








The role of oxytocin in mediating the relationships between social factors and chemotherapy-associated cognitive decline in female patients with breast cancer

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ABSTRACT

While chemotherapy can cause debilitating side effects, social support, particularly that of an intimate partner, can be protective. This study examined the relationships between couple satisfaction and chemotherapy-associated subjective and objective cognitive decline in a cohort of breast cancer patients, in addition to the roles of other social factors. Because of oxytocin's role in social bonding and cognition, circulating oxytocin and oxytocin receptor gene expression in peripheral blood mononuclear cells were investigated as potential mediators. Partnered breast cancer patients ($n = 48$) completed cognitive assessments and provided blood samples at 3 timepoints: pre-chemotherapy, during chemotherapy, and post-chemotherapy. Participants completed a retrospective couple satisfaction questionnaire, provided information about partner duration as well as other social factors (e.g., number of people in the household, number of dependents under 18), and completed a retrospective perceived general social support questionnaire. Analyses were completed using linear mixed effects and regression models. More satisfaction in an intimate relationship related to both less subjective and objective cognitive decline over chemotherapy. Similarly, higher perceived social support related to less overall objective cognitive decline over chemotherapy, though this relationship was less robust than that observed with high couple satisfaction. Remarkably, circulating oxytocin decreased over chemotherapy but was only associated with partner duration and not with cognitive measures. This study suggests a potential benefit of social-directed interventions for the treatment of cognitive side effects of chemotherapy, either from an intimate partner or more generally. Furthermore, understanding biological mechanisms is important to develop novel preventative and interventional therapies to mitigate the adverse side effects of chemotherapy.

1. Introduction

Breast cancer is the most prevalent cancer in females in the United States with most patients receiving chemotherapy as part of their treatment (Siegel et al., 2024). Approximately one-third of these patients experience cognitive decline during and even after treatment

(Argyriou et al., 2011; Whittaker et al., 2022). Cognitive decline can reduce patient quality of life (Asher, 2011) and their ability to return to work (Schmidt et al., 2019), though it is more subtle than clinical cognitive “impairment” (e.g., dementia). Reductions in both subjective and objective cognitive function are common, although they often do not correlate (Hutchinson et al., 2012), and the types of cognitive

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deficits frequently include executive functioning, attention, decision-making, and everyday functioning. Thus, it is important to understand factors that drive or influence chemotherapy-associated cognitive decline so that preventative and therapeutic interventions can be identified.

Social relationships, particularly those of an intimate partner, have numerous health advantages reported outside of the cancer context, including both physical (e.g., reduction of cardiovascular disease, inflammation, and mortality rates) (Liu et al., 2019; Uchino, 2006) and psychological (e.g., buffering against stress responses) (Cohen, 2004; Robles et al., 2014) benefits. Furthermore, partners in more satisfying relationships report better well-being and health outcomes than those in unsatisfying relationships (Robles et al., 2014). Some benefits are also observed in the context of breast cancer, specifically with partners in satisfying relationships displaying attenuated cancer-related symptoms (e.g., pain, inflammation, gut permeability) (Kudel et al., 2008; Shrout et al., 2022, 2020). While perceived cognitive functioning in cancer survivors has not been reported with respect to relationship satisfaction, it has been positively associated with other social factors (e.g., general social support, number of living children, number of close friends) one year into survivorhood (Yang et al., 2022). This prompts the question of whether potential differences exist in the buffering roles of an intimate partner and other general social factors in modulating subjective and objective cognitive decline over chemotherapy.

The biological mechanisms underlying the health benefits of having an intimate partner are unknown, although positive social interactions are associated with increases in circulating oxytocin (OXT) (Carter et al., 1992; Lee et al., 2009). These circulating increases in OXT are transient but can modulate oxytocin receptor (OXTR) expression and thereby lead to potential long-lasting implications for health (Uvnäs-Moberg et al., 2014). OXTR is widely present throughout the brain and body (Zingg and Laporte, 2003), including in peripheral blood mononuclear cells (PBMCs), which consist of a variety of immune cells in circulation (e.g., lymphocytes and monocytes). Furthermore, OXT and OXTR may affect cognition and memory (Wirth, 2015) as abnormalities in OXT and OXTR signaling are associated with social and cognitive dysfunctions (Abramova et al., 2020).

Here, the relationships between couple satisfaction and chemotherapy-associated subjective and objective cognitive decline, in addition to the roles of other social factors, were assessed in a cohort of breast cancer patients. We hypothesized that higher relationship satisfaction associates with less chemotherapy-associated cognitive decline, and that this relationship is mediated by elevated circulating OXT and/or OXTR gene expression in PBMCs. Secondary analyses tested the roles of other social factors (e.g., general perceived social support, number of people in the household, number of dependents under 18) in these relationships.

2. Materials and methods

2.1. Participants

A longitudinal observational parent study (The Intelligit Study) was conducted at The Ohio State University Stefanie Spielman Comprehensive Breast Center in Columbus, Ohio, USA from 2019 to 2022 to assess the relationships among chemotherapy-induced gut microbiome disruption, inflammation, and cognitive decline (Otto-Dobos et al., 2024). Female participants ($n = 77$) were included if they were recently diagnosed with breast cancer (stage IA-IIIB) but had not yet begun their anti-neoplastic chemotherapy treatment plan. Exclusion criteria are noted in the parent study, but briefly, included a prior history of chemotherapy, cognitive impairment, or being greater than 80 years old. The present analyses primarily focused on a subset of partnered participants, as defined by participants who were married and/or cohabitating with an intimate partner ($n = 60$), a portion of whom completed a retrospective couple satisfaction questionnaire ($n = 48$).

