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Research Paper

A pull to be close: The differentiating effects of oxytocin and grief stimulus type on approach behavior in complicated grief

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ABSTRACT

Theoretical models of complicated grief (CG) suggest that maladaptive motivational tendencies (e.g., perseverative proximity-seeking of the deceased; excessive avoidance of reminders) interfere with a person's ability to recover from their loved one's death. Due in part to conflicting evidence, little mechanistic understanding of how these behaviors develop in grief exists. We sought to (1) identify behavioral differences between CG and non-CG groups based on approach/avoidance bias for grief-, deceased-, and social-related stimuli, and (2) test the role of the neuropeptide oxytocin in shaping approach/avoidance bias. Widowed older adults with ($n = 17$) and without ($n = 22$) CG completed an approach/avoidance task measuring implicit bias for both personalized and non-specific grief-related stimuli (among other stimuli). In a double-blinded, randomized, counterbalanced design, each participant attended both an intranasal oxytocin session and a placebo session. Aims were to (1) identify differential effects of CG and stimulus type on implicit approach/avoidance bias [placebo session], and (2) investigate interactive effects of CG, stimulus type, and oxytocin vs. placebo on approach/avoidance bias [both sessions]. In the placebo session, participants in the non-CG group demonstrated an approach bias across all stimuli. Intranasal oxytocin had an overall slowing effect on the CG group's response times. Further, oxytocin decreased avoidance bias in response to photos of the deceased spouse in the CG group only. Findings support the hypothesis that oxytocin has a differential effect on motivational tendency in CG compared to non-CG, strengthening evidence for its role in CG. Findings also emphasize the need to consider differences in personalized vs. generic stimuli when designing grief-relevant tasks.

Introduction

Complicated grief (CG), similar to Prolonged Grief Disorder in DSM-5-TR (Moran, 2020) and ICD-11 (Maercker et al., 2013), affects an estimated one in 10 bereaved individuals (Lundorff et al., 2017). Symptoms include intense grief, yearning for the deceased, functional impairment, and identity disruption. People with CG are more reactive to external reminders and internally generated cues (e.g., memories or intrusive thoughts) related to the deceased or their death than those with Non-CG, leading to conceptualizations of CG focusing on dysregulated approach/avoidance motivation (Boddez, 2018; LeRoy et al., 2019; Maccallum et al., 2015; Maccallum & Bryant, 2019; Shear et al., 2007). Approach and avoidance behaviors are not pathological features of grief per se. However, they become maladaptive in CG when activities like reminiscing about the deceased (i.e., excessive approach) or avoiding all reminders of the deceased or their death (i.e., excessive avoidance) create protracted distress, interfere with functioning, or prevent integration of the loss (Boelen, 2016; Boelen et al., 2006; LeRoy et al., 2019; Maccallum & Bryant, 2013).

A recent review theorized CG is a reward-based syndrome heavily involving the oxytocin signaling system (Kakarala et al., 2020). Oxytocin, a neuropeptide with a central role in affiliative/approach behavior, social reward, and pair-bonding (Bosch et al., 2016; Harari-Dahan & Bernstein, 2014; Shamay-Tsoory & Abu-Akel, 2016), may play a key role in motivational functions in CG. Neuroimaging studies further strengthen the rationale for oxytocin's involvement in CG.

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Individuals with CG demonstrate increased activity in the nucleus accumbens component of the ventral striatum, a known area of interaction between OT, dompamine, and endogenous opioids, when viewing images of the deceased (O'Connor et al., 2008). In other disorders, intranasal oxytocin modulates approach/avoidance behavior through its effects on reward and threat neurocircuitry (Harari-Dahan & Bernstein, 2014). Therefore, intranasal oxytocin is well-suited as an experimental manipulation to probe motivational tendencies in CG.

For the present study, we considered multiple ways that approach and avoidance might be related to oxytocin in CG. First, intranasal oxytocin may increase approach behavior (Preckel et al., 2014), based on the hypothesis that the oxytocin system maintains the reward value of the deceased and thus may perpetuate futile proximity-seeking behavior in CG (O'Connor et al., 2008). Alternatively, oxytocin may decrease approach motivation for the deceased, in order to support a bereaved person's ability to redirect their attachment needs toward living loved ones or new relationships (Bryant et al., 2021). Second, intranasal oxytocin might increase avoidance behavior, as oxytocin has been shown to heighten reactivity to negative social stimuli (Hurlemann & Scheele, 2016). Indeed, participants with severe CG symptoms demonstrated greater amygdala and reward circuitry recruitment during subconscious processing of sad faces than non-bereaved participants with major depressive disorder (Bryant et al., 2021). On the other hand, oxytocin may decrease avoidance, as it has documented anxiolytic and prosocial effects (MacDonald & MacDonald, 2010), including decreased amygdala hyperreactivity (Koch et al., 2016; Radke et al., 2017).

