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RESEARCH ARTICLE

Oxytocin enhances the pain-relieving effects of social support in romantic couples

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Abstract

Social support plays a vital role in physical and mental well-being. The neuropeptide hormone oxytocin (OXT) has been implicated in modulating pair-bonding and affiliative behaviors, but whether OXT contributes to the analgesic effects of a romantic partner's touch remains elusive. In the present randomized placebo-controlled, between-group, functional magnetic resonance imaging study involving 194 healthy volunteers (97 heterosexual couples), we tested the effects of intranasal OXT (24 IU) on handholding as a common mode of expressing emotional support in romantic couples. We scanned the subjects while brief electric shocks were administered. The subjects assumed that they received social support from either their romantic partner or an unfamiliar person. Unbeknown to the subject, in the partner and stranger support conditions, the same male experimenter always held the subject's left hand. Partner support was most effective in reducing the unpleasantness of electric shocks, and OXT further attenuated the unpleasantness across conditions. On the neural level, OXT significantly augmented the beneficial effects of partner support, as evidenced by a stronger decrease of neural responses to shocks in the anterior insula (AI), a stronger activity increase in the middle frontal gyrus (MFG), and a strengthened functional coupling between the AI and MFG. Our results support the notion that OXT specifically modulates the beneficial effects of social support in romantic couples by concomitantly reducing pain-associated activity and increasing activity linked to cognitive control and pain inhibition. We hypothesize that impaired OXT signaling may contribute to the experience of a lack of partner support.

KEYWORDS

fMRI, oxytocin, pain, pair bonding, social support

1 | INTRODUCTION

Humans have evolved as an essentially social species. Positive social relationships propagate physical and mental well-being (Uchino, 2009), whereas loneliness and social isolation increase the risk of premature mortality comparable to established risk factors such as obesity, physical inactivity, and substance abuse (Holt-Lunstad, Smith, & Layton, 2010). The beneficial effects of social support have been linked to immunological (Kiecolt-Glaser, Gouin, & Hantsoo, 2010), cardiovascular, and endocrine responses (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Importantly, it is well established that social support has anti-nociceptive effects, evident in reduced pain intensity and unpleasantness ratings (Brown, Sheffield, Leary, & Robinson, 2003; Eisenberger et al., 2011; Master et al., 2009; Roberts, Klatzkin, & Mechlin, 2015; Younger, Aron, Parke, Chatterjee, & Mackey, 2010) and threat associated with pain anticipation (Coan, Schaefer, & Davidson, 2006). Recent imaging studies revealed that social support decreases pain-related activity in the anterior insula (AI) (Eisenberger et al., 2011), which integrates emotional and interoceptive states (Jensen et al., 2016) and is mainly involved in the emotional processing of pain (Duerden & Albanese, 2013). Additionally, social support has been found to modulate activity in the ventromedial prefrontal cortex (VMPFC), a region that has also been implicated in safety learning (Kong, Monje, Hirsch, & Pollak, 2014) and fear extinction (Graham & Milad, 2011).

Although social support from friends or even strangers reduces pain (Brown et al., 2003; Roberts et al., 2015), there is accumulating evidence for more pronounced effects of support provided by the romantic partner (Eisenberger et al., 2011; Master et al., 2009; Younger et al., 2010). To date, however, the neurobiological mechanisms that mediate the bonding-specific benefits of social support are unclear. The hypothalamic peptide oxytocin (OXT) is released during partner contact (Grewen, Girdler, Amico, & Light, 2005) and contributes to the maintenance of long-term relationships (Ditzen et al., 2009; Kreuder et al., 2017; Scheele et al., 2013). In prairie voles, OXT mediates consolation behavior toward distressed cagemates (Burkett et al., 2016) and social buffering by the male partner in response to immobilization (Smith & Wang, 2013). Likewise, polymorphisms of the OXT receptor (Chen et al., 2011) as well as the intranasal administration of OXT (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) modulate the social buffering of the cortisol response to psychosocial stress in men receiving social support from their female partner or close female friend. A better understanding of the underlying mechanism of action is important because an increasing number of studies indicate that the potential clinical effects of OXT are person- and context-dependent (Bartz, Zaki, Bolger, & Ochsner, 2011; Olff et al., 2013) and vary as a function of attachment organization and social support. For instance, we have found that in the absence of social support, intranasal OXT may produce detrimental effects and enhance the subjective experience of psychosocial stress (Eckstein et al., 2014). Furthermore, it has been shown that OXT not only modulates activity in the insular cortex (Striepens et al., 2012; Wigton et al., 2015) and VMPFC (Aoki et al., 2015; Labuschagne et al., 2012) but also reduces the neural response to stress-associated signals (Maier et al., 2018) and painful stimuli in the amygdala (AMY) (Paloyelis et al., 2016). Additionally, OXT strengthens top-down cognitive control strengthens top-down cognitive control by enhancing activity in the middle frontal gyrus (MFG) (Eckstein et al., 2015; Striepens et al., 2016).

