The Influence of an Attachment-Related Stimulus on Oxytocin Reactivity in Poly-Drug Users Undergoing Maintenance Therapy Compared to Healthy Controls

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Background: Substance use disorders (SUDs) have been described as a dysfunctional way to compensate for deficiencies in that person’s underlying attachment system. Furthermore, the neuropeptide oxytocin (OT), which is a critical component of the neurobiology of the attachment system, has been shown to effectively reduce addictive behavior and therefore has been discussed as a potential medication in SUD treatment. This study investigates variation in peripheral OT plasma levels as a function of exposure to an attachment-related stimulus in SUD patients compared to healthy controls (HCs).

Methods: A total sample of 48 men, 24 inpatients in maintenance treatment who were diagnosed with poly-drug use disorder (PUD) and 24 HC, was investigated. A 15-min exposure to the Adult Attachment Projective Picture System (AAP) was used as an attachment-related stimulus and coded for attachment status. Blood samples before and after the AAP-assessment were taken and assayed for OT levels. Variation in baselines level of OT was examined in relation to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), the Adult Attachment-Scale (AAS), and the Brief Symptom Inventory (BSI).

Results: Following the AAP stimulus controls showed no significant difference in OT levels elevation from baseline compared to the PUD group’s OT levels. Furthermore, in the PUD group only OT-baseline-levels may be negatively associated with the AAS subscale “Comfort with Closeness” and “Anxiety” and lifetime substance use.
INTRODUCTION

Substance use disorders (SUDs) have been characterized as a compulsive substance use without consideration of the negative consequences (1) and are increasingly framed as a neurobiological disorder (2, 3). Currently, the most common form of SUD in patients undergoing treatment in Austria is poly-drug use disorder (PUD), with opioids as the primary drug of choice (4), a pattern which is also found in the majority of SUD patients across Europe (5). In recent years, increasing number of patients are treated within maintenance treatment programmes, which have been shown to be effective treatments by reducing heroin use and risk behaviors as well as improving health, social and criminal justice outcomes (6).

From a psychodynamic perspective, SUD has been understood in relation to attachment disorder (7) and as a dysfunctional way of self-medicating (8). Specifically, insecure attachment has been linked to increased psychopathology for decades (9). Formed by early parent-infant interactions, which are gradually imprinted in neuronal pathways (10, 11), attachment can be understood as a neurobiological system designed to promote social affiliation and primary bonding experiences (12, 13). Recent studies indicate a substantial role of insecure attachment in the etiology of SUDs (14–16)—among other psychiatric disorders (17). This relationship has been linked to the influence of attachment styles on the interpersonal regulation of human emotions particularly fear, anxiety and hedonic experiences within close relationships (18, 19).

Attachment research across mammalian species has suggested that the neuropeptide oxytocin (OT) plays a central role in the neurobiological processes involved in the formation and maintenance of social bonds (20), interpersonal affect regulation (14, 21) and parent-child relationships (22–24), but also protective aggression (25). The OT-system in humans is associated with brain regions including the amygdala, paraventricular nucleus (PVN), supraoptic nucleus (SON), ventral pallidum (VP), ventromedial nucleus of the hypothalamus (VMH), area tegmentalis ventralis (VTA), substantia nigra (SN), and the neuroendocrine systems (26). Consisting of nine amino acids, this neuropeptide is produced by PVN and SON. Through axonal transport OT is centrally released to hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, and the central brain in response to social interactions and stressors (27–30). In line with the Calm and Connect Model (31), which assumes that bonding, experienced through touch and social affection, leads to OT production and thus positively reinforces social connection, several studies have linked insecure attachment patterns to impairments of the OT-system (23, 27, 29, 32).

Discussion: Our results suggest that peripheral OT levels in poly-drug users undergoing maintenance treatment are not significantly different in responsiveness to an attachment related stimulus compared to HC. With regard to non-significant tendencies observed in this study which hint toward decreased OT-reactivity in the PUD group, further research is needed to explore this hypothesis with increased statistical power.

