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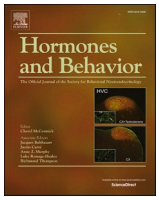

Four-week intranasal oxytocin administration reduces attachment avoidance in older women

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ABSTRACT

The neuropeptide oxytocin (OT) serves as a critical modulator of social cognition and social behavior. Adult attachment is an affiliative process crucial for social interaction across adulthood. Insecure adult attachment comprises two broad dimensions, attachment anxiety and attachment avoidance. Both these dimensions of attachment are currently understudied regarding OT modulation, and especially in older adults. The present study determined the effects of chronic intranasal OT administration on adult attachment in generally healthy older women and men (aged 55–95 years). Embedded in a larger project, participants were randomly assigned to self-administer 24 international units of either OT or a placebo (P) intranasally twice daily for four weeks. The Experiences in Close Relationships Scale assessed adult attachment (anxiety and avoidance) pre- and post-treatment. There was no significant pre- to post-treatment change in attachment avoidance overall, but the treatment x timepoint x sex interaction was significant, in that women (but not men) in the OT (vs. P) group reported decreased attachment avoidance. No comparable effects were observed for attachment anxiety. Results suggest that older women may benefit from chronic intranasal OT treatment by experiencing less attachment avoidance in their adult relationships.

1. Introduction

Oxytocin (OT) is a nine-amino acid neuropeptide produced in the magnocellular cells of the paraventricular and supraoptic nuclei of the hypothalamus (Burbach et al., 2006). Traditionally, OT has been associated with labor and lactation (Veening et al., 2015; White-Traut et al., 2009), but has more recently garnered interest for its role in social-cognitive (e.g., emotion identification; Domes et al., 2007; Graustella and MacLeod, 2012) and affiliative (e.g., attachment, Bartz, 2016; Baumgartner et al., 2008; Gordon et al., 2008) processes.

More specifically, both endogenous and exogenous OT have been documented as prominent contributors to the formation of social bonds and attachment in animal research such as in monogamous prairie voles (see Lim and Young, 2006, for a review). Research in humans regarding OT and attachment is comparatively less rich, but there has been evidence of intranasal OT's effects in facilitating attachment and approach behaviors such as by promoting in-group trust and augmenting emotion recognition (see Van Ijzendoorn and Bakermans-Kranenburg, 2012, for a review), and supporting stress reduction associated with social support from a close friend (Heinrichs et al., 2003; Riem et al., 2020). One possible mechanism underlying OT's effect on attachment as put forth in the affiliative motivation hypothesis is that OT modulates social approach behaviors by increasing the motivation or desire to affiliate with others (Bartz et al., 2011).

Attachment is an affiliative process that refers to the social and emotional bonding with others and is often described in dimensions of secure and insecure attachment (Fraley, 2019). Secure attachment in adulthood refers to companionship, sharing of interests and experiences, feelings of competence, guidance, and assistance (Ainsworth, 1985; Crowell and Treboux, 1995; Weiss, 1974). Greater levels of secure adult attachment have been associated with greater overall health (McWilliams and Bailey, 2010), positive mood (Escolas et al., 2014), and feelings of hope (Blake and Norton, 2014). In contrast, insecure attachment in adulthood refers to discomfort and worry about getting close to others (Fraley and Roisman, 2019). Greater levels of insecure adult attachment have been associated with lower perceived social support (Vogel and

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Wei, 2005), life satisfaction (Waring et al., 2019, and emotion regulation capacity (Mikulincer and Shaver, 2019).

Brennan et al. (1998) conceptualizes adult attachment as a two-dimensional construct in that insecure attachment in adult relationships can comprise attachment anxiety and/or attachment avoidance (see also Hazan and Shaver, 1987; Manning et al., 2017; Shaver and Fraley, 2004). Attachment anxiety is characterized by a fear of rejection and abandonment, whereas attachment avoidance is characterized by distrust and fear of allowing others to get close to oneself (Campbell and Marshall, 2011). Higher levels on either of these dimensions have been associated with lower levels of secure attachment (Brennan et al., 1998; Wei et al., 2007). In further support of this two-dimensional conceptualization, published work using factor analysis showed that individual items on the Experiences in Close Relationships Scale (ECR; Brennan et al., 1998) load on two distinct orthogonal factors – attachment anxiety and attachment avoidance – rather than a single composite construct (Alonso-Arbiol et al., 2008; Brennan et al., 1998; Fraley et al., 2000; Wei et al., 2007).