Secondary analyses included subsets of unpartnered participants ($n = 17$), as defined by being single, in an intimate relationship but unmarried and not cohabitating, separated or divorced, or widowed. These secondary analyses included partnered and unpartnered participants who completed the retrospective social support questionnaire ($n = 60$). This study was approved by The Ohio State University Institutional Review Board and carried out in accordance with The Code of Ethics of the World Medical Association. All participants provided informed consent.

2.2. Study procedure and design

Details of the Intelligit study have been described previously (Otto-Dobos et al., 2024), but briefly, cognitive assessments and blood samples were collected at 3 timepoints: baseline (pre-chemotherapy), at the last chemotherapy infusion appointment (during chemotherapy; mean \pm SD: 3.2 ± 0.8 months; range: 2.0 – 4.9 months after baseline), and after a wash-out period (post-chemotherapy; mean \pm SD: 2.9 ± 1.7 months; range: 0.9 – 8.1 months after the last chemotherapy infusion). Cognitive testing was completed within 3 days of the participants' visits, and if it occurred on the day of the visit, it was completed prior to chemotherapy infusion. Blood samples were collected on the day of the visit coinciding with their regularly scheduled oncology appointment. Self-reported sociodemographic (age, menopausal status, number of people in the household and dependents under 18) and clinical variables from the medical chart (body mass index [BMI]) were collected at baseline. Furthermore, following the study (mean \pm SD: 13.2 ± 4.4 months, range: 5.6 – 33.6 months after final visit), participants completed retrospective, self-reported couple satisfaction and social support questionnaires and provided information regarding their relationship duration.

2.3. Cognitive assessments

Both subjective and objective cognitive functioning were assessed, as previously described (Otto-Dobos et al., 2024). The Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function questionnaire (v2.0 – Abilities Subset – Short Form 8a), which has been validated in patients with breast cancer (Jensen et al., 2017), was used to measure self-reported cognitive deficits in mental acuity, concentration, memory, and verbal fluency, and their effect on quality of life. In the 48 partnered participants, the sample sizes for subjective cognition were $n = 42$ for pre-chemotherapy, $n = 46$ for during chemotherapy, and $n = 42$ for post-chemotherapy.

To measure objective cognition, a battery of cognitive tests were used: Hopkins Verbal Learning Test – Revised (HVLTR), Controlled Oral Word Association Test (COWAT), Trial Making Test (TMT), and Digit Span Test (DST). One component of the HVLTR, the discrimination index (DI), is a measure of objective memory. Due to small sample size and consistent but subtle cognitive changes over these individual measures, “overall objective cognition” was assessed by combining the four objective cognitive measures into a cognition composite score using age- and education- normalized z-scores (Castellon et al., 2004; Phillips et al., 2010) created from published normative data, as previously described (Otto-Dobos et al., 2024). Furthermore, the overall objective cognition composite score allowed for simplified interpretations and reduced the total number of analyses. In the 48 partnered participants, the sample sizes for the overall cognition composite score were $n = 45$ for pre-chemotherapy, $n = 46$ for during chemotherapy, and $n = 43$ for post-chemotherapy.

2.3.1. Classifying clinically-meaningful cognitive decline

As recommended by the International Cognition and Cancer Task Force (Wefel et al., 2011) and as previously described (Otto-Dobos et al., 2024), a reliable change index (RCI) was calculated to determine clinically-meaningful changes in cognition over chemotherapy. Briefly,

the RCI was calculated using:

$$RCI = 1.64 \left(SE_{diff} \right), \text{ where } SE_{diff} = [2(SEM^2)]^{1/2} \text{ and } SEM = SD \left[(1 - r)^{1/2} \right]$$

where SE_{diff} is the standard error of difference, SEM is the standard error of measurement, SD is the standard deviation, and r is the test-retest reliability.

2.4. Measures of partner and social factors

Objective and subjective measures of the participants' intimate relationship and social factors were assessed. Self-reported couple satisfaction and social support were assessed using the Couples Satisfaction Index (CSI) and the Multidimensional Scale of Perceived Social Support (MSPSS), respectively. Participants completed both questionnaires retrospectively following the completion of the study and were asked to answer each of the questions with the following in mind: "thinking back to when you were receiving chemotherapy".

The CSI is a 32-item questionnaire, validated with high precision to assess relationship satisfaction (Funk and Rogge, 2007). Partnered participants were asked to rank statements such as "If I had my life to live over, I would marry (or live with) the same person" and "I have a warm and comfortable relationship with my partner" on a 6-point scale from "Completely True" to "Not at All True". Responses were summed together with possible scores ranging from 0 to 161 with any score below 104.5 indicating notable relationship dissatisfaction (Funk and Rogge, 2007). As an objective measure of intimate relationships, partner duration was also assessed retrospectively, by asking "At the time that you started chemotherapy, how long (in years) had you been romantically involved with your partner?"

The MSPSS is a 12-item questionnaire to assess perceived social support (Zimet et al., 1988). The questions within the MSPSS can be divided based upon three sources of perceived social support (family, friends, and a significant other). Partnered and unpartnered participants completed all sections of the questionnaire and were asked to rank statements such as "my family really tries to help me" and "I can talk about my problems with my friends" on a 7-point scale from "Very Strongly Disagree" to "Very Strongly Agree". Responses were summed together with possible scores ranging from 12 to 84 with any score above 61 indicating high perceived support (Zimet et al., 1988). Objective measures for social factors, including number of people in the household and number of dependents under 18 were also included from a socio-demographic questionnaire completed during the first visit.