Keywords: attachment, maintenance treatment, poly drug use, oxytocin, substance use disorder

In the context of addiction, beneficial effects of administered OT on drug tolerance, withdrawal and seeking have been proposed across various substance classes (33, 34). Individual differences in the endogenous OT-system may therefore affect the vulnerability to addiction. SUDs have been repeatedly linked to decreased levels of OT (35–37). Furthermore, OT is assumed to modulate the mesolimbic dopamine system (38), a structure which is substantially involved with the process of addiction development and bond formation (2, 39). Similarly, there is considerable evidence suggesting interactions between the OT and endogenous opioid system (40). In line with these observations, a recent review by Zanos et al. (41) concluded that the OT system is not only meaningfully influenced by opioid addiction and abstinence but also might serve as a critical target for pharmacological interventions. Such findings inform the first aim of this study to investigate cross sectional relationships between substance use and OT levels.

Previous research indicated a relationship between the administration of stimuli designed to activate the attachment system of participants and the OT-system. One such measure, the Adult Attachment Projective Picture System (AAP) was shown to significantly increase OT levels (42). This study was conducted with a sample of healthy lactating mothers who might be thought to be especially responsive to attachment cues. Moreover, these authors hypothesized that women with more secure attachment patterns should show higher OT-reactivity. However, in this study, the authors were not able to confirm the proposed association between a larger increase in OT and more securely attached mothers. This experimental paradigm using the AAP as an attachment stimulus is adopted in the current study, while our study is focused on substance users compared to healthy controls (HCs).

What is more, in recent years, several reviews have been published which critically assess methodical flaws frequently observed within the research of the human OT system [e.g., (43–45)]. These contributions specifically emphasize the importance targeted hypotheses, consideration of differences between central processing of OT and its peripheral levels, as well studies focussed on peripheral levels making use of plasma samples, and plasma to be assayed for OT levels after extraction.

With this in mind, this study aimed to enhance the understanding the relationship between attachment and the OT-system in patients with SUD. We sought to address two primary aims. First, using baseline levels of peripheral OT, we examined their associations with substance use (using the ASSIST), attachment (using the Adult Attachment-Scale), and current symptoms (using the Brief Symptom Inventory). In relation to
the first aim, we expected to find OT levels negatively associated with insecure attachment patterns and psychopathological symptom burden in the PUD group. Our second aim follows the experimental study by Krause et al. (42), which focuses on the response of the peripheral OT-system in response to an attachment-related stimulus. In the experimental study, we compared PUD patients undergoing maintenance therapy to HCs. Following Krause, we expected to see a rise in the OT levels of health controls when exposed to an attachment stimulus. We were exploring whether the SUD group would show a different OT response to the same stimulus. However, as this is the first time, this experimental paradigm is investigated in patients undergoing maintenance treatment, this hypothesis remains exploratory.

SAMPLE AND METHODS

Participants

The study sample consisted of 48 male participants between 19 to 38 years of age (M = 27.42, SD = 4.82), consisting of one clinical (PUD; n = 24) and one non-clinical group (HC; n = 24). Participants in the clinical group met diagnostic criteria for PUD (F19.2), diagnosed according to the International Classification of Diseases version 10 (ICD 10) (46) by a licensed psychiatrist. Due to the haphazard drug use, one of the main characteristics for PUD, the drugs consumed cannot be reported in detail. At the time of the study, all PUDs were currently participating in maintenance therapy as described below. PUDs with fluid psychotic symptoms were excluded. Comorbidities with other diagnoses were distributed as follows: 9.2% Affective disorders (F3.x), 5.8% Neurotic, stress and somatoform disorders (F4.x), 4.6% Personality and behavioral disorders (F6.x), 2.3% Schizophrenia, schizotypal and delusional disorders (F2.x), 1.2% Behavioral and emotional disorders (F5.x) with onset usually occurring in childhood and adolescence. Before participating in the study PUD patients had been in maintenance therapy for a mean time of 15 weeks (SD = 13.8) and received either Levo-Methasan (n = 21), Bupensan (n = 1), Subtilit Retard (n = 1), or Compansan Retard (n = 1) as a substitution agent, with daily doses ranging from 2 to 320 mg, depending on patient and medication. Furthermore, 21 PUD patients received additional psychopharmacological medication: 16 (66.67%) received antipsychotics and 19 (79.17%) received antidepressants. Participants of the non-clinical group, exclusively non-smoking men, reported either none or just a few previous experiences with illegal substances. With the exception of occasional consumption of alcohol, no use of psychoactive substances was reported by HC in the last 30 days prior to the investigation and no use of psychopharmacological medication. HCs were included if they reported no past or present psychiatric disorder or chronic disease. Exclusion criteria for both groups were insufficient knowledge of the German language. Clinical subjects were assessed at the Johnsdorf therapeutic facility of the Grüner Kreis Society. Non-clinical subjects were recruited through advertising on social networks and via email distribution of the University of Graz. The study was approved by the ethics committee of the University of Graz, Austria and conducted in accordance with the Declaration of Helsinki.