Three previous studies have measured implicit behavioral approach and avoidance in bereavement using grief-related variants of the Approach Avoidance Task (AAT; Rinck & Becker, 2007). In the first study, adults with CG showed a relative approach bias for non-specific grief-relevant scenes (e.g., grave, funeral) (Maccallum et al., 2015), and in the second, for the names of their deceased loved one and a living attachment figure (but also the name of a stranger) (Maccallum & Bryant, 2019). Findings suggest an approach bias in CG for reminders of the deceased, consistent with the idea that CG is in part driven by a proximity-seeking attachment response (Boddez, 2018; LeRoy et al., 2019; Shear et al., 2007), but also for social stimuli in general.

Clinical and empirical evidence supports a significant role of cognitive and behavioral avoidance in CG as well (Baker et al., 2016; Boelen et al., 2006; Shear et al., 2007). The "rumination-as-avoidance" hypothesis posits that engaging in perseverative cognitive activity affords people with CG a way to avoid the painful emotional reality of the loss (Stroebe et al., 2007). In the third study, using a different variant of the grief AAT, Eisma and colleagues (Eisma et al., 2015) found that bereaved individuals who tended to ruminate more showed a greater avoidance bias and shorter gaze fixation to photos of the deceased paired with death-related words. Although they did not find a relationship between CG and behavior on the AAT, high-ruminators as a group were significantly higher in CG symptoms (Eisma et al., 2015). In a 2021 review, Eisma and Stroebe summarize results of laboratory studies of loss-related behavioral avoidance in grief as "equivocal" (Eisma and Stroebe, 2021).

How can we reconcile these findings linking grief severity to both approach and avoidance of grief-relevant stimuli? One possible explanation is that all three studies used different grief-related stimuli, making identification of optimal cues to measure avoidance in a laboratory setting challenging (Esima & Stroebe, 2021). Personally-relevant stimuli (photos, names), compared to non-specific bereavement-related stimuli, may evoke different associations and emotional responses, but have not yet been directly compared.

In the present study, we investigated approach/avoidance behavior in widowed older adults with and without CG, using an AAT variant that included the full range of stimuli images: the deceased spouse, a living loved one, a stranger, non-specific grief stimuli (e.g., grave, casket), and neutral images. Moreover, to test whether the oxytocin system is involved differentially in CG and non-CG adults, all participants attended two experimental sessions (intranasal oxytocin and placebo). Our first aim was to identify whether bereaved individuals would show different motivational responses depending on whether stimuli represented their deceased spouse, or were general reminders of the loss ("non-specific grief"). We hypothesized that participants overall would show an approach bias for stimuli depicting their spouse, but would not show an approach bias for "non-specific grief" stimuli. Our second aim was to investigate whether response bias differed between CG and non-CG participants. Specifically, we hypothesized that participants with CG would exhibit a greater approach bias for spouse stimuli, compared to non-CG participants. Our third aim investigated an oxytocin probe, and proposed differential effects of intranasal oxytocin in CG and non-CG participants (i.e., a group x condition interaction), where oxytocin would specifically increase relative approach bias for the spouse in CG only. This is based on prior work supporting individual differences in socio-emotional functioning as likely moderators of oxytocin effects (Bartz et al., 2011; Seeley et al., 2018).

Methods and materials

Participants

Participants were 39 community-dwelling older adults between the ages of 55–80 (M = 69.34; see Table 1) recruited from the Tucson, Arizona area in 2015–2016. Behavioral data reported here were collected as part of a larger multimethodological study. Recruitment strategies included newspaper advertisements, notices through medical centers, hospices, and retirement communities, and letters mailed to surviving spouses based on published obituaries. Participants had experienced the death of their spouse or long-term romantic partner in the prior 6–36 months (M = 15.41). Exclusion criteria included inability to comprehend English; medical contraindications for other components

Table 1
Sample Characteristics by Group.

	Non-CG (n = 22)		CG (n = 17)			
	Mean / n	SD /%	Mean / n	SD /%	$t(df)$ / χ^2	p
Age (years)	68.96	6.54	69.83	6.68	−0.41 (34.18)	.687
Sex (female)	19	86.4%	9	52.9%	5.29	**.038**$_{(sim)}$
Race (white)	22	100%	16	94.1%	1.33	.456$_{(sim)}$
Ethnicity (non-Hispanic)	22	100%	15	88.2%	2.73	.203$_{(sim)}$
Employment (retired)	19	82.6%	13	76.5%	.23	.687$_{(sim)}$
Education (college graduate)	14	60.9%	10	58.8%	.02 (1)	.896
Relationship length (years)	36.89	11.32	38.85	13.86	−0.48 (30.57)	.638
Time since death (months)	16.70	8.70	13.74	7.61	1.13 (36.38)	.265
Prescription medications (total n meds)	2.95	2.24	2.76	2.49	.25 (32.54)	.810
Taking psychoactive medications	6	27.3%	6	35.3%	.29 (1)	.590
ICG	14.47	6.36	35.18	7.99	−8.84 (30)	**<0.0001**
BDI-II	6.00	4.86	16.41	6.70	−5.40 (28.12)	**<0.0001**