The literature suggests that both attachment anxiety and attachment avoidance can change across adulthood due to factors such as environmental stress or negative life events including loss of an attachment figure (McConnell and Moss, 2011). In particular, several studies consistently found lower self-reported attachment anxiety in older rather than younger adults (Chopik et al., 2019; Kafetsios and Sideridis, 2006; Mickelson et al., 1997; Segal et al., 2009; Zhang and Labouvie-Vief, 2004). Research on attachment avoidance, in contrast, is more mixed, with some studies showing little to no age-related differences (Chopik et al., 2013; Kafetsios and Sideridis, 2006; Segal et al., 2009), while other studies support higher attachment avoidance in older than younger adults (Chopik and Edelstein, 2014; Diehl et al., 1998; Magai et al., 2001; Zhang and Labouvie-Vief, 2004; but see Chopik et al., 2019). Also, going beyond cross-sectional work, a six-year longitudinal study on individuals ranging from 15 to 87 years found that older age was associated with lower attachment anxiety but more attachment avoidance over time (Zhang and Labouvie-Vief, 2004).

Sex differences in attachment anxiety and avoidance have also been well documented, with men reporting higher attachment avoidance and women higher attachment anxiety (Del Giudice, 2011, 2019; Scharfe, 2017). However, there are also studies that do not find sex differences in adult attachment (Mikulincer and Shaver, 2007; van IJzendoorn and Bakermans-Kranenburg, 2010). Furthermore, a meta-analysis of 112 studies that included women and men ranging from 15 to 49 years supported an age-by-sex interaction, in that women reported higher attachment anxiety than men between the ages of 20 to 30, while men reported higher attachment anxiety than women when younger than 20 and when older than 30 (Del Giudice, 2011). Furthermore, attachment avoidance in men increased with age with no age differences in women. This meta-analysis, however, only included individuals up to age 49 and therefore cannot speak to effects among older adults.

This evidence of age and age-by-sex effects on adult attachment combined with findings of sex-dimorphism (Carter, 2014; Dumais and Veenema, 2016; Macdonald, 2013) as well as age and age-by-sex differences (Ebner et al., 2013, 2015; Horta et al., 2020; Huffmeijer et al., 2013; Kanat et al., 2014; Sannino et al., 2017) in OT function, calls for an investigation of intranasal OT administration effects on adult attachment anxiety and attachment avoidance in older women and men. A recent meta-analysis (Zhang et al., 2021) included 22 single-dose studies (dosage ranging from 12 to 40 international units; IUs) across a broad age range (8–65 years) and found that OT reduced self-reported attachment avoidance while no effect was observed for attachment anxiety. Age, however, was not an explicit factor in this meta-analysis. In fact, research on the effects of intranasal OT on adult attachment in aged samples is scarce, which is surprising given evidence of age-related differences in adult attachment (Chopik and Edelstein, 2014; Diehl et al., 1998; Magai et al., 2001; Zhang and Labouvie-Vief, 2004; but see Chopik et al., 2019).

Also, currently close to nothing is known about effects of repeated administration of intranasal OT, which is more reflective of treatment effects than a single-dose administration (Horta et al., 2020), including on affiliative processes in aging. In fact, the only study to date that employed chronic intranasal OT administration (2 weeks, 24 IUs of OT or P daily) comprised only younger men (aged 18–30 years) and found OT-reduced attachment avoidance, with this effect most pronounced in younger men who reported higher levels of insecure attachment (Bernaerts et al., 2017).

Thus, in line with the two-dimensional conceptualization of adult attachment (Bartz et al., 2015; Bradley et al., 2019; Dewitte et al., 2008; Li and Chan, 2012; McKinley and Randa, 2005; Mitchell et al., 2016), evidence that OT treatment may impact attachment avoidance but not attachment anxiety (see Zhang et al., 2021, for a meta-analytic review), and sex-related differences in attachment anxiety vs. attachment avoidance, we analyzed the two ECR scales individually, allowing for consideration of unique variation in each scale. Accordingly, we formulated independent hypotheses for attachment anxiety and attachment avoidance and utilized an independent hypothesis testing approach (Rubin, 2021).

In particular, filling an important gap in the literature, the present study determined the effects of a four-week intranasal OT administration on attachment anxiety and attachment avoidance in a sample of generally healthy older adults. With reference to previous literature (on mostly single-dose regimens and in young males; Bernaerts et al., 2017; Zhang et al., 2021), we hypothesized that four-week intranasal OT would reduce attachment avoidance in older adults; with no such effect for attachment anxiety.

Our sample included both older women and men. Thus, we were able to consider biological sex as a moderator of the effects of intranasal OT on adult attachment among older women and men. While there is previous evidence that women report higher attachment anxiety whereas men report higher attachment avoidance (Del Giudice, 2011, 2019; Scharfe, 2017), we refrained from formulating directional hypotheses regarding these effects given the rather mixed sex-dimorphic evidence around OT as well as the scarcity of previous research on this topic in older adults.

