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FULL-LENGTH REPORT

Alterations in oxytocin and vasopressin in men with problematic pornography use: The role of empathy

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ABSTRACT

Background: Addictive behaviors share clinical, genetic, neurobiological and phenomenological parallels with substance addictions. Despite the prevalence of compulsive sexual behaviors, particularly problematic pornography use (PPU), how neuroendocrine systems relate to PPU is not well understood. Preclinical studies demonstrate alterations in oxytocin and arginine vasopressin (AVP) function in animal models of addiction, but no human study has tested their involvement in PPU. *Method:* Participants included 122 males; 69 reported PPU, and 53 were demographically-matched participants without PPU. Plasma oxytocin and AVP levels and oxytocin-to-AVP balance were measured at baseline. Salivary oxytocin was assessed at baseline and in response to four videos depicting neutral/positive social encounters. Participants reported on empathy and psychiatric symptoms. *Results:* Baseline plasma AVP levels were elevated in men with PPU, and the ratio of oxytocin-to-vasopressin suggested AVP dominance. Men with PPU reacted with greater oxytocin increases to presentation of neutral/positive social stimuli. Decreased empathic tendencies were found in men with PPU, and this reduced empathy mediated links between oxytocin and pornography-related hypersexuality. Structural equation modeling revealed three independent paths to pornography-related hypersexuality; two direct paths via increased AVP and higher psychiatric symptoms and one indirect path from oxytocin to pornography-related hypersexuality mediated by diminished empathy. *Conclusions:* Findings are among the first to implicate neuropeptides sustaining mammalian attachment in the pathophysiology of pornography-related hypersexuality and describe a neurobiological mechanism by which oxytocin-AVP systems and psychiatric symptomatology may operate to reduce empathy and lead to pornography-related hypersexuality.

KEYWORDS

pornography, compulsive sexual behaviors, addictive behaviors, arginine vasopressin, oxytocin, empathy

INTRODUCTION

Although gambling disorder has been reclassified with substance-use disorders (Potenza, 2006), data suggest that excessive engagement in other behaviors (such as sex) share clinical, genetic, neurobiological and phenomenological parallels with substance addictions (Kraus, Voon, & Potenza, 2016a). Problematic pornography use (PPU) may be considered as a form of compulsive sexual behavior disorder (CSBD), which has been recently introduced into the

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11th revision of the International Classification of Diseases (ICD-11) as an impulse control disorder (Kraus et al., 2018; World Health Organization, 2018). However, existing neurobiological data relating to attentional biases, incentive salience attributions, and brain-based cue reactivity suggest that PPU may be considered as a behavioral addiction (Kowalewska et al., 2018; Stark, Klucken, Potenza, Brand, & Strahler, 2018), and some authors have proposed considering the use of the ICD-11 designation of "other specified disorder due to addictive behaviors" when diagnosing PPU (Brand et al., 2020). Investigating further the neurobiological underpinnings of PPU may aid in appropriate classification efforts and prevention and treatment advances (Fuss et al., 2019).

Compulsive sexual behaviors (CSBs) may include difficulties in controlling sexual fantasies and behaviors, sexual urges/cravings or behaviors that generate subjective distress, risky engagement in sexual behaviors, and impairments in daily functioning (Kor, Fogel, Reid, & Potenza, 2013). National US data reveal that 8.6% (7.0% of women and 10.3% of men) endorsed distress associated with difficulties controlling sexual urges, feelings and behaviors (Dickenson, Gleason, Coleman, & Miner, 2018). PPU in particular constitutes a concern of which psychiatrists should be aware (Brand, Blycker, & Potenza, 2019).

The accessibility, availability, affordability and perceived anonymity of the internet have been proposed to have led to increases in pornography consumption (Cooper, Delmonico, & Burg, 2000). In this setting, PPU has become a clinical concern, especially for males and couples (Brand, Blycker, et al., 2019). One in seven men viewing pornography has shown interest in treatment for pornography-viewing, with treatment-interested men reporting more hypersexuality and pornography consumption (Kraus, Martino, & Potenza, 2016). These findings suggest that pornography-related hypersexuality is an important psychiatric construct. Among men in treatment for CSBs, over 80% reported problems with pornography-viewing (Reid et al., 2012). Further, severity of PPU has been correlated with measures of psychopathology and poor attachment (Kor et al., 2014). Thus, a greater understanding of the relationships between pornography-related hypersexuality, psychopathology and attachment, and their neurobiological underpinnings is needed.

Similar neurobiological systems and neural circuits may underlie addiction and attachment (Alvarez-Monjaras, Mayes, Potenza, & Rutherford, 2018). Addictive drugs and behaviors may "highjack" reward pathways and reorganize neural networks evolved to support attachment, leading to reduced neural sensitivity to social rewards (Bowen & Neumann, 2017). Addictions may alter interactions between dopamine and oxytocin in the striatum that may integrate motivation with social focus to imbue the attachment target with reward value and form lasting bonds (Alvarez-Monjaras et al., 2018; Feldman, 2017). Models specifying interactions between oxytocin, dopamine, and glucocorticoid systems have been proposed to link to social, positive valence, and negative valences systems in generating addiction vulnerability (Kim et al., 2017). Disruptions of dopaminergic reward-seeking from oxytocin's social focus may be enhanced in the context of PPU, which may separate sexual reward from lasting pair-bonds (Bisagno & Cadet, 2014). Addiction may also impact neural plasticity; addictive stimuli may reorganize systems subserving attention and memory processes at molecular and cellular levels, particularly with respect to the establishment of social memories (Walker & Nestler, 2018). Notably, the oxytocin system has been implicated in neural plasticity at cellular and network assembly levels, including alterations of signal-to-noise ratio in hippocampal neurons to increase salience of attachment stimuli, and changes in cortical networks that enable the formation of humans' representations-based, empathic, and future-oriented bonds (Althammer, Jirikowski, & Grinevich, 2018; Feldman, 2017). Addiction-related alterations in molecular and cellular plasticity may interfere with oxytocin functionality in mutually-influencing manners (Bisagno & Cadet, 2014).