To disentangle the neural mechanism by which OXT influences and interacts with the bonding-specific effects of social support on the experience of experimentally induced pain, we conducted a randomized, placebo-controlled (PLC), between-group, functional magnetic resonance imaging (fMRI) study involving 97 heterosexual couples. During the fMRI task, brief electric shocks were administered to the subjects' lower arm while they assumed that they would receive support from either their romantic partner or an unfamiliar experimenter of the opposite sex. Following recent studies (Coan et al., 2006; Master et al., 2009), we applied handholding as a common nonverbal mode of expressing emotional support. In reality, the same experimenter held the subject's hand in the partner and the stranger support conditions. In addition, we included a no support control condition in which the subjects held a rubber hand. The fMRI task was designed to carefully control possible confounding factors due to inter-individual preferences or habits in partner support.

We expected that intranasal OXT (24 IU) compared with PLC would reinforce the beneficial effects of partner and stranger support in reducing the unpleasantness of experimentally induced pain. On the neural level, we assumed that OXT would augment the positive effects of partner and stranger support compared with no support by diminishing responses to shocks in pain- and threat-related areas (AI, AMY) and increasing responses in prefrontal areas (VMPFC, MFG) associated with safety signaling and cognitive control. Additionally, based on reports of a positive correlation between marital quality and partner support (Coan et al., 2006), we hypothesized that the beneficial effects of partner support would vary as a function of the subjects' level of romantic love.

2 | METHODS AND MATERIALS

2.1 | Participants

After giving written informed consent, 194 non-smoking, heterosexual healthy volunteers participated in this fMRI study. Depending on the inclusion and exclusion criteria (cf. Supporting Information Methods), either the man (n = 65) (age 25.23 $\pm$ 3.54 years) or the woman (n = 32) (age 25.34 $\pm$ 3.51 years) of the 97 heterosexual couples was scanned. For female participants, the birth of a child or pregnancy during the study were defined as additional exclusion criteria. Considering previous observations (Scheele, Plota, Stoffel-Wagner, Maier, & Hurlemann, 2016), we included only natural cycling women in this fMRI-study. All women except four were tested in the luteal phase of their menstrual cycle and were premenopausal. Exclusion of the four women who were tested in the follicular phase did not change the pattern of results. The cycle phase was validated by blood assays (FSH, LSH, estradiol, progesterone, and testosterone concentrations) collected on the testing day (cf. Supporting Information Table S4). Subjects were free of past and current physical or psychiatric illness, as assessed by medical history and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Screening of the subjects was conducted prior to the fMRI session. All heterosexual couples were romantically in love as measured with the subscale for romantic love ("EROS") of the Marburg attitude inventory of love styles (Bierhoff, Grau, & Ludwig, 1993), an indicator of relationship quality. There were no *a priori* differences regarding demographic and psychometric variables between the treatment groups (cf. Supporting Information Table S5). The study was approved by the institutional review board of the Medical Faculty of the University of Bonn and was conducted in accordance with the Declaration of Helsinki.

2.2 | Experimental design

We performed a randomized, double-blind, PLC-controlled, between-group design study. Subjects were randomly assigned to either the intranasal administration of OXT (24 IU; six puffs per nostril each with 2 IU; n = 49; Novartis, Basel, Switzerland) or PLC (containing all ingredients except the peptide; n = 48). The administration of PLC and OXT was balanced within the female (OXT n = 16, PLC n = 16) and male (OXT n = 33, PLC n = 32) subsamples. Due to extreme head movements (>3 mm/°) and technical problems during the fMRI acquisition, we eliminated five subjects (three men and two women) from the fMRI data analysis. Thus, the fMRI data analysis was performed with 46 subjects (32 men) in the OXT group and 46 subjects (30 men) in the PLC group. The fMRI task began 45 min after the nasal spray administration. Further information regarding the experimental

paradigm, the fMRI acquisition, and the data analysis can be found in the Supporting Information.

2.3 | fMRI paradigm

We applied an adapted version of two previously used paradigms (Coan et al., 2006; Master et al., 2009), to examine the effects of hand-holding as a form of social support on the processing of experimentally induced pain. At the beginning of the scanning session, the subjects were informed that brief electric shocks would be administered to their left (non-dominant) dorsal lower arm while they held their romantic partner's hand, an unfamiliar male/female experimenter's hand, or a rubber hand. The rubber hand condition was included as a no support control condition. We ascertained the subject's individual shock intensity in the screening session prior to the testing day (cf. Supporting Information Methods). The sex of the unfamiliar experimenter was matched to the partner outside the MRI; that is, if a female participant was lying in the scanner, she assumed that she would hold the hand of her male partner, the hand of the male experimenter, or the rubber hand. Unbeknown to the subject, in the partner and stranger support conditions, the same male experimenter always held the subject's left hand, thereby keeping the type of cutaneous stimulation constant across the whole experiment. The male experimenter wore cotton gloves to control for possible temperature and skin differences. Furthermore, the romantic partner entered the MRI room before the experimental runs with partner support and briefly talked with the participant to strengthen the credibility of the task-dependent cover story. The participants in the MRI scanner were instructed to only hold their partners' hand without caressing it. The entire opening of the magnet was covered with a blanket so the subjects were unable to see their own hands or the hands of the experimenter.