2. Methods

Only procedures and measures with relevance for this analysis are described here in detail. For more information about the larger clinical trial see Rung et al. (2021).

2.1. Participants

The sample for this study included 121 generally healthy older adults (84 men and 37 women; 89.7 % White; 3.8 % Hispanic/Latino; See Table 1) from a larger clinical trial investigating the effects of chronic intranasal OT administration on physical, cognitive, and socioemotional functioning in healthy aging (NCT02069431; Oxytocin and Aging Study). This project was completed at the University of Florida Department of Psychology, the Institute on Aging, and the McKnight Brain Institute (see Rung et al., 2021, for details). Only participants with complete data on the central measures relevant to this paper at both pre- and post-intervention were included in this analysis. In addition, we excluded four participants (two women) who reported current use of hormone replacement therapy, given OT's interactions with gonadal hormones (Bale and Dorsa, 1995; Bethlehem et al., 2013; Kanat et al., 2014).

Participants were recruited from Alachua County and surrounding communities through mail outs, fliers, newspaper ads, word-of-mouth, community recruitment services at the University of Florida such as HealthStreet, and university participant registries. Participants received $300 compensation for study completion. Inclusion criteria required participants to be generally healthy (assessed via a lab-internal health

Table 1
Demographics, health, affect, and cognition by treatment group at pre-intervention.

	OT Women ($N = 18$) M(SD)	P Women ($N = 19$) M(SD)	OT Men ($N = 45$) M(SD)	P Men ($N = 39$) M(SD)	Sex (η_p^2)	Treatment (η_p^2)	Treatment*Sex (η_p^2)
Demographics							
Age	71.3 (7.79)	72.3 (6.89)	72.9 (7.74)	69.3 (6.24)	0.002	0.007	0.021
Education[a]	16.1 (3.33)	14.3 (1.95)	17.2 (2.55)	16.4 (4.61)	0.043	0.029	0.003
Health							
Physical	8.11 (1.45)	8.32 (0.94)	8.02 (1.39)	8.00 (1.28)	0.005	0.001	0.002
Mental	8.83 (1.15)	8.37 (1.30)	8.56 (1.32)	8.53 (0.99)	0.001	0.009	0.007
Affect							
Positive[b]	3.75 (0.59)	3.45 (0.74)	3.35 (0.50)	3.55 (0.56)	0.015	0.002	0.038
Negative	1.42 (0.42)	1.38 (0.44)	1.41 (0.38)	1.35 (0.37)	0.001	0.003	<0.001
Cognition							
Crystallized	115 (7.87)	115 (9.39)	122 (12.1)	119 (11.1)	0.051	0.005	0.003
Fluid	88.6 (7.44)	87.5 (9.06)	89.5 (9.63)	90.2 (9.90)	0.008	<0.001	0.002

Note: Age and education are indicated in years. Subjective physical (*Please rate your general physical* health) and mental (*Please rate your general mental health/mood*) were assessed using a Likert scale (1 = *Poor*; 10 = *Excellent*). Affect was assessed via the Positive and Negative Affect Schedule (Watson et al., 1988). Cognition was assessed using the NIH Cognition Toolbox (Akshoomoff et al., 2013); unadjusted mean scores were used. [a] indicates a significant main effect of *sex*; [b] indicates a significant *treatment* x *sex* interaction. Men had significantly more years of education ($t(109) = 2.21$, *MDiff* = 1.58, $p = 0.03$) and significantly higher crystallized cognition ($t(116) = 2.50$, *MDiff* = 5.34, $p = 0.01$) than women. In addition, men in the OT group had significantly lower positive affect than women in the OT group ($t(115) = -2.64$, *MDiff* = −0.40, $p = 0.02$).

review), 55 years of age or older, English-speaking, able to administer intranasal OT (i.e., no nasal obstructions), and have a pre-intervention blood pressure of <180/100 mmHg.[1] Additionally, eligible participants had no indication of cognitive impairment (cut off score < 30 on the Telephone Interview for Cognitive Status; Brandt et al., 1988), no history of hyponatremia or inappropriate antidiuretic hormone secretion, high urine osmolality (>1200 L) paired with low sodium (<134 mEq/L), psychogenic polydipsia, use of vasoconstrictors, or heavy cigarette smoking/alcohol consumption.