2.5. Blood samples

At each timepoint, approximately 8–10 mL of peripheral blood was collected via venipuncture. The average time of the blood draw was at 10:30 AM but ranged between 7:30 AM and 4:45 PM. Plasma was isolated by centrifuging whole blood for 20 min at 1258 x g and 4 °C. PBMCs were isolated from whole blood via a Ficoll gradient and stored at –80 °C until analysis.

2.6. OXTR PBMC quantitative PCR

Total RNA was extracted from PBMCs using RNeasy Mini Kits (QIAGEN, Germantown, MD, USA) according to the manufacturer protocol with the added DNase 1 incubation step. cDNA was reverse transcribed using the qScript cDNA SuperMix (Quantabio, Beverly, MA, USA). Amplification was measured using the Taqman Master Mix and with human Taqman predesigned gene expression probes: *OXTR*

(Hs00168573_m1) and *18S* rRNA Endogenous Control (Catalog #: 4333760 T; ThermoFisher Scientific, Waltham, MA, USA). The Applied Systems QuantStudio 5 Real-Time PCR Machine (ThermoFisher Scientific, Waltham, MA, USA) was used. Gene expression was quantified using the comparative CT method ($2^{-\Delta\Delta CT}$) normalized to *18S*. In the 48 partnered participants, sample sizes for *OXTR* from PBMCs were $n = 30$ for pre- chemotherapy, $n = 32$ for during chemotherapy, and $n = 38$ for post-chemotherapy.

2.7. Circulating OXT ELISA

Circulating OXT was measured in plasma samples from each time-point using the OXT Enzyme Linked Immunoassay (ELISA) Kit following the manufacturer's protocol (Arbor Assays; Ann Arbor, MI, USA; cat. # X016-1EA, lot # 22A079). The reported sensitivity for this kit is 17.0 pg/mL with the limit of detection at 22.9 pg/mL. The highest standard run was 1600 pg/mL, and all samples were within the range of detection. Plasma samples were diluted 1:1 in assay buffer and were not extracted, based on previous reports (Carter, 2023; Carter et al., 2007). All samples were run in duplicate with average intra- and inter-assay CVs both < 10 %. Each participant's plasma samples across all 3 time-points were measured on the sample plate. In the 48 partnered participants, sample sizes for circulating OXT were $n = 43$ for pre-chemotherapy, $n = 46$ for during chemotherapy, and $n = 45$ for post-chemotherapy. Given that each participant's blood sample was collected alongside routine lab work for their oncology appointment, we presume to be measuring basal OXT levels.

2.8. Data analysis

Linear mixed effects models were used to assess changes in cognition measures, circulating OXT, and *OXTR* gene expression over chemotherapy treatment (in separate models). Categorical time (pre-, during, and post-chemotherapy) was included as a fixed effect. All models included a random intercept for participant to account for within-subject correlation over time, and models for individual OXT markers additionally included a random effect for plate. With the few timepoints and lack of a cancer-free control group, the analyses did not accommodate for response shifts in the subjective cognitive measure over time. Based on the deliberate study design, only three participants received tamoxifen during the study (at the post-chemotherapy timepoint, and one participant at the pre-chemotherapy timepoint); therefore, it was not controlled for in the analyses. Due to no other a priori identified potential confounders, initial models were not adjusted for additional variables; subsequent analyses included age, education, days since the last chemotherapy infusion, and household income as described in the Results. Regression models were used to quantify associations between change scores and relationship satisfaction and perceived social support. Change scores were calculated using available data, so if a participant was missing a value at a certain timepoint, then a change value would not be generated incorporating that timepoint. Change scores of a positive value indicate an increase and models controlled for baseline scores to account for regression to the mean. Plate effects were not controlled for in change scores. Furthermore, the high collinearity between *OXTR* change scores and *OXTR* baseline resulted in instability of results, so baseline *OXTR* was not included as a covariate. Additionally, due to small values for *OXTR* change scores, values were multiplied by 10,000. Both OXT and *OXTR* change scores had approximately normal distributions and thus raw values were used in regression models; however, analyses using baseline values of OXT and *OXTR* used natural log-transformed values (ln). All analyses were conducted using R (version 4.4.1, Boston, MA).

3. Results

3.1. Participant characteristics

Participant demographic information and clinical characteristics are provided in Table 1. Among the 48 female, partnered participants (married and/or cohabitating with an intimate partner) who completed the couples satisfaction questionnaire, the average age was 48 years (SD: 11.3; range: 28 – 73) and the average BMI was 28 (SD: 5.6; range: 18 – 43; Table 1). Most of the participants were pre-menopausal (60.4 %), white (97.9 %), and non-Latin/Hispanic (95.8 %). Fifty percent of participants were diagnosed with stage 1 breast cancer and 41.7 % with stage 2. These characteristics are consistent with the demographic and clinical information in the parent cohort of 77 participants (Otto-Dobos et al., 2024). Of the partnered participants, most were married and cohabitating (91.7 %), with four participants unmarried but cohabitating (8.3 %). Overall, there was a broad range of relationship satisfaction (mean \pm SD: 126 \pm 28.1, range: 44 – 161), and most (83 %) were above the threshold for relationship satisfaction, which is 104.5 (Funk and Rogge, 2007). The average relationship duration was 19 years (SD: 11.7; range: 1 – 50 years).