ICG = Inventory of Complicated Grief. BDI-II = Beck Depression Inventory-II. Bolded p values indicate variables for which the two groups were significantly different from each other at α = 0.05 uncorrected for multiple comparisons. $_{(sim)}$ denotes Pearson's Chi-squared test with simulated p-value (based on 2000 replicates using chisq.test in the R `stats` package), given the presence of small cell sizes that may lead to incorrect approximations of p. Degrees of freedom are not applicable when p-values are simulated.

of the study, active suicidality, homicidality, or psychotic symptoms; ongoing major health conditions such as cancer; uncontrolled hypertension; and medications likely to impact the oxytocin system (e.g., systemic corticosteroids). All female participants were post-menopausal. Psychotropic medication use was permitted on a case-by-case basis if dose was stable >3 months, for ecological validity (Maust et al., 2014). Participants prescribed as-needed benzodiazepines were asked not to take them for the visits.

In addition to the 39 participants included, three were excluded after enrollment but before oxytocin administration, due to previously undisclosed medical conditions. Two other participants withdrew or were withdrawn during the study due to reported side effects (e.g., nausea) (CONSORT diagram; Figure S1).

Design and procedure

The University of Arizona Institutional Review Board approved all procedures. Participants gave written informed consent and were compensated $200. Prior to their first session, participants provided three photos of their spouse, and three photos of a living loved one (identified via the WHOTO scale; Fraley & Davis, 1997). They completed self-report measures (e.g., demographics, health, length of relationship, time since the death), the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and Inventory of Complicated Grief (ICG; Prigerson et al., 1995). The ICG is a 19-item measure of complicated grief symptoms distinct from depression or anxiety and predictive of functional impairment, and showed high internal consistency in our sample ($\alpha = 0.92$).

Enrolled participants were categorized in the Complicated Grief (CG; $n = 17$) or Non-Complicated Grief (Non-CG; $n = 22$) group based on a clinical cutoff score of ≥ 25 on the ICG. This cutoff score is considered a reliable threshold to differentiate those with and without significant clinical and functional impairment (Prigerson et al., 1995). However, to accommodate our sample size and maintain power, we used grief severity in all analyses in two ways; 1) using the established cutoff score to identify two groups, and 2) using ICG score as a continuous variable. Stratified sampling achieved representation of a full range of ICG scores ($M = 23.38$, $SD = 12.63$, range = 4–51). A non-bereaved control group was not included in the current study because there was no available analogous stimulus to the deceased spouse for non-bereaved participants, and our specific study questions did not include hypothesized bereaved vs. non-bereaved differences.

Participants attended two experimental sessions 7–10 days apart. At one session, participants received a 24 IU dose of synthetic oxytocin (Syntocinon, Novartis, Switzerland) delivered via self-administered nasal spray. At the other session, they received an identical-appearing placebo nasal spray (all non-active ingredients of Syntocinon; Novartis, Switzerland). Order of oxytocin/placebo session was randomized and counterbalanced across participants in order to account for possible order effects. Whether a participant received oxytocin or placebo at first or second sessions was not a statistically significant predictor of behavioral outcomes. Both participants and investigators were blind to randomization until data analyses were complete. After a 30-minute oxytocin rise-time, participants completed the AAT. They completed state measures before and after the task, and were debriefed after their second visit.

Task description

Participants viewed three different photos from each stimulus category: (1) deceased spouse (provided to us), (2) living loved one (provided to us), (3) stranger, (4) non-specific grief-related scenes such as a tombstone, casket, or hospital room, and (5) neutral scenes such as an outdoor picnic table or living room. Photos of a stranger were sex-matched to the spouse (for the living and deceased stimuli). Neutral environments (for the non-specific grief photos) were used to control for differences in person versus scene processing. Based on previous AAT designs (Derntl et al., 2011), photos were framed by a blue or yellow border. Participants were instructed to push or pull the joystick based on the frame color, not the photo's content. They completed the task twice per session, with reversed instructions on the second run (i.e., "*pull for yellow*" became "*push for yellow*"). Each seven-minute run of the task consisted of 144 2500 ms trials (288 trials per visit, 576 trials total across runs/sessions; 500 ms ITI). Order of instructions (i.e., "push yellow" vs. "pull yellow") was randomized and counterbalanced across participants and sessions, to address potential for order effects/habituation. Stimuli were presented via Inquisit 4 (2014), in a pseudorandomized order determined by genetic algorithm (Wager & Nichols, 2003).

Relative approach/avoidance bias was computed by subtracting median response time (RT; latency to joystick full extension) on PULL/approach trials in each stimulus category from PUSH/avoid trials in the same category (Rinck & Becker, 2007). Positive response bias values indicate relative approach bias; negative values indicate relative avoidance bias.