A sensitivity analysis was conducted using G*Power 3.1 (Faul et al., 2007) to calculate the minimum detectable effect sizes. For our main hypothesis investigating the effect of OT on attachment avoidance and attachment anxiety in the present analysis sample, the repeated-measures ANOVAs had 80 % power to detect a small to medium effect size (Cohen's f = 0.13; $\eta^2 = 0.017$; alpha = 0.05). To address our analysis on interactions with sex, the repeated-measures ANOVAs had 80 % power to detect a small to medium effect size (Cohen's f = 0.15; $\eta^2 = 0.02$; alpha = 0.05). However, it must be noted that although our sensitivity analysis prior to hypothesis testing indicated that we were powered to detect a small to medium effect size (Cohen's f = 0.13), our models may have been less sensitive due to unequal cell sizes (fewer women than men) as unequal cell sizes cannot be considered in sensitivity analysis (G*Power; Faul et al., 2007).

2.2. Study design and procedures

The larger clinical trial was approved by the University of Florida Institutional Review Board, and all procedures were monitored by the Data Safety Monitoring Board at the Institute on Aging and the Food and Drug Administration (IND 100,860). After written informed consent, participants attended a screening visit in which they completed health questionnaires, a cognitive battery, and were examined by a clinician. This was followed by three pre-intervention sessions during which physiological, biological, behavioral, cognitive, and socioemotional measures were administered, including the Experiences in Close Relationships-Short Form (ECR-S; Wei et al., 2007).

The intervention adopted a randomized, double-blind, between-subject design in which participants self-administered 24 IUs OT or P (which contained the same ingredients as the OT spray but no OT) intranasally twice daily (between 7 and 9 AM and 5–7 PM) for four weeks. Participants were contacted weekly during the intervention to assess safety and tolerability of the treatment (see Rung et al., 2021, for details).

To avoid potential withdrawal effects on outcome measures, the three post-intervention visits, which mirrored the pre-intervention visits, were conducted during the final week of the intervention. On mornings of post-intervention visits, participants were instructed not to administer the nasal spray to prevent measurement of acute effects but were instructed to continue with the evening dose of nasal spray until the end of the four-week intervention. Only measures relevant to the current analysis are reported here in detail below.

2.3. Measures

The ECR-S is a valid and reliable measure of adult attachment (Wei et al., 2007). It comprises two scales of six questions each (12 questions total) that assess attachment anxiety (i.e., an individual's fear of being rejected or abandoned by a partner; example item: *I worry that romantic partners won't care about me as much as I care about them*) and attachment avoidance (i.e., an individual's fear of dependence or intimacy with a partner; example item: *I try to avoid getting too close to my partner*), respectively, on a scale from 1 (*Disagree strongly*) to 7 (*Agree strongly*). Individuals scoring low on the two scales are typically viewed as securely attached, whereas high scale scores are indicative of insecure attachment. Participants were instructed to respond to the items regarding their general relationship experiences rather than any specific current relationship. Both of the scales showed good internal reliability, with Cronbach's α = 0.78 ($M = 17.8$, $SD = 6.11$) for attachment anxiety and Cronbach's α = 0.85 ($M = 13.7$, $SD = 5.53$) for attachment avoidance. While attachment anxiety and attachment avoidance at pre-intervention were significantly correlated for men ($r(85) = 0.477$, $p < 0.001$), the two scales were not significantly correlated for women ($r(35) = 0.317$, $p > 0.050$), suggesting a two-dimensional nature of adult

[1] The literature does not suggest cardiovascular side effects (e.g., increased hypertension/blood pressure) from chronic intranasal OT administration in humans (den Boer and Westenberg, 1992; Epperson et al., 1996; see also MacDonald et al., 2011, for a review). However, some research supports cardiovascular changes (e.g., lower blood pressure, change in heart rate variability) from OT administration (see Quintana et al., 2013, for a review). As the present study was the first four-week intranasal OT administration in older adults, we measured blood pressure at both pre- and post-intervention to ensure general health of our participants and to allow capture of any unexpected changes in blood pressure associated with the OT treatment. See Rung et al. (2021) for a detailed report about safety and tolerability of the four-week intranasal OT administration in our sample of older adults.

attachment in our female sample.

2.4. Analyses

To test our hypothesis that chronic intranasal OT would reduce attachment avoidance, but not attachment anxiety, we conducted two separate mixed model repeated-measures ANOVAs on the ECR-S attachment anxiety and the ECR-S attachment avoidance scale sum scores (ranging from a minimum 7 to a maximum 42 per scale) respectively. In both models, the within-subjects independent variable was *timepoint* (pre- vs. post-treatment) and the between-subject independent variables were *treatment* (OT vs. P) and *sex* (female vs. male). Both models controlled for participant age. We followed up significant effects with post-hoc comparisons for interpretation. Given that we had two independent hypotheses regarding the two ECR-S scales, we adopted an individual hypothesis testing approach and did not correct the significance level for multiple comparisons (Rubin, 2021).