Procedure and Design

In order to eliminate any effects due to circadian rhythms the timing of the experiment was standardized. Participants were asked to fast for at least 3 hours before arriving in the laboratory (between 12.00 am and 3.30 pm), avoid caffeinated drinks and to refrain from smoking on the day of participation, before and during the experiment. After written informed consent was obtained and the subjects were notified about the course of the experiment, the first venipuncture and blood collection was performed. Immediately after, the AAP (47) was applied in which participants were asked to tell a story for each of the eight shown pictures with either monadic or dyadic scenes by answering the following questions: “What is happening in the scene?”, “What led up to the scene?”, “What are the characters thinking or feeling?”, and “What might happen next?”. The abstract line drawings indicate scenarios such as illness, separation, and abuse without detailed facial expression, allow a large scope of interpretation (47). The AAP measure is designed around a common assumption in observational and discourse attachment measures that attachment behavior is best observed directly after an attachment related stimulus is delivered or represented such as a separation, loss, illness and so on (48). The interviews lasted on average 16 min (SD = 4.50). The AAP interviews were administered by a trained psychologist in a standardized manner according to the published administration requirements. Following the AAP, and 25 min after the first blood sample a second blood sample was collected, again via venipuncture. The psychometric assessment (described below) took place online via Lime-Survey® before the experiment.

Measures

Addictive Behavior

The German Version of the Alcohol, Smoking and Substance Involvement Screening Test [ASSIST 3.0; (49), German Version; (50)] is a structured short interview designed to record lifetime consumption behavior and its negative effects from the following substance classes: alcohol, tobacco, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, and opiates among others. For this study, the interview was adapted as a self-report questionnaire. Questions about the “Frequency of drug use”, “Craving to use the drug”, “Problems”, and “Failed expectations” are rated on a 7-point Likert scale from 0 (never) to 6 (daily). Questions about “Expressed concerns by relatives or friends”, “Failed attempts to cut down drug use”, and “Drug injection” are rated on a 3-point Likert scale (0 = “no never”, 3 = “yes, but not in the past 3 months”, 6 = “yes, in the past 3 months”). By adding the drug specific symptom scores an overall score for every symptom class (mentioned above), as well as a total score was calculated. Subscales ranged in Cronbach’s alpha from 0.79 to 0.89.

Mental Health Symptoms

The short version of the Brief Symptom Inventory [BSI-18; (51), German Version: (52)] assesses the amount of psychiatric burden of the last 7 days by means of 6 items on each of the
three subscales: (1) Somatization, (2) Depression, and (3) Anxiety. It is rated on a 5-point Likert scale from 0 “absolutely not” to 4 “very strong”. A Global Severity Index (GSI) can be generated for a total of the 18 items. Cronbach’s alpha for the subscales ranged from 0.70 to 0.87. The total Global Severity Index score showed a Cronbach’s alpha of 0.87.

Attachment Styles
The German Version of the Adult Attachment Scale [AAS; (53, 54)] is a self-report method measuring attachment dimensions based on attachment theory (55). This questionnaire consists of three subscales: (1) Anxiety about being rejected or unloved, (2) Comfort with Closeness and Intimacy, and (3) Comfort in Depending on others. This questionnaire consists of 18 items rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Cronbach’s alpha for the scales ranged from 0.68 to 0.79.

Oxytocin Assessment
For measuring the plasma OT levels, blood samples were drawn from antecubital veins into 3-ml vacutainer blood vacuettes (Greiner Bio-One International GmbH, Austria) containing Aprotinin (500 KIU/ml of blood) (Sigma-Aldrich, Germany). Vacuettes were stored at −20°C before use. Vacuettes were centrifuged at 4°C at 1,600 g for 15 min. Supernatants were stored at −80°C until analysis. Extraction of samples was undertaken and OT concentrations in the extracts were determined in duplicate by Oxytocin ELISA kit (AD1-900-153A, Enzo Life Sciences, USA), a colorimetric competitive enzyme immunoassay kit at the Center for Medical Research at the Medical University Graz, Austria. The mean intra-assay and inter-assay coefficients of variability were 23.4% and 13.9%, respectively; sensitivity was 15.0 pg/ml. All procedures were performed according to the manufacturer’s instructions by authorized personnel.