3.2. Associations between partner factors and cognitive outcomes

Within the 48 partnered participants, subjective cognition measured via the PROMIS questionnaire decreased from pre- to during chemotherapy ($p < 0.01$, Supplementary Figure 1A). The subjective cognition trajectory was not associated with age, education, or menopausal status ($p > 0.05$). An age- and education- normalized composite score that combines all four objective cognitive tests, referred to as “overall

objective cognition”, did not significantly change over chemotherapy ($p > 0.05$, Supplementary Figure 1B). The trajectory of the overall objective cognition composite score was significantly associated with menopausal status ($p < 0.01$, data not shown), such that premenopausal status was associated with a smaller objective cognition composite score. However, the HVLt discrimination index, which is a measure of objective memory, decreased from both pre- to post-chemotherapy ($p < 0.001$, Supplementary Figure 1C) and during to post-chemotherapy ($p < 0.0001$) and was not associated with menopausal status. These findings are consistent with the parent study (Otto-Dobos et al., 2024).

To understand the potential protective role of an intimate partner in chemotherapy-associated cognitive decline, associations between these three cognitive outcomes (subjective cognition, overall objective cognition score, and HVLt DI) and partner satisfaction, as well as other partner factors, were assessed. Indeed, scores from the couples satisfaction index were associated with the changes in all three cognitive measures over chemotherapy (Table 2). First, higher couple satisfaction was associated with less subjective cognitive decline from pre- to post-chemotherapy (slope: 0.11, SE: 0.04, $p < 0.01$) and from during to post-chemotherapy (slope: 0.11, SE: 0.03, $p < 0.01$), even when age, education, and time since last chemotherapy infusion were included as covariates. Thirteen participants (27 %) from pre- to post-chemotherapy, and six participants (14 %) from during to post-chemotherapy experienced a clinically-meaningful decline, as determined by the reliable change index. Similarly, participants with higher couple satisfaction displayed attenuated reductions in overall objective cognition and the HVLt DI from pre- to post-chemotherapy (slope: 0.0058, SE: 0.003, $p < 0.05$; and slope: 0.025, SE: 0.01, $p < 0.01$, respectively) and from during to post-chemotherapy (slope: 0.0060, SE: 0.003, $p < 0.05$; and slope: 0.023, SE: 0.01, $p < 0.05$, respectively), even when time since last chemotherapy infusion was included in the analyses. Eleven participants (25 %) had a clinically-meaningful decline, as determined by the RCI, in overall objective cognition from pre- to post-chemotherapy; a clinically-meaningful decline was absent in the HVLt DI across all timepoints. All these associations held when controlling for perceived general social support, except for the association between couple satisfaction and overall objective cognition from pre- to post-chemotherapy ($p > 0.05$). Together, these data indicate that being more satisfied in an intimate relationship was related to both less subjective and objective cognitive decline over chemotherapy, independent of perceived general social support. Duration of intimate partnership was not associated with changes in any of the cognitive variables over chemotherapy ($p > 0.05$ for all), even when age, education, and time since last chemotherapy infusion were included as covariates.

Next, to explore the role of simple partner “status” (i.e., marital status) in chemotherapy-associated cognitive decline, regardless of relationship satisfaction or duration, analyses incorporating both the 60 partnered and 17 unpartnered participants were conducted. While partner status did not moderate subjective cognition over chemotherapy ($p > 0.05$ for all), there were significant interactions between partner status and the overall objective cognition composite score as well as the HVLt DI ($p < 0.05$, data not shown). There were not meaningful differences in the trajectories of the overall objective cognition composite score by partner status; although, partnered participants had higher HVLt DI during chemotherapy which resolved post-chemotherapy.

3.3. Associations between other social factors and cognitive outcomes

After observing the possible protective effects of having a satisfying intimate relationship, the roles of other social factors, outside of one’s romantic partnership, were assessed with respect to chemotherapy-associated cognitive decline. The majority of the 48 partnered participants had high perceived general social support (mean \pm SD: 75 \pm 14.2; range: 12 – 84) as measured via the MSPSS questionnaire, which considers support from three sources (family, friends, and a significant

Table 1
Partnered participant demographic information and clinical characteristics (N = 48).

	Number (%)
Age	
< 45	21 (43.8 %)
45–55	15 (31.3 %)
> 55	12 (25.0 %)
Menopausal Status	
Pre-menopausal	29 (60.4 %)
Post-menopausal	19 (39.6 %)
Race	
White	47 (97.9 %)
Unknown/Not reported	1 (2.1 %)
Ethnicity	
Latin/Hispanic	2 (4.2 %)
Non-Latin/Hispanic	46 (95.8 %)
BMI	
< 25	16 (33.3 %)
25–30	19 (39.6 %)
\geq 30	13 (27.1 %)
Partner status	
Married and cohabitating	44 (91.7 %)
Married but not cohabitating	0 (0 %)
Not married but cohabitating	4 (8.3 %)
Household Income	
less than \$50,000	2 (4.2 %)
\$50,000–\$150,000	29 (60.4 %)
over \$150,000	14 (29.2 %)
Not reported	3 (6.3 %)
Highest level of education	
High School	2 (4.2 %)
Technical/Associates	9 (18.8 %)
College graduate	37 (77.1 %)
Cancer Stage	
I	24 (50.0 %)
II	20 (41.7 %)
III	4 (8.3 %)

Note: All participants were married and/or cohabitating with an intimate partner.

Table 2
Associations between partner factors and cognitive outcomes.