To confirm that our data met model assumptions, we conducted Levene's tests for homogeneity of variances, which was non-significant thereby indicating that the variances across conditions (treatment, sex) were homogenous. No outliers ±3 SD were identified on either scale of the ECR-S. Data was also assessed for missingness. Comparable results using multiple imputation by chained equations (MICE) are reported in the Supplemental Material. MICE is an approach that imputes missing data values by creating multiple copies of the dataset, replacing missing data with imputed values, and then combining the results of the imputed datasets (Azur et al., 2011). All data and analysis code is archived under the Open Science Framework repository: https://osf.io/jbwqd/?view_only=b6beb745509b443184843e7a01993732 (Wright, 2023).

3. Results[2]

Attachment Anxiety. For attachment anxiety, the *treatment* X *timepoint* interaction was not significant ($F(1,116) = 0.54$, $p = 0.47$, $\eta_p^2 = 0.005$), nor was the *treatment* X *timepoint* X *sex* interaction ($F(1,116) = 0.91$, $p = 0.34$, $\eta_p^2 = 0.008$). That is, chronic intranasal OT did not show an overall or sex-dimorphic reduction in attachment anxiety post- vs. pre-treatment in older adults in line with our hypothesis (see Fig. 1A).

The *treatment* X *sex* interaction was also not significant ($F(1,116)$, $= 1.32$, $p = 0.253$, $\eta_p^2 = 0.011$). However, the *timepoint* X *sex* interaction was significant ($F(1,116) = 5.06$, $p = 0.026$, $\eta_p^2 = 0.042$), in that men reported higher attachment anxiety than women pre-treatment (*Mdiff* $= 3.90$, $t(116) = 2.95$, $SE = 1.32$, $p = 0.004$), while men and women did not differ in attachment anxiety post-treatment (*Mdiff* $= 1.41$, $t(116) = 1.11$, $SE = 1.27$, $p = 0.27$). The main effects of *treatment* ($F(1,116) = 4.12$, $p = 0.045$, $\eta_p^2 = 0.034$), *sex* ($F(1,116) = 5.14$, $p = 0.03$, $\eta p^2 = 0.042$), and *timepoint* ($F(1,116) = 5.82$, $p = 0.017$, $\eta_p^2 = 0.048$) were also significant.

Attachment Avoidance. For attachment avoidance, the *treatment* X *timepoint* interaction was not significant ($F(1,115) = 1.07$, $p = 0.30$, $\eta_p^2 = 0.009$), but the *treatment* X *timepoint* X *sex* interaction was significant ($F(1,115) = 4.30$, $p = 0.040$, $\eta_p^2 = 0.036$), in that chronic intranasal OT showed sex-dimorphic reduction of attachment avoidance post- vs. pre-treatment (see Fig. 1B). In particular, follow-up analyses showed that women in the OT group reported lower attachment avoidance post- vs. pre-treatment (*Mpre* $= 13.1$, *Mpost* $= 10.9$; $t(115) = 2.12$, $SE = 1.02$, $p = 0.04$), while women in the P group did not report significantly different attachment avoidance post- vs. pre-treatment (*Mpre* $= 13.4$, *Mpost* $= 14$; $t(115) = -0.52$, $SE = 1.00$, $p = 0.60$). Also, men did not report such difference in attachment avoidance post- vs. pre-treatment in either the OT (*Mpre* $= 12.9$, *Mpost* $= 13.5$; $t(115) = -0.94$, $SE = 0.65$, $p = 0.35$) or the P (*Mpre* $= 15.2$, *Mpost* $= 14.9$; $t(115) = 0.42$, $SE = 0.71$, $p = 0.68$) group.

None of the other effects were significant: *timepoint* ($F(1,115) = 0.80$, $p = 0.37$, $\eta_p^2 = 0.007$), *treatment* ($F(1,115) = 2.50$, $p = 0.12$, $\eta_p^2 = 0.021$), *sex* ($F(1,115) = 1.26$, $p = 0.27$, $\eta p^2 = 0.011$), *timepoint* X *sex* ($F(1,115) = 1.31$, $p = 0.25$, $\eta_p^2 = 0.011$), *treatment* X *sex* ($F(1,115) = 0.003$, $p = 0.96$, $\eta_p^2 < 0.001$).