Oxytocin and arginine vasopressin (AVP) are neuropeptides implicated in parenting, bond-formation, and group-living that help support stress management and sociality across animal evolution (Feldman, Monakhov, Pratt, & Ebstein, 2016). Oxytocin has been implicated in multiple socially interactive behaviors including foot massages, gaze-mediated bonding between dogs and humans, and eye-contact during virtual-reality pornography (Dekker, Wenzlaff, Biedermann, Briken, & Fuss, 2021; Krüger et al., 2003; Li et al., 2019; Nagasawa et al., 2015). Oxytocin and AVP neuropetide systems and receptors interact, utilizing each other's pathways (Carter & Perkeybile, 2018). However, whereas oxytocin is implicated in affiliative behavior, anxiety reduction, social engagement, and safety, AVP is involved in territorial defense, social avoidance, and aggressive behavior, particularly in males, and is associated with flight-and-fight responses via links with stress response systems and sympathetic arousal (Baracz & Cornish, 2016). Animal research demonstrates greater distributions of AVP in males and greater centrality of this system to male bonding and dysfunction of oxytocin and AVP in addictions, expressed in alterations in mRNA, receptor availability, and, for AVP, augmented stress reactivity (Bisagno & Cadet, 2014; Kraus, Voon, & Potenza, 2016b).

Balance of oxytocin-AVP systems is important in addictions. Oxytocin acts mainly through the oxytocin receptor (OTR) to enable physiological quiescence critical for bond-formation, whereas AVP mobilizes vigilance, fear, and aggression in social-affiliative contexts. Under stress, oxytocin functions via the AVP system; AVP is more closely evolutionarily linked to vasotocin that may sustain stress management under harsh ecological conditions in non-mammalian vertebrates (Feldman, 2016, 2020). Such activation of oxytocin via the AVP system is associated with greater stress reactivity, a higher sympathetic-to-parasympathetic balance, greater propensity to fear and dissociations, and difficulties in maintaining calm states or prosocial orientations (Carter & Perkeybile, 2018; Weisman, Schneiderman, Zagoory-Sharon, & Feldman, 2013). Thus, investigations into

human addiction should include not only assessments of oxytocin and AVP, but also balance between the two. Such balance is dimorphic, as the AVP system is impacted by endogenous sex hormones, particularly testosterone (Bisagno & Cadet, 2014), which may influence the balance of the extended oxytocin-AVP pathway in the direction of vulnerability versus resilience (Bisagno & Cadet, 2014).

Although the importance of the oxytocin-AVP pathway in addictions has been acknowledged (Bowen & Neumann, 2017), little research has been conducted in humans with behavioral addictions (Sarnyai, 2011). Alterations in oxytocin-AVP pathways may directly impact vulnerability to CSBs and indirectly do so via key social processes supported by oxytocin, particularly empathy. Empathy, the capacity to resonate and understand others' emotions and reflect on others' mental states, is core to human social functions. Human empathy is supported by the oxytocinergic system, and oxytocin administration enhances empathy (Feldman, 2012; Fragkaki & Cima, 2019). Oxytocin increases social salience and, in low-risk contexts, such increases may lead to affiliation, engagement, and bonding (Feldman, 2016). Further, reduced empathic responses behaviorally and neurally have been associated with viewing of sexually objectified women (Cogoni, Carnaghi, & Silani, 2018), and pornography has been linked to sexual objectification of women (Seabrook, Ward, & Giaccardi, 2019). Hence, taken together, it is plausible that diminished empathy may mediate effects of low levels of oxytocin on increased severity of PPU. The effects of oxytocin on empathic tendencies (Carter & Perkeybile, 2018; Feldman, 2016) suggest that disruptions to empathy and mentalization may influence potential relationships between oxytocin and PPU. Clinically, oxytocin is being investigated in the treatment of people with addictions (Bowen & Neumann, 2017; Lee & Weerts, 2016). Thus, an improved understanding of oxytocin systems and their correlates in people with PPU could offer novel insight into how to advance treatment development efforts for PPU.

Oxytocin has also been implicated in sexual behaviors. Specifically, oxytocin has been linked to sexual arousal, penile erection, masturbation to orgasm, ejaculation, orgasm intensity, viewing of pornography and sexual satiety (Argiolas, 1992; Burri, Heinrichs, Schedlowski, & Kruger, 2008; Carmichael, Warburton, Dixen, & Davidson, 1994; Dekker et al., 2021; Krüger et al., 2003; Melis, Argiolas, & Gessa, 1986; Thackare, Nicholson, & Whittington, 2006). As such, it is plausible that pornography use may impact oxytocin levels. Opioid receptor antagonists, a drug class that has shown some preliminary support in the treatment of PPU (Kraus, Meshberg-Cohen, Martino, Quinones, & Potenza, 2015), may inhibit oxytocin release during orgasm (Murphy, Checkley, Seckl, & Lightman, 1990). Recently, an epigenetic study involving predominantly men implicated oxytocin signaling pathways in CSBs (Boström et al., 2020). However, the precise mechanisms by which oxytocin and AVP may operate in PPU has not been directly examined.