Data Reduction and Statistical Analyses
For group comparisons in the experimental design, one-way analyses of variance and χ² tests were conducted. To evaluate the reactivity of OT, the amount of the difference value of pre- and post-OT-level was considered. To investigate the relationship between OT and behavioral measures Pearson’s correlation coefficients were calculated separated for the PUD group. Alpha was set to p < 0.05 in ANOVAs and Pearson’s correlations. However, with regard to recent critical reviews of OT-literature [e.g., (43, 44)], we additionally corrected for multiple comparisons via the Bonferroni correction. In order to ensure a better evaluation of the results, effect sizes were included.

RESULTS
Demographics and Clinical Characteristics
Socio-demographic variables, scores for addictive behavior as well as requirements prior to the interview of both groups are presented in Table 1.

Hypothesis-Testing Results
Group Differences in OT and Attachment
As depicted in Table 2, group comparisons showed that PUD had higher levels of OT compared to HC before at baseline (F(1, 46) = 7.02; p < 0.05). No other significant group differences regarding OT were observed (all p > 0.05) [for comparative means see (56)]. Following the administration of the AAP as attachment stimuli, the HC seemed to increase in OT levels whereas the PUD group’s OT remained flat. However, this difference was not significant (F(1, 46) = 3.25; p = 0.08).

Furthermore, the between group tests for differences in the measures of mental health and attachment the PUD group showed a tendency toward less Comfort with closeness (F(1, 46) = 3.97; p = 0.05) and Comfort with depending on others (F(1, 46) = 3.61; p = 0.06) and higher depressive symptom burden (F(1, 46) = 8.27; p < 0.05). With regard to the Bonferroni corrected alpha level, no group differences remained significant (all p > 0.003).

Intercorrelations of Oxytocin, Attachment, and Personality Characteristics for PUD
Correlations over PUD showed that baseline OT-levels were related to less Comfort with closeness (r = −0.41, p < 0.05) and lifetime substance use over all substance classes (r = −0.48, p < 0.05). Furthermore, OT-reactivity showed non-significant tendencies with Comfort with closeness (r = .34, p < 0.10) and Lifetime substance use (r = .37; p = 0.07). Moreover, as shown in Table 3, insecure attachment patterns were related to Depression (r = −.51 −.49; all p < 0.05). No correlation remained significant if corrected for multiple comparisons (all p > 0.003).

DISCUSSION
In order to enhance the understanding of the relationship of OT to SUD, we investigated the differences in psychopathology, attachment, and the OT-system between PUD patients undergoing maintenance treatment compared to HC, as well as differences in peripheral OT response to an attachment-related stimulus. Our results suggest that PUD patients were higher OT at baseline compared to a HC group. In response to the attachment stimulus containing the AAP procedure, differences between the PUD and HC groups regarding OT-reactivity remained non-significant. Furthermore, baseline OT-levels showed a significant relationship with decreased Comfort with closeness in PUD patients.

However, these results should be interpreted with caution. In the first instance, the sample size of the study was small and there were numerous significance tests run. Following Nave et al. (44) and McCullough et al. (43), who proposed the necessity for correcting for multiple comparisons, no finding remained significant based on a Bonferroni corrected alpha level. While the Bonferroni correction has been criticized as being overly conservative (57, 58), the findings of this study are tentative and require replication in a larger study.
The finding of increased OT-baseline in the PUD group is in contrast to many other studies (41). The interpretation of this result needs to remain speculative at this point. However, it is conceivable that this finding might be traced back to the characteristics of living in the therapeutic community which is characterized by high social cohesion and an attachment focused treatment approach (59). Furthermore, in contrast to the HC group, PUD participants traveled to the OT measuring in groups, which might have

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TABLE 1 | Group differences in demographic and conditions prior to investigation.

|                         | PUD (n = 24) | HC (n = 24) | T    | df | p   |
|-------------------------|--------------|-------------|------|----|-----|
| Age                     | 28.50 5.85   | 26.33 3.25  | -1.59 | 35.99 | 0.119 |
| Risk of substance use   |              |             |      |     |     |
| Lifetime substance use  | 23.63 4.79   | 8.63 4.18   | -11.56* | 45.17 | 0.000 |
| Global continuum        | 29.04 4.43   | 13.75 7.04  | -9.01 | 46  | 0.000 |
| Conditions day of       |              |             |      |     |     |
| Waking up               | 467.17 79.61 | 371.96 138.38 | -2.92* | 46 | 0.005 |
| Caffeine consumption a  | 440.63 178.57 | - | - | - | - |
| Nicotine consumption a  | 103.54 195.23 | - | - | - | - |
| Last meal a             | 272.63 133.84 | 360.04 258.75 | 1.48 | 34.64 | 0.146 |
| Sexual activity         | 700.43 138.25 | 621.25 231.45 | -1.43 | 37.83 | 0.161 |