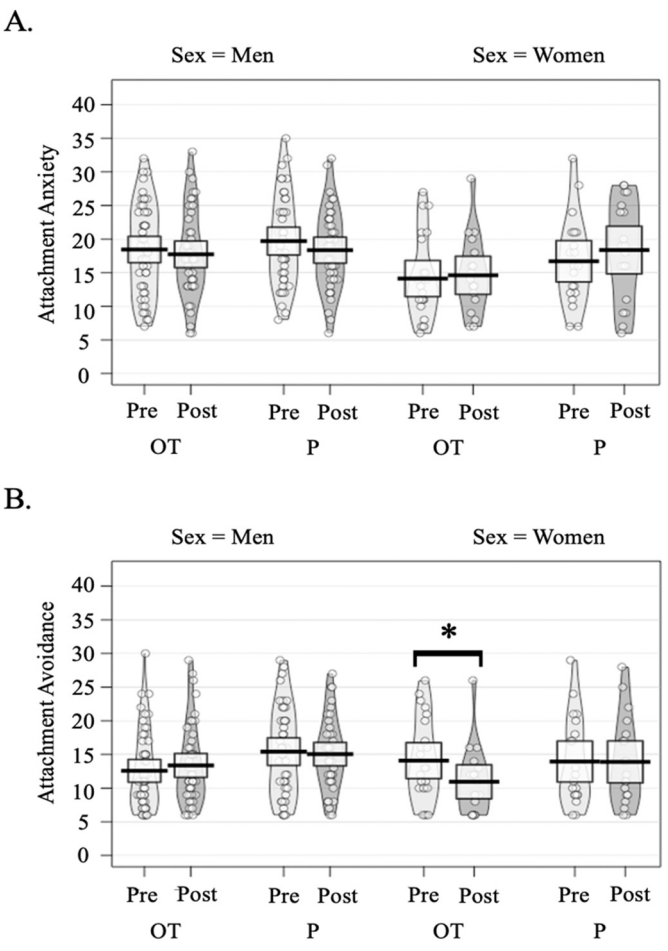

Fig. 1. Effects of chronic intranasal OT administration on adult attachment in generally healthy older women and men. A) For attachment anxiety, neither the *treatment* X *timepoint* nor the *treatment* X *timepoint* X *sex* interactions were significant; B) For attachment avoidance, the *treatment* X *timepoint* interaction was not significant but the *treatment* X *timepoint* X *sex* interaction was significant ($F(1,115) = 4.30$, $p = 0.040$, $\eta_p^2 = 0.036$). In particular, women (but not men) in the OT (but not in the P) group reported lower attachment avoidance post- vs. pre-treatment ($t(115) = 2.12$, $SE = 1.02$, $p = 0.036$).

4. Discussion

This study is the first to investigate the effects of chronic intranasal OT administration on adult attachment in generally healthy older women and men and suggests a (small to medium) effect of four-week intranasal OT administration on reducing attachment avoidance among older women. In contrast, there was no effect on attachment avoidance in older men, nor on attachment anxiety in either older women or men. We discuss these key findings next.

The affiliative-motivation hypothesis (Bartz, 2016) offers an interpretation of our observation that chronic OT reduced attachment avoidance in older women while no comparable effect was observed for attachment anxiety. This hypothesis posits that OT enhances the desire to affiliate with others such that intranasal OT should only affect attachment avoidance but not attachment anxiety. In particular, individuals who are anxiously attached exhibit a natural bias for affiliating

[2] See Supplemental Material for comparable results following MICE to impute missing values.

with others and seeking close relationships whereas avoidantly attached individuals show the opposite by avoiding close relationships with others (Bartz et al., 2015). Thus, intranasal OT might reduce attachment avoidance by promoting affiliative behavior, while individuals who are anxiously attached already naturally behave in an affiliative manner and thus are not/less affected by intranasal OT.

Our findings are largely in line with results of a two-week intranasal OT intervention (Bernaerts et al., 2017) as well as with evidence from the Zhang et al. (2021) meta-analysis, both of which found a reduction in attachment avoidance but not attachment anxiety. However, Zhang et al. only considered single-dose intranasal OT effects and included very few older women and men and only up to the age of 65. Bernaerts et al., while administering OT repeatedly over 2 weeks, only included younger men. Our study, in contrast, went significantly beyond this previous work by covering a wide older adult age range (from 55 to 95 years), included both women and men, and followed a four-week daily OT administration regimen; thus, extending previous evidence to older adults and to chronic intranasal OT administration, with effects present in older women only.