The current study measured, for the first time, peripheral baseline levels of oxytocin and AVP in plasma and reactive salivary oxytocin to neutral/positive social stimuli in men with PPU versus matched comparison subjects without. We examined functionality of the oxytocin and AVP system in relation to PPU, taking into consideration psychiatric symptoms and empathy. Since no prior research addressed the associations between oxytocin, AVP, psychopathology, and empathy in PPU, our study was mainly exploratory and our hypotheses were framed as research questions. We examined whether among males with PPU, as compared to those without, there would be higher levels of AVP, lower levels of oxytocin, and higher AVP-to-oxytocin ratios. We further tested patterns of oxytocin reactivity and examined whether exposure to naturalistic social stimuli would trigger differential responses in the men with and without PPU. In part due to limited prior research and the role of oxytocin in social processes, we used daily, neutrally/positively valenced social stimuli to examine oxytocin and AVP reactivity. We also asked whether men with PPU relative to those without would exhibit lower empathy and whether such reduced empathy would be associated with oxytocin levels, in light of the reported associations between oxytocin and empathy. Given links between psychopathology and PPU (Kor et al., 2014) and psychopathology and empathy (Decety & Moriguchi, 2007), we also explored the relationship between psychiatric functioning, empathy, and pornography-related hypersexuality.

METHODS

Participants

Participants included 122 males recruited in two groups. The PPU group (n = 69) included men recruited from support groups/clinical settings for helping people with CSBs or sex addiction, and comparison men (n = 53) were recruited by advertisements at universities and surrounding areas. Participants were recruited for a study on sexual behavior through ads in support groups and university campuses, and groups were matched on demographic variables (Table 1). Few participants (N = 4 with PPU; n = 1 without PPU) reported using medication. In the PPU group, 2 reported using levothyroxine and 2 escitalopram, and in the participant in the non-PPU group used escitalopram.

For the PPU group, screening was conducted using a Hebrew version of the Hypersexual Disorder Questionnaire (HDQ) and assessment of pornography-related behaviors. All participants met proposed diagnostic criteria for hypersexual disorder on the HDQ (Reid et al., 2012). Only men who scored 4 (often applies), 5 (very often applies), or 6 (almost always applies) on all 10 items of the HDQ and had a score of 5 or 6 on at least 5 items were included in the PPU group.

The second part of the HDQ assessment modified for PPU (HDQ-PPU) included fifteen statements related to pornography use, and participants rated the degree to which each statement described them on a scale from 1 (not at all)

Table 1. Group differences in demographic and study variables

Variable		*Non-PPU* %	*PPU* %	*t-test/χ^2*
Socioeconomic Status	Above average	9.43	10.14	$\chi^2_{(2)} = 0.23$, $P > 0.05$, $\varphi_c = 0.04$
	Average	62.26	57.97	
	Under average	28.30	31.88	
	Mean	*SD*	*Mean*	*SD*	
Age (years)	28.4	4.58	29.7	4.85	$t_{(120)} = -1.55$, $P > 0.05$, Cohen's $d = 0.28$
Education (years)	14.3	3.57	13.8	4.08	$t_{(116)} = 0.66$, $P > 0.05$ Cohen's $d = 0.12$
OT (Blood)	236.13	73.78	217.71	48.43	$t_{(100)} = 1.52$, $P > 0.05$, Cohen's $d = 0.3$
AVP (Blood)	190.75	47.39	227.01	57.69	$t_{(105)} = -3.42$, $P < 0.001$, Cohen's $d = 0.69$
OT over AVP (Blood)	1.21	0.47	0.97	0.34	$t_{(113)} = 3.07$, $P < 0.01$, Cohen's $d = 0.57$
Empathy	42.88	10.12	39.37	9.24	$t_{(119)} = 1.99$, $P < 0.05$, Cohen's $d = 0.36$
BSI	0.62	0.39	1.13	0.63	$t_{(119)} = -5.17$, $P < 0.001$, Cohen's $d = 0.98$
HDQ - PPU	2.31	0.88	3.93	0.84	$t_{(119)} = -8.51$, $P < 0.001$, Cohen's $d = 1.58$

to five (very much) (see description below). As a main measure of interest in this study was pornography-related hypersexuality and there are no formal criteria for PPU, we describe in this manuscript the group as having PPU, with greater pornography-related hypersexuality reflective of greater PPU severity. Exclusion criteria included chronic physical illness, known psychiatric disorders, or history of incarceration or pedophilia. All men were 21 years or older. Of 125 participants initially recruited, 3 participants in the PPU group and two in the comparison group did not give blood or had insufficient saliva and were excluded from the following analyses.

Procedure

Lab visits were conducted between 6 and 7:30 PM to control for diurnal variability and plasma, and salivary measures were collected to assess both baseline and reactivity patterns. While the diurnal patterns of oxytocin in humans are still largely unknown, a study of diurnal patterns of plasma oxytocin and AVP in men showed that hormones peak at 2 AM and gradually decline during the morning, reaching low flat levels from 4 to 8 PM, a time-point that is preferable for detecting individual differences (Forsling, Montgomery, Halpin, Windle, & Treacher, 1998). Upon arrival, baseline plasma and saliva were collected. Next, participants completed self-report measures of demographic and health variables, PPU and other psychological constructs.

Experimental manipulation. Participants were exposed to a 16-min video that included highly social, positive, and daily video vignettes. Prior research has shown that exposure to positive social stimuli for 15 min triggers oxytocin release in parents (mothers and fathers) and infants (Feldman, Gordon, & Zagoory-Sharon, 2011). In adults, oxytocin administration has been shown to increase participants' group cohesion as well as ethnocentric and parochial behavior and an "us-versus-them" attitude which is thought to be underpinned by fear to the in-group (Zhang, Gross, De Dreu, & Ma, 2019). We thus exposed participants to four positive social video clips including activities of a close and cohesive group of male friends, each lasting for 4 min, with a 20 s interval between videos to keep the participants' attention.