|                         | PUD (n = 24) | HC (n = 24) | X² | df | p   |
|-------------------------|--------------|-------------|----|----|-----|
| Nationality             |              |             |    |    |     |
| Austria                 | 16           | 19          |    |    |     |
| Other Country           | 8            | 5           |    |    |     |
| German language skills  |              |             |    |    |     |
| Mother tongue           | 16           | 22          |    |    |     |
| Very well               | 7            | 2           |    |    |     |
| Less well               | 1            | 0           |    |    |     |
| Education               |              |             |    |    |     |
| No completed Education  | 1            | 0           |    |    |     |
| Secondary school        | 10           | 0           |    |    |     |
| Apprenticeship          | 12           | 0           |    |    |     |
| High School             | 1            | 14          |    |    |     |
| Bachelor                | 0            | 5           |    |    |     |
| Master/Doctor           | 0            | 5           |    |    |     |
| Psychiatric diagnosis   |              |             |    |    |     |
| Yes                     | 24           | 0           |    |    |     |
| Current psychotherapy   |              |             |    |    |     |
| Yes                     | 24           | 0           |    |    |     |
| Chronic physical health |              |             |    |    |     |
| problems               |              |             |    |    |     |
| Yes                     | 3            | 0           |    |    |     |
| Regular medication      |              |             |    |    |     |
| Yes                     | 24           | 0           |    |    |     |

*p < 0.05; PUD, Poly-drug use disordered patients; HC, Healthy controls. | Past time in minutes since last consumption on test day.

TABLE 2 | Group differences (ANOVA) in behavioral and biological measures.

| Measures                      | PUD (n = 24) | HC (n = 24) | F (1, 46) | η²  | p   |
|-------------------------------|--------------|-------------|-----------|-----|-----|
| BSI-18                        |              |             |           |     |     |
| Somatization                  | 0.690 2.17   | 2.73        | 2.13 2.35 | 0.00 | 0.00 | 0.955 |
| Depression                    | 0.852 6.25   | 5.57        | 2.71 2.33 | 8.27* | 0.15 | 0.006 |
| Anxiety                       | 0.816 4.54   | 5.01        | 3.46 2.41 | 0.91 | 0.02 | 0.344 |
| Total Score                   | 0.869 12.96  | 11.14       | 8.71 5.39 | 2.83 | 0.06 | 0.099 |
| Oxytocin Pre (pg/ml)          | 60.64 24.87  | 44.74       | 15.68     | 7.02* | 0.13 | 0.011 |
| Oxytocin Post (pg/ml)         | 60.38 17.25  | 60.46 38.73 | 0.00     | 0.00 | 0.992 |
| Reactivity                    | -0.26 17.64  | 15.72       | 39.66     | 3.25 | 0.06 | 0.078 |
| AAS                           |              |             |           |     |     |
| Dependence                    | 0.731 16.13  | 4.89        | 18.42 3.31 | 3.61 | 0.07 | 0.064 |
| Closeness                     | 0.786 11.63  | 3.92        | 13.92 4.00 | 3.97 | 0.08 | 0.052 |
| Anxiety                       | 0.678 12.26  | 3.91        | 12.29 3.75 | 0.00 | 0.00 | 1.000 |

Bonferroni corrected p = 0.005; *p < 0.05; PUD, Poly-drug use disordered patients; HC, Healthy controls; Pre, baseline OT-levels; Post, OT-levels after confrontation with attachment related cue.
further contributed to inflated OT baseline levels (60). Another possibility would be an influence of the various medications used for maintenance therapy which interact with the opioid system, or indeed the use of antidepressant or antipsychotic medications in PUD participants. However, while not extensively researched, recent literature indicates no influence of antidepressant pharmacological treatments on OT (61) but there have been some animal studies suggesting a relationship between antidepressants and OT metabolism (62).