The meta-analysis by Zhang et al. (2021) included 22 studies with sample sizes ranging from 17 to 100 participants, with an average of roughly 40 participants for studies included. In fact, the median of current intranasal OT studies is 49 (Walum et al., 2016). In addition, Bernaerts et al., 2017), which is to date the most similar study to ours, included a total of 40 young men. Thus, the present study with a total of 121 participants had a larger sample size than what is typically reported in the literature, and thus more statistical power to detect smaller effect sizes, whereas much of the previous intranasal OT research was only powered to detect medium to large effects (Mierop et al., 2020; Walum et al., 2016).

Our results contribute to a growing notion of sex-dimorphism in OT effects on social-cognitive and affiliative processes in humans (Ebner et al., 2015; Huffmeijer et al., 2013; Kanat et al., 2014; Plasencia et al., 2019) and rodents (Bredewold and Veenema, 2018; Dumais et al., 2013; Lu and Hu, 2021), which may be driven by differences in concentrations of sex hormones. The female sex hormone estrogen promotes endogenous OT production, resulting in higher concentrations of plasma OT levels and greater presence of OT receptors (Choleris et al., 2008; Patisaul et al., 2003; Windle et al., 2006; see also Macdonald and Feifel, 2013), which may provide potential for increased binding for exogenous OT in females. Furthermore, testosterone promotes the production of arginine vasopressin (AVP; Delville et al., 1996; Han and De Vries, 2003; Macdonald and Feifel, 2013), a neuropeptide very similar in structure and found to act in opposition to OT (Macdonald and Feifel, 2013; Neumann and Landgraf, 2012). In fact, males have higher plasma AVP levels than females (Ishunina and Swaab, 1999; Share et al., 1988; Wenner and Stachenfeld, 2012; but see Plasencia et al., 2019), which may result in less OT receptors available for exogenous OT binding in males. Huang et al. (2014) furthermore demonstrated that chronic OT administration in male rodents resulted in overstimulation of the OT system, rendering the OT system less sensitive to intervention. These interpretations of differences between females and males in OT effects on attachment due to differences in sex hormones, however, are speculative at this point and will need to be confirmed in future research.

5. Limitations and future directions

The present study had some limitations. First, due to the unequal cell sizes with fewer women than men, our design was less sensitive to detecting small effects than our sensitivity analysis suggested. Also, given the relatively small number of women in the sample, we cannot exclude that the effect of OT-reduced attachment avoidance in older women occurred by chance and future research on a larger sample is warranted to confirm the present study's findings. Second, the majority of our sample was white, thus possibly reducing generalizability of the results to individuals from diverse backgrounds. Third, the present study tested only one administration regimen. Future research to determine the optimal dosage and frequency of administration towards optimizing attachment in older adults is needed. This research should be followed up with longitudinal repeated administration and multiple sampling of OT (and AVP as well as sex hormones) system and function over time. Future studies should also consider fluctuations in attachment throughout the intervention phase, instead of only comparing pre-vs post-intervention attachment levels. In doing so, future research will benefit from a systemic capture of possible fluctuations in adult attachment as a function of OT dynamics across situations and time. Finally, the present study tested a sample of generally healthy older adults. The literature, however, suggests that adult attachment (Bakermans-Kranenburg and van Ijzendoorn, 2009) and the effects of intranasal OT on affiliative processes (Bartz et al., 2011; Horta et al., 2020; Macdonald and Feifel, 2013; Pincus et al., 2010) may differ in healthy vs. clinical populations (but see Labuschagne et al., 2010 and Zink and Meyer-Lindenberg, 2012, for comparable effects in clinical and non-clinical samples). In particular, a secondary data analysis of studies assessing adult attachment across a wide age range (adolescence through age 75) found that clinical samples report more insecure attachment than healthy samples (Bakermans-Kranenburg and van Ijzendoorn, 2009). Thus, extension of the present work into a clinical population of older adults who experience challenges in adult attachment (e.g., depression, anxiety, and suicidality; Oon-arom et al., 2019) may be a relevant future avenue to evaluate treatment potential of intranasal OT.

6. Conclusions

We found that four weeks of intranasal OT lowered self-reported attachment avoidance in older women, while there was no effect in older men; and no effect on attachment anxiety in women or men from the intervention. Our findings importantly extend previous evidence of OT's role in affiliative processes to an older adult sample and suggest chronic intranasal OT administration as a possibly beneficial intervention to reducing attachment avoidance among older women, a currently still largely understudied demographic in OT research.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

I have shared my data and code on OSF (https://osf.io/jbwqd/)

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Appendix A. Supplemental material

Data was assessed for missingness. In the present study 96 men (49 OT, 46 P) and 48 women (27 OT, 23 P) were enrolled. However, 22 participants did not complete the intervention, leaving complete data for 85 men (45 OT, 40 P) and 37 women (18 OT, 19 P). Because ANOVA is sensitive to missing cases and discards records based on incomplete data, we assessed the pattern of missingness to determine if methods to handle missing data were appropriate to use in this study. Results of Little's MCAR test were not significant (χ^2 (68) = 81.8, $p = 0.12$) indicating that data was missing completely at random. Multiple imputation by chained equations (MICE) is one of the most common strategies for dealing with missing data. In using this approach, multiple copies of the dataset were created, and missing values were replaced with imputed values, and then the results of the imputed datasets were combined (Azur et al., 2011). Here we report the statistics obtained from our models controlling for participant age after using MICE to impute missing values in the ECR scales.