Statistical analysis

Trials with RTs ≤1st percentile (placebo: 463 ms, oxytocin: 473 ms) or ≥99th percentile (placebo: 1717 ms, oxytocin: 1711 ms) were discarded as per previous AAT studies (Rinck & Becker, 2007). After discarding outliers and missed trials, none had >10% missing data except for one participant (14% in the placebo condition). Data cleaning, visualization, and analysis were completed with R 3.6.3 using `dplyr`, 'ggplot2`, `afex`, `emmeans`, `nlme`, and `psych` packages (Lenth, n.d.; Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team (2019), n.d.; Revelle, n.d.; Singmann, Bolker, Westfall & Aust, n.d.; Wickham, H., François, R., Henry, L. & Müller, K., n.d.).

Statistical analyses included repeated measures ANOVAs with tests of *a priori* contrasts on the estimated marginal means to predict bias scores. Pairwise comparisons were corrected for multiple tests using the Holm approach (Holm, 1979). Due to the sample size, we repeated each analysis using mixed effects linear modeling. Mixed effects models yield higher power due to the larger number of observations at the trial level (288 observations per participant, per session) compared to the bias scores, which are computed from median RTs averaged across trials (five observations per participant, per session). The mixed effects linear models used individual PUSH/PULL trial RTs as the outcome rather than bias scores, and thus included joystick response direction (PUSH or PULL) as an additional fixed effect. Results did not change substantively using the mixed effects models, and are more difficult to interpret because of the added predictor. Further, an RT in one direction alone (rather than relative to the other direction) does not necessarily measure approach/avoidance *bias,* which was our outcome of interest. Therefore, we present the ANOVA results in the main text, and report the mixed effects models in supplementary material to demonstrate results requiring more power. Finally, we performed analyses using ICG score as both a categorical (CG vs. non-CG) and continuous variable. As results were largely consistent across both approaches, we report categorical analysis results in the main text to facilitate interpretation of interaction effects.

Results

Demographics and self-report

CG and non-CG groups did not differ significantly by age, race, ethnicity, employment status, educational attainment, years partnered, time since loss, total number of prescription medications, or psychoactive medication use. Men were overrepresented in the CG group (Table 1). We did not examine baseline (i.e., placebo session) sex differences in approach/avoidance behavior. Because of the unequal

distribution of men in the two groups (47% of CG vs. 14% of non-CG), we would not be able to determine whether a potential observed effect of sex was due to sex differences or differences in CG symptom severity. Further, we had no a priori hypotheses about whether sex would affect approach/avoidance behavior generally. We did check whether results involving oxytocin session data survived when we included sex as covariate, given that circulating sex hormones such as estrogen interact with the oxytocin system.

Differential response bias for personalized and non-specific grief-related stimuli (placebo condition, all participants)

Our first aim was to identify whether bereaved individuals would show different behavioral responses to personal photos of the deceased ("spouse") vs. non-specific death- or grief-related scenes similar to those used in published grief elicitation tasks ("non-specific grief"). A repeated-measures ANOVA with **stimulus** as the within-subjects factor and **response bias** as the outcome showed a main effect of stimulus, $F(4152) = 4.49$, Greenhouse-Geisser corrected $p = .002$, partial Cohen's $f = 0.34$ (Figure S2).

Pairwise comparisons indicated significantly greater approach bias for spouse vs. both control stimuli (spouse vs. stranger: estimate = 37.26, SE = 10.60, t[38] = 3.51, $p = .012$; spouse vs. neutral: estimate = 36.45, SE = 11.90, t[38] = 3.07, $p = .035$) (Table S1). There was no response bias to non-specific grief images vs. any other stimulus category, likely due to wide interindividual variance in the responses to non-specific grief stimuli.

We hypothesized that the contrast of spouse vs. stranger would produce a greater response bias than the contrast of non-specific grief vs. neutral. To test this hypothesis, we analyzed the difference between the two contrast estimates (**spouse vs. stranger** and **non-specific grief vs. neutral)**. The contrast comparisons indicated that participants showed significantly more approach bias on spouse vs. stranger trials (estimate = 37.3, SE = 10.6, t[38] = 3.51, $p = .001$), whereas response bias did not significantly differ in non-specific grief trials vs. neutral trials (estimate = −13.7, SE = 16.4, t[38] = −0.84, $p = .408$). There was a statistically significant difference between the **spouse vs. stranger** contrast and the **non-specific grief vs. neutral** contrast (estimate = 51.0, SE = 21.3, t[38] = 2.40, $p = .022$).