OT-reactivity in PUD patients did not significantly differ from variability of HC participants. Based on previous research it might be speculated (29, 42), that an increase in OT in response to an attachment related stimulus is associated with seeking and finding of an internalized positive attachment representation. Furthermore, animal research has shown that the administration of morphine potently inhibits the secretion of OT and depresses the OT-sensitivity of the mammary gland, due to inhibition of the firing of supraoptic OT-neurons (63–66). Considering potential ceiling effects of methadone on the endogenous OT-system, its chronic administration could cause a maximum release of OT, so that further increases in OT are diminished, regardless of whether the person is triggered with an attachment related stimulus or not. Regarding the statistical tendencies observed in our sample which hints in the direction described above, more data is needed to further evaluate this line of interpretation.

Contradicting recent literature (15, 67), no significant differences between PUD patients and HC were found regarding adult attachment attitude using the AAS measure. Nevertheless, the non-significant associations showed there may be important relationships here which the current study was underpowered to detect and are consistent with the pattern observed in previous research (14, 67–69).

In general, the main results in this study may be influenced by several effects brought about by a combination of psychopharmacology, maintenance, and long-term psychotherapeutic treatment.

In addition, our findings designate a negative relationship between baseline OT-level and Comfort with Closeness in PUD patients. Corresponding to recent findings by Torres et al. (70), which suggested a negative correlation between the dose of maintenance therapy and Closeness as well as decreased Anxiety in patients undergoing maintenance therapy. Therefore, the mechanism of maintenance therapy might operate on the surface but helps PUD patients only to a limited extent in the formation of healthy interpersonal relationships and positive attachment representations that can be relied on in times of distress (15, 21).

Moreover, we observed tentative hints toward a link between OT-reactivity and increased Comfort with closeness which, however, did not achieve statistical significance. Similarly, Krause et al. (42) did not find significant associations between attachment security and OT-reactivity in lactating mothers. Hence, while a relationship between attachment and OT-reactivity may be a reasonable premise, more research should be done to further analyze this subject matter.

### Limitations and Future Perspectives

Findings of the present study are mainly limited by the sample size, the exclusion of the female gender and the use of self-report measures. Furthermore, the measurement of OT is controversially discussed in literature (43, 71).

Furthermore, nicotine abstinence was not given in PUD patients prior to the investigation in this study, which might be seen as a characteristic of PUD patients in maintenance treatment. However, in line with previous research, nicotine abuse was not related to OT (72, 73). Moreover, due to the explorative nature of this study, no control condition was administered, which limits the interpretability of the effects of the AAP on OT-levels. This shortcoming needs to be addressed in future studies. What is more, a recent study by Fuchshuber et al. (74) indicated a medium effect size regarding the difference in attachment security comparing PUD and HC groups (74). With respect to the relatively small sample size employed in this study, future research addressing this subject might take this into account regarding the estimation of the required sample size. Along, to gain a more complete understanding of the relationship between attachment, OT and maintenance treatment, the investigation of abstinent SUD patients who are not undergoing maintenance therapy is of interest for future studies. Finally, cortisol and vasopressin, both known for their close interrelatedness with OT, should be taken into account (29, 30, 75, 76).

### CONCLUSION

This study suggests that peripheral OT levels in poly-drug users undergoing maintenance treatment do not show significant

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**TABLE 3 | Intercorrelations for behavioral and biological measures for PUD (n = 24).**

| Variable                  | 1     | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     | 10    | 11    |
|---------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| BSI-18 Somatization       | .40   | .79** | −.21  | −.03  | .27   | −.11  | −.15  | .19   | .17   | .14   |       |
| BSI-18 Depression         | .48*  | −.04  | .01   | .06   | −.51* | −.46* | .49*  | .21   | .21   |       |       |
| BSI-18 Anxiety            | −1.13 | −.08  | .09   | .10   | −.02  | −.12  | .22   | .14   | .34   |       |       |
| OT Pre                    | .70** | −.72* | .05   | −.41  | −.37  | −.48* | .11   |       |       |       |       |
| OT Post                   | −.02  | .07   | −.24  | −.33  | −.31  | −.04  |       |       |       |       |       |
| OT Reactivity             | .00   | .34   | .08   | .36   | −.05  | −.20  |       |       |       |       |       |
| AAS Closeness             |       | .68** | .36   | −.02  | −.04  | −.22  |       |       |       |       | −.16  |
| AAS Anxiety               |       |       | .34   | .20   | .37   | −.19  |       |       |       |       | .24   |
| ASSIST Lifetime SU        |       |       |       | .22   |       |       |       |       |       |       | −.18  |
| ASSIST GC of SR           |       |       |       |       | .27   |       |       |       |       |       | .24   |