Attachment Anxiety. For attachment anxiety the *treatment* X *timepoint* interaction was not significant ($F(1,155) = 0.94$, $p = 0.33$, $\eta_p^2 = 0.006$), nor was the *treatment* X *timepoint* X *sex* interaction ($F(1,155) = 0.96$, $p = 0.33$, $\eta_p^2 = 0.006$), or the *treatment* X *sex* interaction ($F(1,155) = 0.01$, $p = 0.91$, $\eta_p^2 < 0.001$). The *timepoint* X *sex* interaction was significant ($F(1,155) = 8.03$, $p = 0.005$, $\eta_p^2 = 0.049$) in that men reported higher attachment anxiety than women pre-treatment (*Mdiff* = 3.64, $t(155) = 3.11$, $SE = 1.17$, $p = 0.002$), but they did not differ in attachment anxiety at post-treatment (*Mdiff* = 1.24, $SE = 1.12$, $p = 0.69$). The main effects of *treatment* ($F(1,155) = 1.24$, $p = 0.27$, $\eta_p^2 = 0.008$) and *sex* ($F(1,155) = 3.42$, $p = 0.07$, $\eta_p^2 = 0.022$) were not significant, however, the main effect of *timepoint* ($F(1,155) = 7.03$, $p = 0.009$, $\eta_p^2 = 0.043$) was significant. These results are in line with those reported in the main text with the exception that the main effects of *treatment* and *sex* were no longer significant.

Attachment Avoidance. For attachment avoidance, the *treatment* X *timepoint* interaction was not significant ($F(1,155) = 0.98$, $p = 0.32$, $\eta_p^2 = 0.006$), but the *treatment* X *timepoint* X *sex* interaction was significant ($F(1,155) = 6.89$, $p = 0.01$, $\eta_p^2 = 0.043$) in that chronic intranasal OT showed sex-dimorphic reduction of attachment avoidance post- vs. pre-treatment. In particular, follow-up analyses showed that women in the OT group reported lower attachment avoidance post- vs. pre-treatment (*Mpre* = 15.1, *Mpost* = 12.3; $t(155) = 3.36$, $SE = 0.84$, $p < 0.001$), while women in the P group did not report a significant difference in attachment avoidance post- vs. pre-treatment (*Mpre* = 13.6, *Mpost* = 13.5; $t(155) = 0.10$, $SE = 0.91$, $p = 0.92$). Men, in contrast, did not report a difference in attachment avoidance post- vs. pre-treatment in either the OT (*Mpre* = 12.4, *Mpost* = 13.7; $t(155) = -0.23$, $SE = 1.52$, $p = 0.98$) or the P (*Mpre* = 15.0, *Mpost* = 15.0; $t(155) = 0.02$, $SE = 0.61$, $p = 0.99$) group. The main effects of *treatment* ($F(1,155) = 0.91$, $p = 0.34$, $\eta_p^2 = 0.006$), *timepoint* ($F(1,155) = 2.31$, $p = 0.13$, $\eta_p^2 = 0.015$), and *sex* ($F(1,155) = 0.16$, $p = 0.69$, $\eta_p^2 = 0.001$) were not significant. Likewise, the *treatment* X *sex* interaction was not significant ($F(1,155) = 1.12$, $p = 0.29$, $\eta_p^2 = 0.007$). The *timepoint* X *sex* interaction, however, was significant ($F(1,155) = 7.63$, $p = 0.006$, $\eta_p^2 = 0.047$) in that women reported significantly lower attachment avoidance at post-intervention (*Mpre* = 14.4, *Mpost* = 12.9; $t(155) = 2.35$, $SE = 0.62$, $p = 0.02$) compared to men (*Mpre* = 13.7, *Mpost* = 14.3; $t(155) = -1.46$, $p = 0.15$). These results are in line with those reported in the main text, with the exception that the *timepoint* X *sex* interaction was not significant, however the qualifying *treatment* X *timepoint* X *sex* still was.

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