Differential response bias for personalized and non-specific grief-related stimuli by group (placebo condition, all participants)

Our second aim was to investigate whether response bias differed between CG and non-CG. We used a repeated-measures ANOVA with **stimulus** as the within-subjects factor, **group** as the between-subjects factor, and **response bias** as the outcome. We observed main effects of both group (F[1,37] = 6.31, $p = .017$, partial Cohen's $f = 0.41$) and stimulus (F[4148] = 4.42, $p = .006$, partial Cohen's $f = 0.35$). There was no **group x stimulus** interaction (F[4, 148] = 0.16, Greenhouse-Geisser corrected $p = .923$, partial Cohen's $f = 0.07$). As in Aim 1, pairwise comparisons within **stimulus** showed greater approach bias for spouse vs. stranger and spouse vs. neutral (Table S2). Statistical comparison of the two contrasts indicated a significant difference in response bias for **spouse vs. stranger** compared to **non-specific grief vs. neutral** (estimate = 51.3, SE = 21.7, t[37] = 2.36, $p = .024$). The pairwise comparison within **group** suggested that, averaging across all stimulus categories, the non-CG group demonstrated greater approach bias (estimated marginal mean = 26.31, SE = 7.88) than the CG group (estimated marginal mean = −3.66, SE = 8.96) and the groups were significantly different (estimate = 30.0, SE = 11.9, t[37] = 2.51, $p = .017$) (Fig. 1).

Differential effects of intranasal oxytocin on response bias to grief-related and person-related stimuli (placebo and oxytocin conditions, all participants)

Our third aim was to identify whether intranasal oxytocin had differential effects on CG and non-CG individuals. A repeated-measures ANOVA specified **stimulus** and **condition (oxytocin or placebo)** as within-subjects factors, **group** as the between-subjects factor, and **response bias** as the outcome. A main effect of **stimulus** (F[4148] = 8.64, $p < .001$, partial Cohen's $f = 0.48$) was found, as well as a **group x condition** interaction (F[1,37] = 7.28, $p = .010$, partial Cohen's $f = 0.44$) (Table S4). Effects held when we treated grief severity as a continuous measure (Supplemental Material Analysis S1), and when sex, anxious attachment specific to the deceased spouse, and depression symptoms were included as covariates (Analysis S3A), none of the added covariates were substantially associated with the dependent variable.

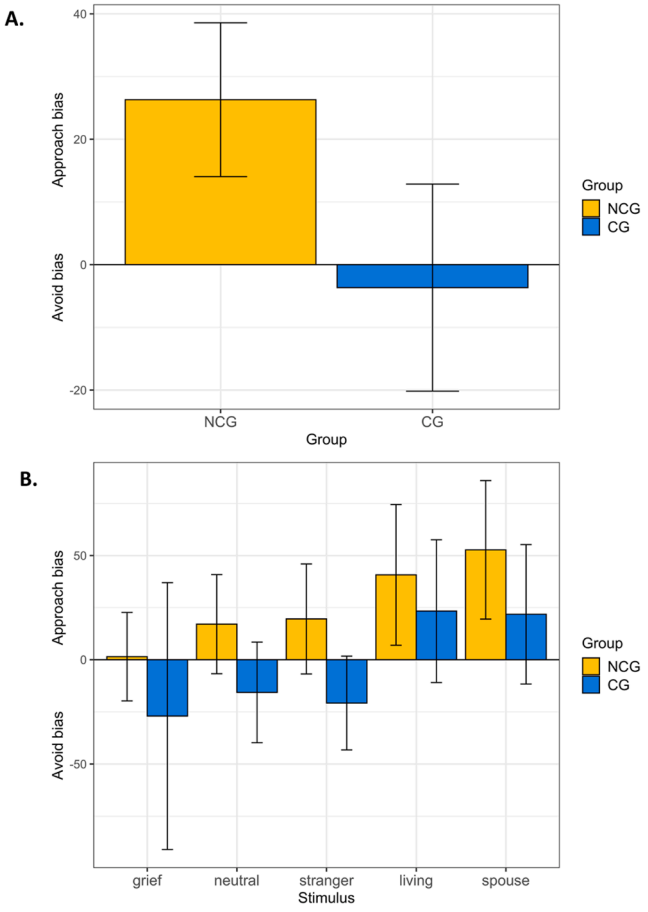

Fig. 1. Group (non-CG vs. CG) moderates AAT performance across stimulus categories (placebo condition).
Plots show mean approach/avoidance bias in group and each stimulus category in the placebo condition. Error bars represent 95% confidence intervals. Estimated marginal means by group and stimulus category presented in Table S3. A. Main effect of group on AAT performance in the placebo condition. B. AAT performance by stimulus category and group, in the placebo condition. Overall, the non-CG group showed greater approach bias regardless of stimulus category (i.e., no group x stimulus interaction).

In the **group x condition** interaction, intranasal oxytocin increased approach bias only in the CG group (Fig. 2). Pairwise comparison of **group** within **condition** showed that in the placebo condition, the CG was significantly more avoidance-biased compared to the non-CG group, averaging across all stimuli (estimate = −29.97, SE = 11.9, t[37] = 2.51, $p = .017$). In the oxytocin condition, responses in the two groups were comparable (estimate = 3.48, SE = 14.2, t[37] = 0.25, $p = .807$). The pairwise comparison of **condition** within **group** showed that approach bias significantly increased in the CG group under oxytocin (estimate = 20.50, SE = 9.31, t[37] = 2.198, $p = .034$). Oxytocin did not produce a significant change in the non-CG group's behavior (estimate = −13.0, SE = 8.19, t[37] = −1.59, $p = .121$).

