeswehr, the study was approved by the Ethics Committee of the Free University of Berlin (reference number: 85/2014; addendum: 116/2016). The study complies with the ethical standards of the Declaration of Helsinki in its expanded form of 1975 and its supplements of 1983, 1989, and 1996. As described in the article, all study participants agreed to participate after being informed about the study goals, the study procedure, and the voluntary nature of participation, The article contains no information that indicates the identity of the person.

Disclosure Statement

OFA Heinrich Rau and Dr. Gerd-Dieter Willmund are employed by the German Armed Forces. Their employment influenced neither the study design nor the collection, analysis, and interpretation of the data. There are no conflicts of interest among the other authors.

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