Outcome	Pre- to During Chemotherapy			Pre- to Post-Chemotherapy			During to Post-Chemotherapy		
	B	SE	p value	B	SE	p value	B	SE	p value
Couple Satisfaction									
Subjective Cognition	0.014	0.04	0.71	0.11	0.04	0.009 *	0.11	0.03	0.002 *
Overall Objective Cognition	0.00089	0.003	0.75	0.0058	0.003	0.03 *	0.0060	0.003	0.03 *
HVLT DI	0.0016	0.004	0.68	0.025	0.01	0.006 *	0.023	0.01	0.02 *
Partner Duration (years)									
Subjective Cognition	0.14	0.10	0.17	0.12	0.12	0.30	0.044	0.11	0.69
Overall Objective Cognition	0.010	0.01	0.14	0.011	0.01	0.15	0.0091	0.01	0.23
HVLT DI	0.0085	0.01	0.38	0.035	0.02	0.09	0.028	0.02	0.21

B = slope. SE = standard error. DI = discrimination index. N = 41–46. Bold and * = p < 0.05.

other). Objectively, partnered subjects also had an average of 3.5 people in their household (SD: 1.5; range: 2 – 9) and an average of 2.1 dependents under the age of 18 (SD: 0.96; range: 0 – 4).

Perceived social support from the MSPSS was positively associated with the changes in overall objective cognition and HVLT DI from pre- to during chemotherapy, such that having higher perceived social support, similar to high partner satisfaction, was related to less overall objective cognitive decline over chemotherapy (slope: 0.014, SE: 0.01, p < 0.05 and slope: 0.021, SE: 0.01, p < 0.01, respectively; Table 3). Using the RCI, five participants (11 %) had a clinically-meaningful decline in the overall composite score from pre- to during chemotherapy. Following this same pattern but over a delayed timescale, perceived social support tended to also be positively associated with the change in overall objective cognition and HVLT DI from pre- to post-chemotherapy (slope: 0.0085, SE: 0.01, p = 0.10 and slope: 0.031, SE: 0.02, p = 0.097, respectively), even when time since chemotherapy was included in the analyses. In contrast, perceived social support was not related to the changes in subjective cognition over any timepoints (p > 0.05 for all), even when controlling for age, education, and time since chemotherapy. All the significant associations held even when controlling for couple satisfaction in these analyses (p < 0.05 for all). Together, these data indicate that having greater perceived social support is related to less objective cognitive decline over chemotherapy, though the potential protective role may be more transient than that of a highly satisfying intimate partnership and not beneficial for perceived cognitive function. Of note, the associations between perceived social support and cognitive measures remained the same when the component of social support due to a significant other was selectively removed from the analyses, leaving only support from friends and family. Additionally, the associations also held when social support from a significant other was assessed independently (data not shown).

Next, the objective social factors (number of people in the household and number of dependents under the age of 18) were examined. Higher numbers of individuals in the participants' household were associated

with greater decline in overall objective cognition from during to post-chemotherapy (slope: -0.14, SE: 0.05, p < 0.01), and tended to be associated from before to after chemotherapy completion (slope: -0.11, SE: 0.05, p = 0.06; Table 3). There tended to be an association between greater number in household and worse HVLT DI from before to during chemotherapy (slope: -0.14, SE: 0.07, p = 0.05) and with subjective cognition from before to after chemotherapy completion (slope: -1.4, SE: 0.79, p = 0.08), following the same relationship as the composite score. There were no associations between number in household and the changes in subjective cognition and the HVLT DI at other timepoints (p > 0.05 for all). Similarly, greater number of dependents under 18 was associated with a greater decline in overall objective cognition from during to post-chemotherapy (slope: -0.15, SE: 0.06, p < 0.05), and in subjective cognition from pre- to post-chemotherapy (slope: -1.90, SE: 0.92, p < 0.05). When age and education were included as covariates for the subjective cognition outcome, the association with the number of dependents under 18 was no longer statistically significant (p > 0.05). Finally, there tended to be an association with greater number of dependents under 18 and greater decline in overall objective cognition and HVLT DI from before to after chemotherapy completion (slope: -0.10, SE: 0.06, p = 0.096; and slope: -0.38, SE: 0.21, p = 0.08, respectively). When household income and time since last chemotherapy infusion were included as covariates, all the relationships between these objective social factors and objective cognition over chemotherapy were no longer statistically significant (p > 0.05, data not shown), primarily driven by household income.

Exploratory analyses adding the 12 unpartnered participants that also completed the MSPSS (i.e., perceived social support) questionnaire into the analyses revealed that the associations between social factors and cognition over chemotherapy were similar to the findings noted above in the cohort of 48 partnered participants (data not shown), with some exceptions. First, the association between perceived social support and the change in HVLT DI from before to during chemotherapy was no longer significant (p > 0.05, data not shown) and the same happened to

Table 3
Associations between social factors and cognitive outcomes.