To pilot the stimuli, we selected seven video clips of highly social episodes among all-male groups of friends (e.g., friends drinking beer in a bar, a person winning a sport's competition cheered on by his "buddies," a group of friends completing a long hike and sitting for a brief rest). We showed these clips to a group of 15 graduate students in psychology and asked them to rate each clip on a scale of 1 (little) to 5 (a lot) for the following dimensions: 1. *Sociality* – the degree of social closeness and cohesion among participants. 2. *Positive arousal* – the degree to which the vignettes elicit positive emotions and 3. *Negative arousal* – the degree to which the vignettes elicit negative feelings. The four vignettes chosen were those which scored lowest on negative (rated 1 by all viewers), and highest on positive arousal and sociality. Order of presentation was counter-balanced. The reason for selecting positive social stimuli was to understand the baseline response of the oxytocin and AVP systems to naturalistic daily social experiences which can serve as the basis for future research involving more stimulating exposures (e.g., fearful, angry, or sexually-charged contexts). Because hormonal responses typically have long latencies, in comparison to, for instance, heart rate or EEG responses, mixing positive social stimuli with negative ones has challenges as it would complicate disentangling endocrine responses to positive and negative stimuli due to possible carryover effects.

After viewing, a second salivary sample was collected. Participants were asked to refrain from any food intake 2 h prior to laboratory visit.

Brief Symptom Inventory (BSI) The BSI (Derogatis, 1975) is a widely-used brief assessment of current (past-month) psychiatric symptoms. Symptoms consider nine primary dimensions: Somatization, Obsessive-Compulsive,

Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism. Items are rated from 0- "not at all" to 4- "extremely". Internal consistency was excellent (Cronbach $\alpha = 0.97$).

The *Empathy Quotient (EQ)* is a 40-item scale with 20 filler (distraction) items. Questions are rated on 4-point Likert scale ranging from 1- "Strongly agree" to 4– "strongly disagree." Responses are coded as 0, 1 or 2 depending on item (Baron-Cohen & Wheelwright, 2004) and summed to create overall scores. Internal consistency was good (Cronbach $\alpha = 0.86$).

The *Hypersexual Disorder Questionnaire modified for PPU (HDQ-PPU)* The HDQ was used in the DSM-5 field trial for hypersexual disorder and was used here to divide participants into the PPU and non-PPU groups (Reid et al., 2012). To address the severity of pornography use, we used a pornography-specific addition to the HDQ that has been previously tested and validated (Kor et al., 2014). This section includes 15 statements describing reasons, ways, and situation when individuals use pornography and participants rated the applicability of each statement on a scale of 1 (not at all applies) to 5 (fully applies). Statements included: "Using pornography gives me an opportunity to avoid dealing with daily problems", "I use pornography often to arouse myself sexually", "I use pornography to escape into a world of fantasy", or "I use pornography to detach from feeling sad, lonely, or depressed." The final score was the average of the 15 items (Cronbach $\alpha = 0.92$) and a cutoff score of 3 was used for inclusion in the PPU group, indicating moderate-to-severe pornography use severity.

Sample collection and analysis. We collected hormones in both plasma and saliva, and participants were ask to refrain from drinking coffee and smoking three hours prior to the visit and drinking water 1 h prior to saliva collection and throughout the procedure until the second saliva sampling. Saliva samples were collected by passive drooling into a clean 5 mL tube. All samples were then stored at −20 °C.

To prepare for measurement, samples underwent three freeze-thaw cycles, with freeze at −80 °C and thaw at 4 °C to precipitate the mucus. The tubes were subsequently centrifuged at 1500g (4,000 rpm) for 30 min. The supernatant was transferred into a clean tube and stored at minus 80 °C until freeze-dried for four days, generating a cotton-like material. Prior to assaying, the dry samples were resuspended with the OT-ENZO kit's assay-buffer in one fourth of the original volume.

For plasma measurement, a certified nurse drew blood from antecubital veins into 9-mL chilled vacutainer tubes containing lithium heparin supplemented with 400 KIU Aprotinin (Sigma-Aldrich, St. Louis, MI, USA) per 1 mL blood. Samples were ice-chilled for up to 2 h before being centrifuged at 4 °C at 1000g for 15 min. Supernatants were aliquotted into 1.5-mL tubes and stored at –80 °C.

Oxytocin extraction from blood samples was conducted as previously (Feldman et al., 2011). Blood samples were acidified with 0.1% trifluoracetic acid (TFA), ratio 1:1, centrifuged and loaded on HBL extraction cartridges 3cc/60 mg (Waters Oasis, MA, USA). Cartridge were washed twice with 0.1% TFA and 10% acetonitrile solution, eluted with 0.1% TFA and 80% acetonitrile, lyophilized, and kept at −20 °C until assayed. Extractions were performed in duplicates. Efficacy was controlled with spiked samples and vacant samples. Lyophilized samples were reconstructed in assay buffer immediately before analysis.

Determination of hormone levels was performed using 96-sample-plate commercial OT-ELISA kit ADI-900-153A (ENZO, NY) and Arg8VP-EIA kit ADI 900-017 (Assay-Design, MI, USA), as previously (Feldman et al., 2011). Dilutions gave results within linear portions of standard curves. Measurements were performed in duplicates.

Sample concentrations of oxytocin or AVP were calculated by MatLab-7 (MathWorks, Natick, MA) according to relevant standard curves. Inter-assay coefficients of variation of blood oxytocin, salivary oxytocin and blood AVP were less than 25.3%, 6.8% and 6.1%, respectively. Oxytocin was calculated using an area-under-the-curve approach with respect to ground (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Statistical analysis

ANOVAs and *t*-tests compared study variables between groups. Pearson's correlations tested relationships among variables. For modeling direct and mediated paths from AVP, oxytocin, and psychiatric symptoms to pornography-related hypersexuality via empathy, path analysis was conducted using Lavaan 0.5-23.1097 (Rosseel, 2012) in R 3.4.4 (R Core Team, 2014). Path analysis was based on maximum-likelihood estimations, and indicators of model fit were: chi-square, root mean square error of approximation (RMSEA), and comparative fit index (CFI), with Tucker-Lewis index (TLI) values >0.95 considered a good fit (Hu & Bentler, 1999). To assess mediation, we used Hayes' procedure and calculated the 95% confidence intervals (95%CIs) of 5,000 bias-corrected and accelerated bootstrapping analyses (Hayes, 2013). When the value zero is not included in the 95%CI, significance at $\alpha < 0.05$ is indicated.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and according to requirements of all applicable local and international standards and received the approval of the Institutional Review Board at Bar Ilan University. All participants signed an informed consent.