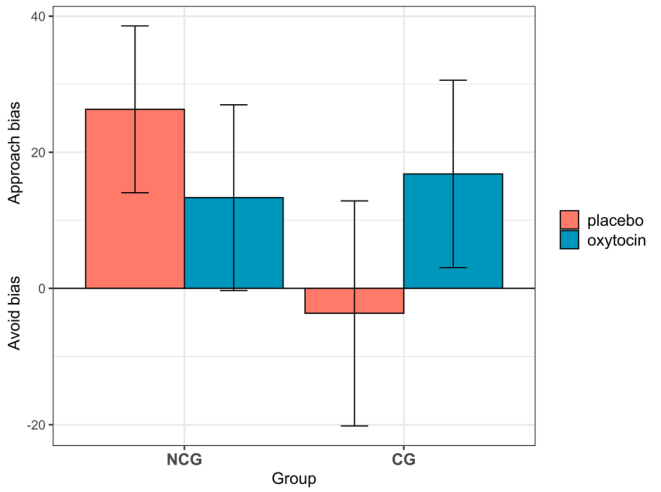

Fig. 2. Group x Condition interaction.
Bar height indicates mean approach/avoidance in each group and condition. Error bars represent 95% confidence intervals. Positive bias scores indicate relative approach bias (quicker to pull than push), while negative bias scores indicate relative avoidance bias (quicker to push than pull). The line at zero indicates no bias for either approach or avoidance. In the placebo condition, averaging across all stimuli, the CG group is significantly more avoidance-biased compared to the non-CG group. In the oxytocin condition, the groups do not differ significantly as the CG group becomes significantly more approach-biased under oxytocin while the non-CG group's behavior does not change significantly from the placebo condition.

Exploratory aim: differential effects of intranasal oxytocin on response bias to the deceased in CG and non-CG groups (placebo and oxytocin conditions, all participants)

Although we did not see a group x stimulus x condition interaction, we were specifically interested in whether oxytocin altered behavioral responses to photos of the deceased spouse, the stimulus most relevant to CG phenomenology – and whether the effect would differ by group. To investigate whether effects of oxytocin were specific to spouse-related bias, we calculated the effect of oxytocin (vs. placebo) separately for spouse and stranger stimuli. We then compared the relative effects of oxytocin on spouse vs. stranger to test whether oxytocin had an effect on spouse-related responses specifically. In other words, we contructed a contrast matrix in which 'spouse' was coded as 1, 'stranger' was coded as −1 (with all other stimuli coded as 0) in order to test 'spouse versus stranger' specifically.

We tested planned nested [$spouse_{oxytocin}$] vs. [$spouse_{placebo}$] contrasts in each group separately. Oxytocin produced a large, but statistically non-significant increase in approach bias for the spouse in the CG group (estimate = 34.71, SE = 18.3, t[37] = 1.90, $p = .066$). Oxytocin did not significantly alter response bias for the spouse in the non-CG group (estimate = −8.86, SE = 16.1, t[37] = −0.55, $p = .585$). The difference between each group's estimate for the [$spouse_{oxytocin}$] vs. [$spouse_{placebo}$] contrast did not meet the threshold for statistical significance, t(37) = 1.79, $p = 0.082$.

We then examined whether this result was a consequence of low statistical power or a true absence of an effect by testing the same contrast using the trial-level data. The trial-level data provided much greater power, as each participant had over 25 times the number of observations (500+ trials/person) versus condition-level data, where trials were aggregated across condition and stimulus (20 observations/person). We re-ran the **group x stimulus** [dummy-coded for spouse/non-spouse] **x condition** analysis as a multilevel random-intercept model, with participant as a random effect and added fixed effect of **response direction** (PUSH or PULL) (Analysis S2). Consistent with the ANOVA results, but reaching statistical significance with the trial-level data, this model indicated that oxytocin produced a significantly greater approach bias towards the spouse in the CG group than the non-CG group (estimate = 52.8, SE = 23, t[21,955] = 2.29, $p = .022$; Fig. 3). Results did not change when sex, anxious attachment specific to the spouse, and depressive symptoms were included as covariates (Analysis S3B), as none of the added covariates were substantially associated with the dependent variable. Table S6 shows the contrast specification and results.