Outcome	Pre- to During Chemotherapy			Pre- to Post-Chemotherapy			During to Post-Chemotherapy		
	B	SE	p value	B	SE	p value	B	SE	p value
Perceived Social Support									
Subjective Cognition	-0.012	0.07	0.88	0.065	0.08	0.44	0.090	0.07	0.23
Overall Objective Cognition	0.014	0.01	0.01 *	0.0085	0.01	0.10	-0.00034	0.01	0.95
HVLT DI	0.021	0.01	0.004 *	0.031	0.02	0.097	0.010	0.02	0.62
Number in Household									
Subjective Cognition	-0.26	0.71	0.72	-1.4	0.79	0.08	-0.94	0.72	0.20
Overall Objective Cognition	-0.0036	0.06	0.95	-0.11	0.05	0.06	-0.14	0.05	0.0048 *
HVLT DI	-0.14	0.07	0.05	-0.29	0.18	0.12	-0.12	0.19	0.55
Number of Dependents under 18									
Subjective Cognition	0.21	0.86	0.81	-1.90	0.92	0.046 *	-1.51	0.86	0.09
Overall Objective Cognition	0.0077	0.07	0.91	-0.10	0.06	0.096	-0.15	0.06	0.012 *
HVLT DI	-0.13	0.09	0.16	-0.38	0.21	0.08	-0.20	0.23	0.38

B = slope. SE = standard error. DI = discrimination index. N = 42–46. Bold and * = p < 0.05.

the trends with overall objective cognition and HVLTI DI from before to after chemotherapy completion ($p > 0.1$, data not shown).

Finally, analyses incorporating all 77 partnered and unpartnered participants, even those that did not complete the MSPSS, were conducted to assess associations between the objective social factors and chemotherapy-associated cognitive decline. The associations described above between higher number of individuals in the participants' household and worse overall objective cognition over chemotherapy remained the same. Additional associations between higher number in household and worse HVLTI DI were observed from pre- to post-chemotherapy and during to post-chemotherapy (slope: -0.37 , SE: 0.14 , $p < 0.01$ and slope: -0.33 , SE: 0.14 , $p < 0.05$, respectively), such that participants with more people in their household were associated with worse objective cognition over chemotherapy. Furthermore, new associations were detected between the number of dependents under 18 and subjective cognition. Higher number of dependents under 18 was associated with worse subjective cognition from during to post-chemotherapy (slope: -1.55 , SE: 0.69 , $p < 0.05$).

3.4. Trajectories of OXT and OXTR over chemotherapy treatment

After establishing relationships between social factors and chemotherapy-associated cognitive decline, the potential mediating roles of circulating OXT concentrations and/or OXTR gene expression in PBMCs were assessed. First, the trajectories of OXT and OXTR over chemotherapy were examined (Fig. 1). Plasma OXT decreased during chemotherapy ($p < 0.01$, Fig. 1A) but returned to levels comparable to baseline after the chemotherapy washout period. PBMC OXTR tended to increase from pre- to during chemotherapy ($p = 0.07$, Fig. 1B) and significantly increased from pre- to post-chemotherapy ($p < 0.01$). In analyses incorporating all 77 unpartnered and partnered participants, there were no statistically-significant differences in the trajectories or cross-sectional measurements of the plasma OXT or PBMC OXTR between the two partner statuses.

3.5. Associations between partner and other social factors and OXT/OXTR

There were no associations between higher couple satisfaction and baseline OXT or the changes in OXT over chemotherapy treatment ($p > 0.05$; Supplementary Table 1). Longer relationships were associated with higher OXT concentrations at baseline (slope: 0.012 , SE: 0.006 , $p < 0.05$), as well as decreased OXT concentrations over chemotherapy (slope: -1.6 , SE: 0.727 , $p < 0.05$; Table 4). Given the high collinearity between partner duration and age, age was subsequently assessed in this model. While older age, independent of partner duration, was associated with decreased circulating OXT from pre- to during chemotherapy (slope: -0.008 , SE: 0.004 , $p < 0.05$), this

Table 4

Associations between partner duration and OXT.

Outcome	Partner Duration (years)		
	B	SE	p value
Baseline OXT	0.012	0.006	0.032 *
Change in OXT from Pre- to During Chemotherapy	-1.6	0.73	0.035 *
Change in OXT from During to Post-Chemotherapy	3.8	2.37	0.12

B = slope. SE = standard error. N = 40–41. Bold and * = $p < 0.05$.

association went away when partner duration was included in the model ($p > 0.05$, data not shown) and the association with partner duration remained as a trend ($p = 0.08$, data not shown). Furthermore, age was neither associated with baseline OXT concentrations ($p > 0.05$, data not shown) nor the change in OXT from during to post-chemotherapy ($p > 0.05$, data not shown). In terms of OXTR gene expression, neither couple satisfaction nor partner duration were associated with baseline OXTR or changes in OXTR over chemotherapy ($p > 0.05$ for all; Supplementary Table 2), even when time since last chemotherapy infusion was included as a covariate in the analyses.

With respect to social support outside of an intimate partner, neither perceived general social support nor the objective social support measures (numbers of people in the household and dependents under 18) were significantly associated with baseline OXT or any of the changes in OXT over chemotherapy timepoints ($p > 0.05$ for all; Supplementary Table 1), even when time since chemotherapy was included in the analyses. However, higher perceived general social support tended to be associated with reductions in OXTR PBMC gene expression from pre- to during chemotherapy (slope: 0.003 , SE: 0.001 , $p = 0.07$). The objective social support measures were also not associated with baseline OXTR or any of the changes in OXTR over chemotherapy ($p > 0.05$ for all; Supplementary Table 2), even when time since chemotherapy was included as a covariate. Finally, exploratory analyses of simple partner status indicated that partner status did not moderate the changes in OXT or OXTR at baseline or over chemotherapy ($p > 0.05$, data not shown).

3.6. Associations between OXT/OXTR and cognitive outcomes

The changes in plasma OXT concentrations and OXTR gene expression over chemotherapy were not associated with the changes in subjective or objective cognitive measures over chemotherapy ($p > 0.05$ for all; Supplementary Table 3), even when time since chemotherapy was included in the analyses.