RESULTS

Demographic information for the PPU and non-PPU groups showed no between-group differences in age, education, and socioeconomic status (Table 1). *T*-tests (Fig. 1, Table 1) indicated that the PPU group had higher levels of AVP,

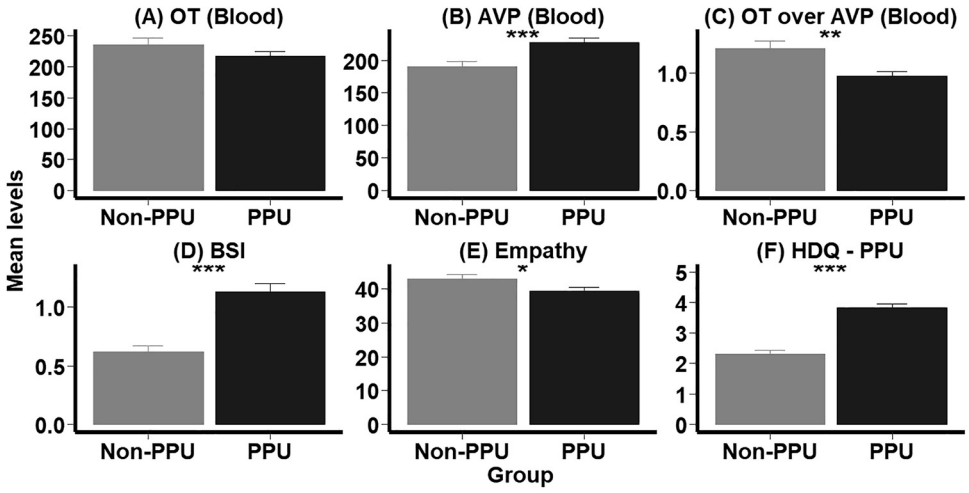

Fig. 1. T-tests for main study variables between groups with and without PPU

Note: Participants with PPU as compared to those without had significantly higher levels of AVP ($t_{(105)} = -3.42$, $P < 0.001$, Cohen's $d = 0.69$), lower oxytocin/AVP ratios ($t_{(113)} = 3.07$, $P < 0.01$, Cohen's $d = 0.57$), higher psychiatric symptom ($t_{(119)} = -5.17$, $P < 0.001$, Cohen's $d = 0.98$) and HDQ scores ($t_{(119)} = -8.51$, $P < 0.001$, Cohen's $d = 1.58$). However, the control group had higher levels of empathy ($t_{(119)} = 1.99$, $P < 0.05$, Cohen's $d = 0.36$). Blood oxytocin levels were not significantly different ($t_{(100)} = 1.52$, $P = 0.13$, Cohen's $d = 0.3$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

psychiatric symptoms, and pornography-related hypersexuality, whereas the non-PPU group had higher empathy and blood oxytocin/AVP ratios. Group differences in BSI subscales appear in Supplementary Table S1.

AVP levels were positively associated with psychiatric symptoms, pornography-related hypersexuality, and oxytocin levels and negatively with empathy scores (Table 2). Oxytocin positively correlated with empathy, which was negatively associated with psychiatric symptoms and pornography-related hypersexuality. The oxytocin-to-AVP ratio correlated with empathy and negatively with pornography-related hypersexuality. Psychiatric symptoms correlated with pornography-related hypersexuality. Notably the magnitudes of the correlations were similar in the PPU and non-PPU groups, and no correlations differed significantly between groups according to Fisher *Z* tests.

Repeated measures ANOVA (Fig. 2) evaluating the change in salivary oxytocin levels from baseline to the post-video assessment revealed two main effects and one interaction effect. First, oxytocin levels increased for all participants from the first (baseline) to the second assessment; ($F_{(1,120)} = 35.5$, $P < 0.001$, $\eta^2_P = 0.23$). This suggests that positive social experiences marked by social synchrony and positive arousal lead to oxytocin increase. Second, higher oxytocin levels were found for men with PPU, ($F_{(1,120)} = 8.93$, $P < 0.001$, $\eta^2_P = 0.07$). Finally, an interaction of time and group emerged ($F_{(1,120)} = 7.48$, $P < 0.001$, $\eta^2_P = 0.06$), indicating that the, the increase in oxytocin were greater for men with PPU, and while no group differences were found at baseline, differences emerged at the post-video assessments (non-PPU: baseline $M = 20.9$, SD = 9.20, post $M = 24.8$, SD = 11.7, $P < 0.001$; PPU: baseline $M = 24.8$, SD = 14.7, post $M = 36.4$, SD = 22.8, $P < 0.001$).