Discussion

Evidence continues to mount in support of a theory positing implicit reward seeking as a central component of CG onset and maintenance (e.g., Kakarala et al., 2020). To further explore this theoretical model, the present study investigated implicit approach/avoid motivation as a putative mechanism of CG using a lab-based task and experimental manipulation (intranasal oxytocin). We used the grief variant of the AAT to compare responses to two types of grief-relevant stimuli: personal photos of the deceased spouse (vs. photos of a stranger) and non-specific grief-related scenes (vs. neutral scenes). Our aim was to disentangle prior accounts of approach/avoidance behavior in CG (Eisma & Stroebe, 2021). Prior studies conflictingly indicated that people with CG show greater approach bias for both deceased- and person-related stimuli (Maccallum & Bryant, 2019) and non-social grief-relevant stimuli (Maccallum et al., 2015), while other work showed avoidance bias for deceased-related stimuli in people with high levels of grief-related rumination (Eisma et al., 2015), a common feature of CG. The practical importance of the present study is that experimental approach/-avoidance paradigms distinguishing clinically-relevant grief symptoms from resilient grieving could be used to test whether implicit approach/avoid motivations in CG resolve with psychotherapeutic treatment, as avoidance or proximity-seeking behaviors in the real world may be more difficult to capture in a standardized way across

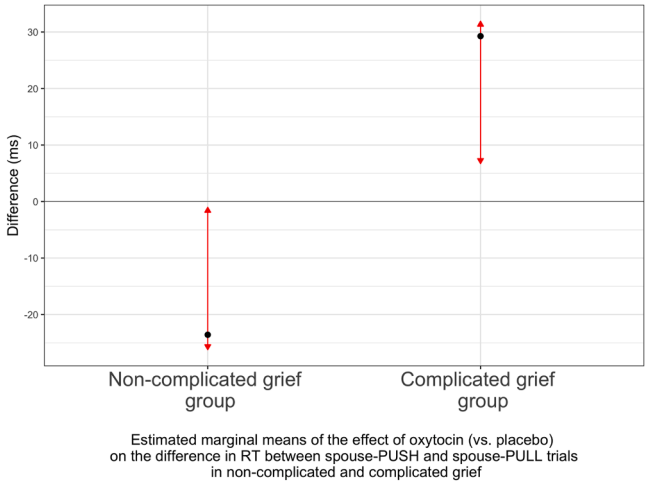

Fig. 3. Contrasts of the effect of oxytocin vs placebo trials on response times to spouse photos in CG and non-CG (estimates derived from trial-level response times).
To investigate whether effects of oxytocin were specific to spouse-related approach/avoidance bias, we calculated the effect of oxytocin (vs. placebo) separately for spouse and stranger stimuli. We then compared the relative effects of oxytocin on spouse versus stranger in order to test whether oxytocin had an effect on spouse-related responses specifically, or whether the behavioral effect of oxytocin on spouse-related responses was simply a function of spouse photos being social stimuli. As shown in the plot above, oxytocin decreased approach/increased avoidance for the spouse in the non-CG group. Oxytocin increased approach/decreased avoidance for the spouse.. The black dots indicate the overall estimated marginal mean for each group. Red arrows illustrate the difference between oxytocin and placebo trial means for each group. The non-overlapping red arrows in this plot illustrate the statistically significant difference between the two contrasts.

individuals.

Our results indicate that widowed older adults show different approach/avoid biases depending on whether the "grief-related" stimulus is a personal photo of the deceased, or a non-specific reminder of death (such as a photo of a casket). Participants broadly demonstrated a greater approach bias for the spouse compared to non-specific grief images. Thus, conflicting accounts of approach/avoidance in CG could be reconciled by considering the targets of that behavior. For example, a person might be motivated to engage in proximity-seeking behavior (e.g., reminiscence) when reminded of their deceased loved one, and also motivated to avoid confronting the reality of their death (as in the rumination-as-avoidance hypothesis). Indeed, in our sample, behavioral responses to spouse photos much more closely resembled responses to a living loved one, and both yielded greater relative approach bias than non-specific grief stimuli (Tables S2; S5). These data corroborate Boelen and colleagues' (Boelen & Huntjens, 2008) finding that intrusive mental imagery of the deceased and imagery related to the death are each associated with distinct outcomes. Differential response results also corroborate Eisma and colleagues' (Eisma et al., 2015) finding that rumination was only predictive of avoidance when photos of the deceased were paired with grief-related words such as "dead", but not when photos of the deceased were paired with neutral words.

Lower grief severity is associated with greater approach bias across all stimuli

Non-CG participants were more approach-biased across all stimulus categories than those with CG (Fig. 1A). For humans, having a social approach bias is likely beneficial (Raposa et al., 2016). The CG group did show the typical approach bias for spouse, but to a lesser degree than those with non-CG. This approach bias for the spouse was also found in previous work using names as stimuli (Maccallum & Bryant, 2019). Recent work identified a similar approach bias for the (living) ex-partner in people experiencing recurrent yearning, distress, and a strong desire for continued attachment after a breakup (Eisma et al., 2022).

Notably, the CG group showed a wide variability in their responses to stimuli. This diverse pattern of responses in those with CG was also noted by Maccallum and colleagues (Maccallum & Bryant, 2019) and suggests interindividual, idiosyncratic differences in loss-related responses even within the group of people experiencing higher distress.