4. Discussion

The goal of this study was to investigate associations between chemotherapy-induced cognitive decline and couple satisfaction, in addition to other social factors, in female patients with breast cancer, as well as explore OXT signaling as a potential underlying mechanism. Consistent with our hypothesis, higher couple satisfaction was associated with less chemotherapy-related cognitive decline. Independently, chemotherapy decreased circulating OXT, although this change did not mediate the relationship between couple satisfaction and chemotherapy-associated cognitive function. This study expanded upon previous work by assessing variables longitudinally over chemotherapy treatment, measuring both subjective and objective cognitive performance and social factors, and investigating a proposed underlying biological mechanism of action.

To our knowledge, this is the first time couple satisfaction has been studied with chemotherapy-associated cognitive decline. The potential protective effects of couple satisfaction in this cohort of breast cancer patients is consistent with other studies linking relationship satisfaction with other positive health benefits (e.g., decreased stress, inflammation, depressive systems and fatigue) during cancer and chemotherapy (Shrout et al., 2021, 2020). While the majority of participants did not

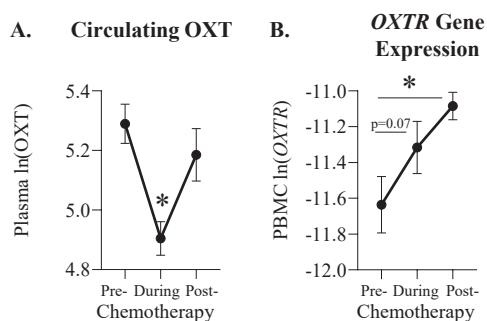


Fig. 1. OXT and OXTR over chemotherapy treatment. Trajectories of A) circulating OXT and B) OXTR gene expression in PBMCs over chemotherapy treatment. Results shown are mean \pm standard error from linear mixed effects models. * $p < 0.05$.

experience clinically-meaningful cognitive “impairment” (e.g., dementia), the cognitive decline that they did experience is likely to impact their daily functioning and quality of life (Asher, 2011). Together, this suggests that satisfaction in an intimate relationship is robustly beneficial for various side effects of chemotherapy.

In parallel, having greater levels of perceived social support, beyond an intimate relationship, was also associated with attenuated chemotherapy-associated cognitive decline. This finding is in line with another study in breast cancer survivors (Yang et al., 2022) and is consistent with reports of other psychological outcomes in cancer patients (e.g., depression (Fisher et al., 2021), anxiety (Escalera et al., 2019), quality of life (Hofman et al., 2021), and coping strategies (Calderon et al., 2021)), albeit the previous observations do not occur acutely during chemotherapy treatment. This study measured perceived social support, which is more subject to individual differences and relies on perceptions of availability or satisfaction of support rather than quantitative measures of actual received support. Received support may more accurately represent supportive environments and behaviors, though it can be less predictive of outcomes (Haber et al., 2007). Similarly, perceived (i.e., subjective) measures of social support can differ from objective social factors (Solomon et al., 1987), which was observed in the present study. For example, perceived social support was potentially acutely protective of cognition during chemotherapy, whereas objective measures of social factors (i.e., number of people in the household and dependents under 18) related to worse cognition over chemotherapy. These differences are similar to another study that found that cancer patients one year into survivorship had lower levels of cognitive function when they had greater than 6 living children, despite the protective effects of other social factors (e.g., perceived social support) (Yang et al., 2022). Furthermore, lower socioeconomic status seemed to drive the relationship between larger families and worse chemotherapy cognitive symptoms, although other factors associated with larger families may also contribute (e.g., psychological stress) (Nye et al., 1970).

While both high couple satisfaction and perceived social support appeared protective against chemotherapy-associated cognitive decline, the effects of high couple satisfaction were more robust and enduring than the latter. These findings could be due to intimate partners often being the primary source of social support (Rivers and Sanford, 2020), and thus having a greater impact on the participant’s cognitive outcomes. Interestingly, most studies do not directly compare the potential protective role of an intimate partner with other general social factors, including that of family and friends (Kroenke et al., 2013; Kudel et al., 2008; Shrout et al., 2021). In this study, the effects of couple satisfaction and perceived social support were independent of each other, as the statistical significance still held even when controlling for each other. Another unique observation in the present study was that the subjective and objective cognitive measures were both similarly associated with couple satisfaction across the same time points and with the same direction, though this was not the case for simple marital status or the other general social factors. Often, subjective and objective cognition function over chemotherapy do not correlate with each other (Hutchinson et al., 2012). Although, when both types of assessment do agree, it tends to be in breast cancer patients, as opposed to other types of cancer, and if the objective cognitive measurements assessed memory (Hutchinson et al., 2012); both were the case in this study. Lastly, one subset of the MSPSS questionnaire assessing perceived social support included support from a “special person”. A study found that respondents may indicate this “special person” to be 1–3 different people (e.g., spouse, children, parents), though participants who were married almost always indicated their spouse (Prezza and Pacilli, 2002). In the present study, there was no confirmation that participants were indicating the “special person” to be their intimate partner, which could further explain the differing associations between the couples satisfaction index and the MSPSS questionnaire.