Path analysis tested the exploratory model (Fig. 3). The overall model provided an excellent fit: $\chi^2_{(1)} = 0.029$, $P = 0.865$, RMSEA < 0.001 with lower 90%CI < 0.01 and higher 90%CI = 0.13, PCLOSE = 0.883, CFI = 1.00, TLI = 1.195. Of five identified paths, the first and second charted direct connection between AVP and psychiatric symptoms with pornography-related hypersexuality (95%CI = 0.033, 0.335, and 95%CI = 0.336, 0.633, respectively). The third path linked oxytocin with higher empathy, which led to lower pornography-related hypersexuality. Test of mediation indicated that this path was significant (95%CI = −0.125, −0.011). The last two paths started with AVP and

Table 2. Pearson correlations among study variables

	OT (Blood)	AVP (Blood)	OT/AVP ratio	Empathy	BSI
OT (Blood)					
AVP (Blood)	0.21*				
OT/AVP ratio	0.61***	−0.52***			
Empathy	0.26**	−0.23*	0.20*		
BSI	−0.08	0.24*	−0.09	−0.26**	
HDQ-PPU	−0.05	0.33***	−0.26**	−0.34***	0.56***

Note: $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$; OT = oxytocin; AVP = arginine vasopressin; BSI = Brief Symptom Inventory; HDQ-PPU = Hypersexual Disorder Questionnaire modified for Problematic Pornography Use.

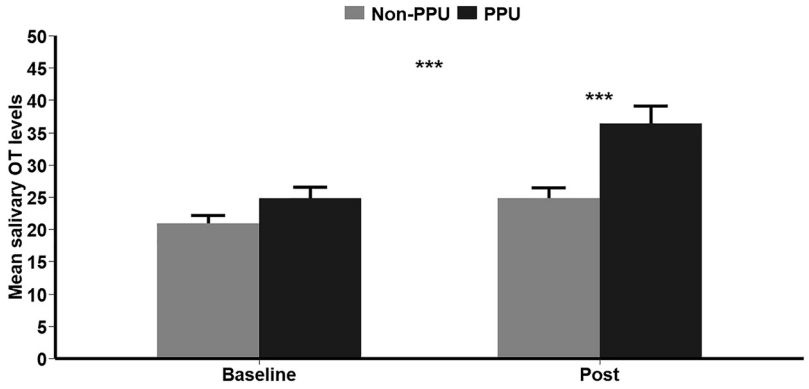

Fig. 2. Repeated measure ANOVA for men with and without PPU and salivary oxytocin
Note: Significant main effects for group ($F_{(1,120)} = 8.93$, $P < 0.001$, $\eta^2_p = 0.07$), assessment time, ($F_{(1,120)} = 35.5$, $P < 0.001$, $\eta^2_p = 0.23$), and their interaction ($F_{(1,120)} = 7.48$, $P < 0.001$, $\eta^2_p = 0.06$) were found. Across the measures, the PPU group had higher oxytocin levels (M = 30.6, SD = 20 vs M = 22.9, SD = 10.7), and across the groups, the second measure was higher (M = 31.5, SD = 19.7 vs M = 23.1, SD = 12.8). However, the interaction between group and measure revealed that while there was no significant difference between the groups at baseline ($P > 0.05$), the post-experiment measure was significant (non-PPU: M = 24.8, SD = 11.7, PPU: M = 36.4, SD = 22.8, $P < 0.001$)

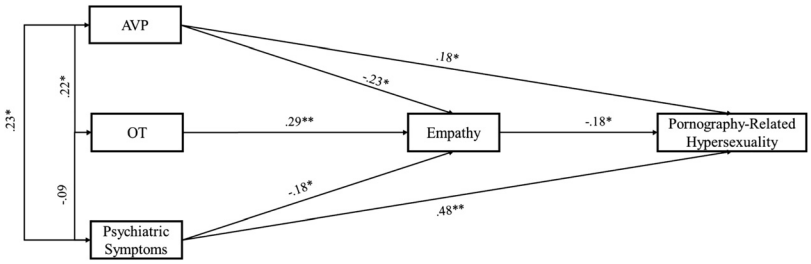

Fig. 3. Path analysis for the link between AVP, oxytocin and psychiatric symptoms to pornography-related hypersexuality
Note: *$P < 0.05$, **$P < 0.01$. Model fit: $\chi^2_{(1)} = 0.029$, $P = 0.865$, RMSEA = 0.000 with lower 90% CI = 0.00 and higher 90% CI = 0.13, PCLOSE = 0.883, CFI = 1.00, TLI = 1.195.
RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index, TLI = Tucker-Lewis Index

psychiatric symptoms and converged into the third path (95%CI = 0.008, 0.103, and 95%CI = 0.003, 0.085, respectively).

DISCUSSION

With CSBD in ICD-11 and PPU representing important clinical concerns, additional research into neurobiological systems underlying PPU is needed. The current findings suggest several alterations in neuropeptide functioning in PPU and demonstrate their links to lower empathy and more severe psychological symptoms. Furthermore, our findings suggest specific relationships between psychiatric symptomatology, AVP, oxytocin, empathy and pornography-related hypersexuality, and understanding these relationships may help guide clinical interventions. Implications are discussed below.

Although preclinical studies repeatedly demonstrate alterations in oxytocin and AVP functionality in animal models of addiction, no prior human study has tested their joint involvement in people with PPU. The current results suggest alterations in oxytocin and AVP in men with PPU as expressed in baseline levels, reactivity patterns, neuropeptide balance, and links with pornography-related hypersexuality. First, we found that baseline plasma AVP levels are increased in men with CSBs compared with a matched comparison group without PPU, and, although no group differences emerged in baseline plasma oxytocin levels, the ratio of oxytocin-to-vasopressin among men with PPU pointed to dominance of AVP. Second, men with PPU reacted with oxytocin increase to the presentation of neutral/positive social stimuli. Although both groups showed increase in oxytocin following the social stimuli, the group with PPU exhibited a steeper rise. Third, decreased empathic tendencies were found in men with PPU, reflecting poorer tendencies to understand others' emotions and mental states, and this reduced empathy mediated links between oxytocin and pornography-related hypersexuality. Finally, structural equation modeling revealed three independent paths to increased pornography-related hypersexuality; two direct paths via increased AVP and higher psychiatric symptoms and one indirect path, through the mediating role of diminished empathy. Overall, our findings are among the first to implicate neuropeptides sustaining mammalian affiliation and human attachment in the pathophysiology of CSBs and PPU.