Effects of intranasal oxytocin on approach/avoid bias are moderated by grief severity

If the oxytocin system is a mechanism in the development or maintenance of CG, we would expect to see a differential impact of intranasal oxytocin by grief severity, and we did. In the placebo condition, the CG group showed a general avoidance bias across stimuli, unlike the non-CG group. In the oxytocin condition, the two groups showed similar levels of approach bias (Fig. 2): oxytocin significantly increased approach bias in the CG group, and decreased approach bias in the non-CG group (although the latter finding was not statistically significant). The effect remained after accounting for the fixed effect of depression and of anxious attachment style specific to the spouse (Analysis S3.1, S3.2), though we acknowledge that this study was underpowered to examine more complex interactions between depression/attachment style and the other variables in the model. The differential impact of oxytocin on CG is consistent with attachment-related conceptualizations of CG and with oxytocin's role in separation distress in humans and other species (Bosch et al., 2016; Young, 2015). Recent studies have proposed oxytocin's role in CG (Bui et al., 2019; Schiele et al., 2018), although those studies may have certain methodological limitations (Hewitt, 2012; Szeto et al., 2011).

Effects of intranasal oxytocin in response to the deceased spouse are moderated by grief severity

If the oxytocin system has a role in maintaining the appetitive salience of the deceased spouse in people with CG (Hurlemann & Scheele, 2016), then we would expect to see a group difference specifically for photos of the spouse, and we found this as well. In exploratory analyses using both the aggregate response times and the more robustly-powered trial-level analyses, we observed the effect of oxytocin (vs. placebo) on relative response bias to spouse photos in the CG group was greater than in the non-CG group (Fig. 3). Oxytocin made the CG group slower to push spouse photos away (vs. placebo), but not any faster to pull spouse photos. This may suggest that oxytocin decreases avoidance behavior towards reminders of the spouse in people with CG.

Limitations

Our results should be considered in light of several limitations. First, central release of oxytocin has widespread, interactive effects on the brain via multiple pathways (Seeley et al., 2018). Thus, we cannot speak to a precise mechanism through which oxytocin might influence bereavement adaptation. Second, our sample is limited in both size and demographic diversity. Because of oxytocin's interactions with circulating hormones that decrease with age, results may not generalize to younger bereaved people. At the same time, the fact that sex hormone levels in men and women become more similar with age may mitigate the impact of males being overrepresented in the CG group (47% vs. 14% in the non-CG group). Small sample size is another limitation. We attempted to address the concern about low statistical power by confirming results using grief severity as a continuous measure and by repeating analyses in the trial-level dataset, which had a much larger number of data points. However, our results still may not generalize to the larger bereaved population. Without pre-bereavement data, we cannot speak to whether motivational biases seen here could be observed in participants prior to their partner's death. Lastly, we limited our sample to those who experienced the death of a spouse (or long-term romantic partner) to enhance comparability across individual participants, while attempting to identify living loved ones who represented a current close attachment relationship. However, in future studies it may be useful to investigate the influence of relationship type (e.g., romantic vs. kinship) in differential responses to the living vs. deceased loved one.

Conclusion

Our results highlight the interplay of approach and avoidance, pinpointing that motivational bias in bereaved people depends on the target of approach/avoidance. First, across different categories of grief-related, social, and neutral stimuli, those with lower grief severity show a general approach bias not present in those who are having greater difficulty adapting to the loss. Our finding that intranasal oxytocin decreased implicit avoidance of the deceased spouse only in the CG group supports recent models of reward as a mechanism in grief-related disorders (Kakarala et al., 2020). Second, the study advances the scientific conversation regarding conceptual clarity in designing grief-relevant experimental paradigms, especially with regard to stimuli choice, and reifies the importance of continued progress toward disentangling behavioral responses to reminders of deceased person from reminders of their death event. Further, the pathophysiology of CG may involve disturbances in implicit motivational and attachment processes, potentially related to the oxytocin system maintaining attachment desire for the deceased and/or worsening preoccupying thoughts through increased social salience (Maccallum & Bryant, 2010; Shamay-Tsoory & Abu-Akel, 2016; Seeley et al., 2023).

Author contribution statement

Mary-Frances O'Connor conceptualized and designed the parent study and obtained grant funding. Brian J. Arizmendi developed the study's hypotheses and approach, led data collection and data analyses, obtained grant funding, and drafted the original manuscript. Saren H. Seeley contributed to data collection, data analyses, and writing the original manuscript. John J. B. Allen, William D. S. Killgore, and Jessica Andrews-Hanna contributed substantially to study resources, hypothesis refinement, data analysis, and interpretation of results. Karen Weihs contributed to study resources and provided oversight during data collection. All authors contributed to and approved the final study manuscript.

BJA: Conceptualization, Analysis, Investigation, Funding, Original Draft, Review/Edit;

SHS: Analysis, Investigation, Visualization, Review/Edit;

JJBA, WDSK, JA-H: Methodology, Resources, Review/Edit;

KW: Supervision, Review/Edit;

M-FO: Conceptualization, Resources, Project administration, Funding acquisition, Review/Edit

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Supplementary materials

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