N = 24; Bonferroni corrected p = 0.004; "p < .01, "p < .05; Pre, baseline OT-levels; Post, OT-levels after confrontation with attachment related cue; GC, global continuum; SU, substance use; SR, substance risk.
differences regarding responsive to an attachment related stimulus delivered via the Adult Attachment projective task compared to HCs. The meaning of this finding is complicated by a number of confound in the PUD group related to both the pharmacological and psycho-social treatments they are receiving. The current findings which indicate non-significant tendencies however are an important preliminary finding which we hope will motivate more research using an experimental paradigm to further explore this hypothesis.

DATA AVAILABILITY STATEMENT

This article contains previously unpublished data. Datasets are available on request.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethics guidelines of the Karl Franzens University of Graz, Austria. The protocol was approved by the ethics committee of the Karl Franzens University of Graz, Austria. Written informed consent in accordance with the Declaration of Helsinki was given by all subjects.

AUTHOR CONTRIBUTIONS

JT, EW, and HU conceptualized the study. JT, AK, FT, AR, and collected the data. JT, AB, SS, BR, TP, and KL analyzed the data. JT and AB interpreted the AAP data. JT, MH-R, HU, and AL drafted and revised the manuscript. EW, H-PK, AB, MH-R, HU, JF, and AL critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.460506/full#supplementary-material

REFERENCES

1. World Health Organization. WHO Expert Committee on Addiction-Producing Drugs [meeting held in Geneva from 25 to 30 November 1963]: thirteenth report. World Health Organization (1964).
2. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med (2016) 374(4):363–71. doi: 10.1056/NEJMra1511480
3. Zellner MR, Watt DF, Solms M, Panksepp J. Affective neuroscientific and neuropsychoanalytic approaches to two intractable psychiatric problems: why depression feels so bad and what addicts really want. Neurosci Biobehav Rev (2011) (2011) 35:2000–8. doi: 10.1016/j.neubiorev.2011.01.003
4. Weigl M, Anzenberger J, Busch M, Horvath I, Turscher E. Bericht zur Drogen situation 2015. Vienna: Gesundheit Österreich GmbH (2015).
5. EMCDDA. Annual report 2009: The State of the Drugs Problem in Europe. EMCDDA: Lisbon (2009).
6. Hedrich D, Alves P, Farrell M, Stöver H, Møller L, Mayet S. The effectiveness of opioid maintenance treatment in prison settings: a systematic review. Addiction (2012) 107(3):501–17. doi: 10.1111/j.1360-0443.2011.03676.x
7. Flores PJ. Addiction as an attachment disorder: Implications for group therapy. Int J Group Psychother (2001) 51(1):63–81. doi: 10.1521/ijgp.51.1.63.49730
8. Khantzian EJ. Self-regulation and self-medicating drugs in alcoholism and the addictions. Similarities and differences. Recent developments in alcoholism: An official publication of the American Medical Society on Alcoholism, the Research Society on Alcoholism, and the National Council on Alcoholism. (1990) 8:255–71.
9. Bowlby J. The making and breaking of affectional bonds: I. Aetiology and psychopathology in the light of attachment theory. Br J Psychiatry (1977) 130(3):201–10. doi: 10.1192/bjp.130.5.421
10. Bowlby J. A secure base: Clinical applications of attachment theory (collected papers). London: Tavistock (1988).
11. Milch W, Sahhar N. Zur Bedeutung der Bindungstheorie für die Psychotherapie Erwachsener. Psychotherapie (2010) 15(1):44–55.
12. Bretherton I, Munholland KA. Internal working models in attachment: A construct revisited. In: Handbook of Attachment: Theory, Research and Clinical Application. New York: Guildord Publications (1999). p. 89–111.
13. Thompson RA. Early attachment and later development. In: Cassidy J, Shaver PR, editors. Handbook of attachment: Theory, Research and clinical applications. New York, New York: Guildord Press (1999). p. 265–86.
14. Schindler A, Thomasius R, Sack PM, Gemeinhardt B, KÜStner E, Eckert J. Attachment and substance use disorders: A review of the literature and a study in drug dependent adolescents. Attachment Hum Dev (2005) 7(3):207–28. doi: 10.1080/1461673050173918
15. Schindler A, Bröning S. A review on attachment and adolescent substance abuse: empirical evidence and implications for prevention and treatment. Subst Abus (2015) 36(3):304–13. doi: 10.1080/08897077.2014.983586
16. Fairbairn CE, Briley DA, Kang D, Fraley RC, Hankin BL, Ariss T. A meta-analysis of longitudinal associations between substance use and interpersonal attachment security. Psychol Bull (2018) 144(5):532. doi: 10.1037/bul0000141
17. Mikulincer M, Shaver PR. An attachment perspective on psychopathology. World Psychiatry (2012) 11(1):11–5. doi: 10.1001/j.wspych.2012.01.003
18. Fuchshuber J, Hieber-Ragaller M, Kresse A, Kaphammer HP, Unterrainer HF. The influence of attachment styles and personality organization on emotional functioning after childhood trauma. Front Psychiatry (2019) 10:643. doi: 10.3389/fpsyt.2019.00643
19. Fuchshuber J, Hieber-Ragaller M, Unterrainer HF. The Role of Attachment in Poly-Drug Use Disorder: An Overview of the Literature, Recent Findings and Clinical Implications. Front Psychiatry (2019) 10:579. doi: 10.3389/fpsyt.2019.00579
20. Feldman R. The neurobiology of human attachments. Trends Cognit Sci (2017) 21(2):80–99. doi: 10.1016/j.tics.2016.11.007
21. Fonagy P, Gergely G, Target M. The parent–infant dyad and the construction of the subjective self. J Child Psychol Psychiatry (2007) 48(4–5):288–328. doi: 10.1111/j.1469-7610.2007.01727.x
22. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc Natl Acad Sci (2010) 107(9):4389–94. doi: 10.1073/pnas.0910249107
23. Gallbally M, Lewis AJ, IJzendoorn MV, Permezel M. The role of oxytocin in mother–infant relations: a systematic review of human studies. Harv Rev Psychiatry (2011) 19(1):1–14. doi: 10.3109/10673229.2011.549771
24. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry (2010) 67(7):692–4. doi: 10.1016/j.biopsych.2009.09.020
69. Schindler A, Thomasius R, Petersen K, Sack PM. Heroin as an attachment substitute? Differences in attachment representations between opioid, ecstasy and cannabis abusers. *Attach Hum Dev* (2009) 11(3):307–30. doi: 10.1080/14616730902815009