The extended oxytocin-vasopressin system evolved to support the formation of parental and pair bonding (Carter & Perkeybile, 2018; Feldman, 2016, 2017). However, oxytocin and AVP contribute oppositely to bond formation and stress reduction, with oxytocin linked to affiliation and anxiolysis and AVP to territorial defense, aggression, and fight-or-flight responses (Baracz & Cornish, 2016; Carter & Perkeybile, 2018). Our findings of increased baseline AVP levels in men with PPU resonate with human studies on the role of AVP in men's social-mediated and partner-related stress, aggression, and vigilance. For instance, AVP administration increased cortisol response in social-evaluative contexts (Shalev et al., 2011), and AVP's effects were specific to men, reducing friendliness, increasing autonomic response to angry faces, and augmenting men's tendencies to use avoidant and aggressive social strategies (Shalev et al., 2011). Men, but not women, who had experienced distressed partner relationships showed higher plasma AVP (Taylor, Saphire-Bernstein, & Seeman, 2010). AVP receptor variability has also been previously linked to addictive behaviors like drug use (Maher et al., 2011), suggesting another possible biological mechanism related to the current findings. Our findings raise the possibility that vulnerabilities associated with AVP-related increases in suspicion, vigilance, defensive aggression, and poor tendencies to use social bonds for stress reduction may contribute to pornography-related hypersexuality or addictive use of pornography, and suggest these domains as potential targets for interventions in men with PPU.

In addition to increased AVP, we found altered AVP-to-oxytocin balance suggesting AVP dominance, which echoes human studies on parental care and pair-bonding (Buisman-Pijlman et al., 2014). Similar to findings in animal models, human studies show crosstalk between the two systems; for instance, intranasal oxytocin administration increased peripheral AVP levels (Weisman et al., 2013), and parents' plasma oxytocin and AVP were inter-related. Higher plasma AVP coupled with early-life stress increased men's acuity in detecting marital infidelity, while higher plasma oxytocin decreased such detection. Higher plasma AVP in new parents predicted lower parent-infant reciprocity and reduced infant-focused attention, while higher plasma oxytocin related to greater synchrony and diminished negative emotionality (Apeter-Levi, Zagoory-Sharon, & Feldman, 2014).

The overarching role of the oxytocin system in social affiliation is due, in part, to its role in facilitating neural plasticity (Feldman, 2020). Oxytocin neurons can co-express with multiple neurotransmitter systems, and multiple oxytocin-expressing neurons include GABAergic interneurons, glutamatergic pyramidal cells, and other neuroendocrine cells (Althammer et al., 2018). When oxytocin interacts with OTRs, it induces a sense of calm and safety and supports an individual's search for lasting bonds for stress buffering; however, in the context of increased AVP, oxytocin engages AVP receptors, leading to fear, vigilance, and defensive aggression. Furthermore, oxytocin's effects on affiliation may function via creating a ventral-to-dorsal corticostriatal shifts that, through interactions with dopamine, serotonin, and opioid systems, may enable shifts from more ventral reactive pathways to dorsal representational loops, changing from novelty-seeking to compulsive or habitual strategies. These pathways have been proposed to underlie internet use disorders including PPU (Brand, Wegmann, et al., 2019). One possible interpretation for the current findings is that the dispositional tendency toward greater AVP and oxytocin-to-AVP balance implicating AVP dominance tilts the system toward negative reactivity, vigilance, and fear in the formation of lasting bonds, which may, in turn, initiate a shift from affiliative motivations toward PPU. However, alternate interpretations exist. For instance, men with poorer social attachment or with reduced empathy and sense of reward from reciprocal social relationships may preferentially engage in pornography viewing at problematic levels, and these relationships warrant additional testing in longitudinal studies. In these studies, types of pornography viewed should be considered given violent and misogynistic content found in pornography readily available on the internet.

In addition to higher AVP and greater AVP-to-oxytocin balance, we also found greater oxytocin increases following exposure to daily social encounters in men with PPU as compared to the milder increase in comparison subjects. The reasons for this steep increase are not fully clear and require further research, but several plausible explanations exist. For instance, animal studies show that peripheral oxytocin release occurs in response to stress (Bowen & Neumann, 2017), and human studies pinpoint this to attachment-related stress. Girls with histories of sexual and physical abuse, but not those without, showed peripheral oxytocin increase to social stressors (Seltzer, Ziegler, Connolly, Prososki, & Pollak, 2014); parents with greater parental stress showed oxytocin increases to interactions with their infants and conceived such interactions as stress-inducing (Feldman et al., 2011); and children exposed to early maltreatment increased oxytocin production from morning to evening in the absence of trauma reminders (Mizushima et al., 2015). One possibility is that even neutral social stimuli within a positive social-affiliative context may be stressful to men with PPU.

Another possibility is that among men with PPU there are greater tendencies to experience poor attachment (Kor et al., 2014). Early-attachment disruptions may exert long-term effects on oxytocin-system functionality which express not only by altering set-points but also in activating the system in response to daily social stimuli which typically do not induce such responses. It is possible that among men with PPU, even benign social stimuli may trigger fear and suspicion, and the heightened oxytocin release may mark attempts to elicit safety and quiescence when such a sense of safety has not been internalized by secure early attachments. In this way, an increase in peripheral release may reflect an attempt at regulating a system that has become dysregulated (Carter & Perkeybile, 2018). Another possibility may relate to the frequent use of pornography, which may elicit oxytocin responses through sexual arousal, penile erections and orgasms, and such frequent experiences of oxytocin increase in response to video vignettes may have altered responses to

such stimuli, regardless of content. While we cannot determine whether such increased reactivity reflects specific long-term impacts of sexual behaviors, anxious responses to pleasant social moments, habitual responses to visual stimuli, reactions to reminders of close human bonds that may elude individuals with PPU or other possibilities, our findings represent a first step that describe alterations in oxytocin and AVP reactivity that can be used to guide future research.