While the protective effects of general social support are well-

reported, investigation of potential mechanisms are not. Remarkably, this study is the first to study and report changes in circulating OXT and OXTR gene expression in PBMCs over chemotherapy. Indeed, research involving OXT and breast cancer has instead focused on its potential involvement in tumor development and progression (Liu et al., 2020). Here, chemotherapy reduced circulating OXT concentrations acutely during chemotherapy. This finding is consistent with reductions in another circulating hormone (estradiol) due to chemotherapy treatment, attributed to chemotherapy-induced damage to the ovaries (Codacci-Pisanelli et al., 2017), but inconsistent with the reports of circulating OXT increasing with stressors (Carter, 2022). Given that both estradiol and OXT are regulated by the hypothalamus and pituitary gland, these data suggest that chemotherapy may be acting at these upstream tissues. Chemotherapy-induced reductions in OXT may have broader implications for health (Liu et al., 2022; Tom and Assinder, 2010) beyond cognitive function and should be investigated further. Interestingly, elevated plasma OXT levels in breast cancer patients have been previously reported cross-sectionally compared to healthy controls (Ariana et al., 2019), though none of the participants were undergoing chemotherapy. The impact of chemotherapy on OXTR gene expression in PBMCs was more modest, although consistent with the biological phenomenon that when a ligand decreases, the receptor increases (Gimpl and Fahrenholz, 2001). An in vitro study reported an increase in the expression of OXTR in PBMCs due to inflammation (Szeto et al., 2017), which is likely consistent with the present elevation in OXTR given that chemotherapy increases circulating markers of inflammation in the parent study (Otto-Dobos et al., 2024). Much like OXT, existing studies of OXTR in breast cancer focus instead on tumorigenesis (Ariana et al., 2019; Behtaji et al., 2021).

Baseline circulating OXT and the change in OXT over chemotherapy were associated with partner duration, but not with any other social factors. In contrast, another study found an association between high marital quality and higher plasma OXT (Holt-Lunstad et al., 2014), although other studies report elevated OXT in people with relationship distress (Taylor et al., 2006, 2010; Turner et al., 1999). These differences could be due to the complexity and often paradoxical nature of OXT signaling or differences in OXT measurement. The present study measured presumed basal levels of OXT, whereas other studies tend to measure stimulated OXT, such as after hand holding with their intimate partner (Holt-Lunstad et al., 2014). Furthermore, while OXT is thought to be important for the formation of intimate relationships (Schneiderman et al., 2012), there is not much evidence linking OXT to relationship duration (VanLaningham et al., 2001). Associations between social factors and OXTR gene expression were absent in this study, despite some evidence that genetic variations within the OXTR gene can relate to relationship satisfaction and other social factors (Kanthak et al., 2016; Mattson et al., 2019; Monin et al., 2019). Finally, circulating OXT and OXTR gene expression in PBMCs were not related to cognitive functioning over chemotherapy. Much is still unknown about how OXT affects human cognition, though prior studies have found OXT to play a role in social cognition, including memory and social behavior (Heinrichs et al., 2009; Ross and Young, 2009), while others have found OXT to impair memory and labeled it as an “amnesic peptide” (Herzmann et al., 2012). Overall, further investigation of the role of OXT signaling in the context of chemotherapy treatment and resulting side effects is warranted.

Strengths of this study include that it investigated a potential biological mechanism and had a longitudinal design. The latter allowed for assessment of both subjective and objective cognitive outcomes throughout chemotherapy, as well as before chemotherapy commenced; baseline is often absent in other studies (Yang et al., 2022). Furthermore, this study assessed multiple social factors objectively and subjectively and observed a broad range of values. Limitations of this study include a lack of cancer-free controls and some drawbacks measuring circulating OXT and social factors. For example, OXT measurement is transient and may have been affected by slightly varying times of day of blood

collection (Amico et al., 1989) or varying environments. Additionally, circulating OXT is not representative of brain OXT in the context of cognition (Handlin et al., 2023). Social factors were only assessed at one time point and retrospectively, which may reduce accuracy. While relationship satisfaction is generally considered relatively stable over time (Karney and Bradbury, 2020), the cancer experience, and associated cognitive changes specifically, may be disruptive (Valente et al., 2021). Lastly, this study did not assess the potential role of chemotherapy-induced ovarian failure, which may contribute to the results (Vearncombe et al., 2011).

Taken together, this study suggests a potential benefit of social support-targeted interventions (Leung et al., 2015) in the treatment of subjective and objective cognitive side effects of chemotherapy, either from an intimate partner or more generally. Understanding biological mechanisms is necessary to develop novel preventative and interventional therapies to mitigate the adverse side effects of chemotherapy. Future studies should explore additional biological mechanisms linking social support to health outcomes, including investigating changes in cardiovascular, neuroendocrine, and immune function (Uchino, 2006).

CRedit authorship contribution statement

Otto-Dobos Lauren D: Writing – review & editing, Validation, Project administration, Data curation. **Adarkwah Yiadom Seth:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Pyter Leah M:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Seng Melina M:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Investigation, Formal analysis, Data curation. **Andridge Rebecca R:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Glasper Erica R:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Way Baldwin M:** Writing – review & editing, Resources, Methodology. **Wesolowski Robert:** Writing – review & editing, Resources. **Dawson Erica:** Methodology, Writing – review & editing. **Stover Daniel G:** Writing – review & editing, Resources. **Sudheendra Preeti K:** Resources, Writing – review & editing. **Gatti-Mays Margaret E:** Writing – review & editing, Resources. **Williams Nicole O:** Writing – review & editing, Resources. **Sardesai Sagar D:** Writing – review & editing, Resources.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psyneuen.2025.107428](https://doi.org/10.1016/j.psyneuen.2025.107428).

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