70. Torres N, Oliveira D, Dias F, Shaver P, Panksepp J. Testing a neuro-evolutionary theory of social bonds and addiction. Poster session at the Neuroscience of Affect, Attachment and Social Cognition Conference, Imperial College, London. (2013).

71. Robinson KJ, Hazon N, Lonergan M, Pomeroy PP. Validation of an enzyme-linked immunoassay (ELISA) for plasma oxytocin in a novel mammal species reveals potential errors induced by sampling procedure. *J Neurosci Methods* (2014) 226:73–9. doi: 10.1016/j.jneumeth.2014.01.019

72. Chiodera P, Volpi R, Capretti L, Bocchi R, Caffarri G, Marcato A, et al. Gamma-aminobutyric acid mediation of the inhibitory effect of endogenous opioids on the arginine vasopressin and oxytocin responses to nicotine from cigarette smoking. *Metabolism* (1993) 42(6):762–5. doi: 10.1016/0026-0495(93)90246-k

73. Seckl JR, Johnson M, Shakespear C, Ughtman S. Endogenous opioids inhibit oxytocin release during nicotine-stimulated secretion of vasopressin in man. *Clin Endocrinol (Oxf)* (1988) 28(5):509–14. doi: 10.1111/j.1365-2265.1988.tb03685.x

74. Fuchshuber J, Unterrainer HF, Hieber-Ragger M, Koschutnig K, Papousek I, Weiss E, et al. Pinpointing neural correlates of attachment in poly-drug use: A Diffusion Tensor Imaging study. *Front Neurosci* (2020) 14:596. doi: 10.3389/fnins.2020.00596

75. Gordon I, Zagoory-Sharon O, Schneiderman I, Leckman JF, Weller A, Feldman R. Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. *Psychophysiology* (2008) 45(3):349–52. doi: 10.1111/j.1469-8986.2008.00649.x

76. Torres N, Martins D, Santos AJ, Prata D, Veríssimo M. How do hypothalamic nonapeptides shape youth’s sociality? a systematic review on oxytocin, vasopressin and human socio-emotional development. *Neurosci Biobehav Rev* (2018) 90:309–31. doi: 10.1016/j.neubiorev.2018.05.004

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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