Diminished empathy is found across multiple psychiatric conditions including addictive, affective, autism-spectrum, borderline and antisocial personality disorders, psychotic, and obsessive-compulsive disorders (Decety & Moriguchi, 2007; Nguyen, Clark, & Belgrave, 2011; Thirioux, Harika-Germaneau, Langbour, & Jaafari, 2020). Empathy develops within attachment relationships and is sustained by the oxytocin system. Empathy was reduced in men with PPU, and this mediated the link between oxytocin and pornography-related hypersexuality. Findings have important clinical implications as disruptions to cognitive and affective empathy may be amenable to interventions. As empathy has been proposed as a target in treating sexual-offending individuals (Schwartz, 1994), similar approaches may be tested in men with CSBD/PPU. Abilities or tendencies to understand and mentalize on others' internal states may be improved by mentalization-based interventions (Bateman & Fonagy, 2013), and difficulties in bottom-up automatic affective empathy may be increased via dialogue interventions that focus on behavioral resonance (Guendelman, Medeiros, & Rampes, 2017). Adapting insights from different types of intervention, one targeting cognitive empathy, the other affective empathy, in addition to factors linked to greater involvement of the AVP system, including fear, vigilance, social aggression, and mistrust in the context of dyadic relationships, should be considered in the development of novel treatments for CSBD/PPU. Direct targeting of oxytocin systems (via exogenous administration) also warrants consideration.

Study limitations include the lack of formal diagnostic assessment of CSBD as defined in the ICD-11, lack of use of structured instruments to assess for PPU, absence of measurement of CSBD/PPU measures in comparison subjects, cross-sectional design, all-male composition, limited geographic variability, limited assessment of variables that could have influenced neuroendocrine and PPU measures (recency of medication use, religious beliefs, social and personal expectations), and lack of information on sexual orientation. Additionally, specific groups of individuals were excluded (e.g., individuals with pedophilia given specific biological differences linked to pedophilia) (Ponseti et al., 2018; Tenbergen et al., 2015). Additionally, individuals with a history of incarceration were excluded given potential differences in AVP/oxytocin systems, and future studies may examine such populations. Inter-assay variability in biological measurements (e.g., of oxytocin) may also be considered a limitation, and thus findings from this initial study warrant replication in future investigations. Since this was the first study of its kind, it was exploratory in nature. Future studies including diagnostic assessments, longitudinal designs, and more diverse samples are needed to examine the replicability, generalizability and etiologies of the observed findings. Our study focused on pornography-related hypersexuality; hence, future research should also examine individuals with other CSBs. The study also provides a foundation for future ones investigating responses to more stimulating or stressful stimuli. Despite these limitations, the study has multiple strengths including the use of validated measures and relevance to understanding biological mechanisms underlying clinically relevant behaviors. Additional research should pursue these lines of research and determine the extent to which findings extend to substance and behavioral addictions like gambling and gaming disorders.

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APPENDIX

Table S1. T-tests, means and standard deviation for BSI symptom by groups

Variable		Non-PPU		PPU		*t*-test
		Mean	SD	Mean	SD	
BSI	Somatization	0.33	0.48	0.59	0.63	$t_{(119)} = -2.45$, $P < 0.05$, Cohen's $d = -0.46$
	Obsession Compulsion	0.84	0.66	1.40	0.87	$t_{(119)} = -3.86$, $P < 0.001$, Cohen's $d = -0.72$
	Interpersonal Sensitivity	0.59	0.60	1.54	1.02	$t_{(119)} = -5.94$, $P < 0.001$, Cohen's $d = -1.13$
	Depression	0.83	0.70	1.63	1.02	$t_{(119)} = -4.86$, $P < 0.001$, Cohen's $d = -0.91$
	Anxiety	0.77	0.52	1.32	0.84	$t_{(119)} = -4.11$, $P < 0.001$, Cohen's $d = -0.78$
	Hostility	0.65	0.50	0.99	0.83	$t_{(119)} = -2.61$, $P < 0.05$, Cohen's $d = -0.49$
	Phobic Anxiety	0.39	0.48	0.80	0.71	$t_{(119)} = -3.61$, $P < 0.001$, Cohen's $d = -0.68$
	Paranoid Ideation	0.63	0.49	1.43	0.94	$t_{(119)} = -5.53$, $P < 0.001$, Cohen's $d = -1.06$
	Psychoticism	0.61	0.55	1.51	0.91	$t_{(119)} = -6.33$, $P < 0.001$, Cohen's $d = -1.2$
OT (Blood)		236.13	73.78	217.71	48.43	$t_{(100)} = 1.52$, $P > 0.05$, Cohen's $d = 0.3$
AVP (Blood)		190.75	47.39	227.01	57.69	$t_{(105)} = -3.42$, $P < 0.001$, Cohen's $d = -0.69$
OT over AVP (Blood)		1.21	0.47	0.97	0.34	$t_{(113)} = 3.07$, $P < 0.01$, Cohen's $d = 0.57$
Empathy		42.88	10.12	39.37	9.24	$t_{(119)} = 1.99$, $P < 0.05$, Cohen's $d = 0.36$
BSI		0.62	0.39	1.13	0.63	$t_{(119)} = -5.17$, $P < 0.001$, Cohen's $d = -0.98$
HDQ - PPU		2.31	0.88	3.83	1.04	$t_{(119)} = -8.51$, $P < 0.001$, Cohen's $d = -1.58$