The entire experiment consisted of three experimental runs (partner support, stranger support, no support). At the beginning of the experimental runs, a photograph of the male/female experimenter, the partner, or the rubber hand was presented for 15 s on a screen to indicate the current support condition. The order of the runs was counterbalanced across sex and treatment groups. Each experimental run contained 20 shock and 20 no shock events. During both shock and no shock trials, a red fixation-cross on a black background was shown for 1 s (cf. Supporting Information Figure S3). During the shock trials the presentation of the red fixation cross occurred parallel with a brief electric shock (4 ms) delivered to the subject's left lower arm. The order of shock and no shock events was pseudo-randomized (a maximum of two shock or no shock events directly followed each other) and always interleaved with an inter-stimulus interval (ISI) that was jittered between 4 and 6 s (mean: 5 s). During the ISIs, the subjects viewed a white fixation cross on a black background. After each shock and no shock trial, subjects rated the unpleasantness of the trial by using a visual analog scale ranging from 0 (very pleasant) to 100 (very unpleasant). The rating scale was presented for 4 s. One experimental run lasted 7 min.

2.4 | Acquisition and analysis of fMRI data

A 3 T Siemens Trio MRI system (Siemens, Erlangen, Germany) was used to acquire the MRI data, which were preprocessed (cf. Supporting Information Methods) and analyzed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (The MathWorks Inc., Natick, MA). A two-level random effects approach based on the general linear model as implemented in SPM12 was used for statistical analyses. On the first level, six conditions ($Partner_{No\ Shock}$, $Partner_{Shock}$, $Stranger_{No\ Shock}$, $Stranger_{Shock}$, $No\ Support_{No\ Shock}$, $No\ Support_{Shock}$) were modeled in a mini-epoch design convolved with a hemodynamic response function (Friston, 1995). The movement parameters were included as confounders in the design matrix. Each condition was compared with the low level baseline (white fixation cross). On the first level, we computed the following contrasts for each subject: [Shock > No Shock]; [$Partner_{Shock} > Partner_{No\ Shock}$]; [$Stranger_{Shock} > Stranger_{No\ Shock}$]; [$No\ Support_{Shock} > No\ Support_{No\ Shock}$]; [$Partner_{Shock > No\ Shock} > Stranger_{Shock > No\ Shock}$]; [$Partner_{Shock > No\ Shock} > No\ Support_{Shock > No\ Shock}$], and [$Stranger_{Shock > No\ Shock} > No\ Support_{Shock > No\ Shock}$]. Unspecific, domain-general effects of OXT (i.e., the main effect of treatment) were analyzed by comparing all conditions with the low level baseline ([OXT > PLC]).

On the second level, the whole brain analysis was conducted with a height threshold of $p < .001$. The p values were corrected for multiple comparisons (family-wise error [FWE]), and $p < .05$ was considered significant.

Based on our *a priori* hypothesis, the analysis of treatment effects focused on the AI, prefrontal regions, and the AMY as key neural substrates of pain processing, safety-signaling, and cognitive control. AMY, MFG, VMPFC, and AI were anatomically defined as regions of interest (ROIs) according to the Wake Forest University Pick Atlas (Version 3.0). The VMPFC ROI was defined as the medial orbitofrontal cortex implemented in the Wake Forest University Pick Atlas. The structural ROI of the bilateral AI was created by applying a caudal boundary of $y = 8$ (Eisenberger et al., 2011), corresponding to the agranular insula (Ongur, Ferry, & Price, 2003). The threshold for significance was set to $p < .05$, FWE-corrected for multiple comparisons based on the size of the ROI. To probe the neuromodulatory effects of intranasal OXT on the beneficial effect of partner and stranger support, we compared responses to the contrasts [$Partner_{Shock > No\ Shock} > No\ Support_{Shock > No\ Shock}$], [$Partner_{Shock > No\ Shock} > Stranger_{Shock > No\ Shock}$], and [$Stranger_{Shock > No\ Shock} > No\ Support_{Shock > No\ Shock}$] between the treatment groups.

To determine the direction and specificity of the OXT effects, the MarsBaR toolbox (http://marsbar.sourceforge.net/) was used to extract parameter estimates and time courses from the voxel cluster in the brain regions showing significant effects. To further explore the modulatory effects of OXT on the functional interplay of brain regions involved in the processing of pain and social support, a generalized form of context-dependent psychophysiological interactions analysis was conducted (McLaren, Ries, Xu, & Johnson, 2012). In contrast to the standard PPIs implementation in SPM, a gPPI analysis allows modeling of more than two task conditions in the same PPI by spanning the entire experimental space to improve model fit, specificity to true-negative and sensitivity to true-positive findings. Hemodynamic deconvolution was performed on the extracted time series to remove the effects of canonical hemodynamic response function (HRF). The resulting time series were multiplied by the psychological variables and reconvolved with the HRF to obtain the PPIs interaction terms.

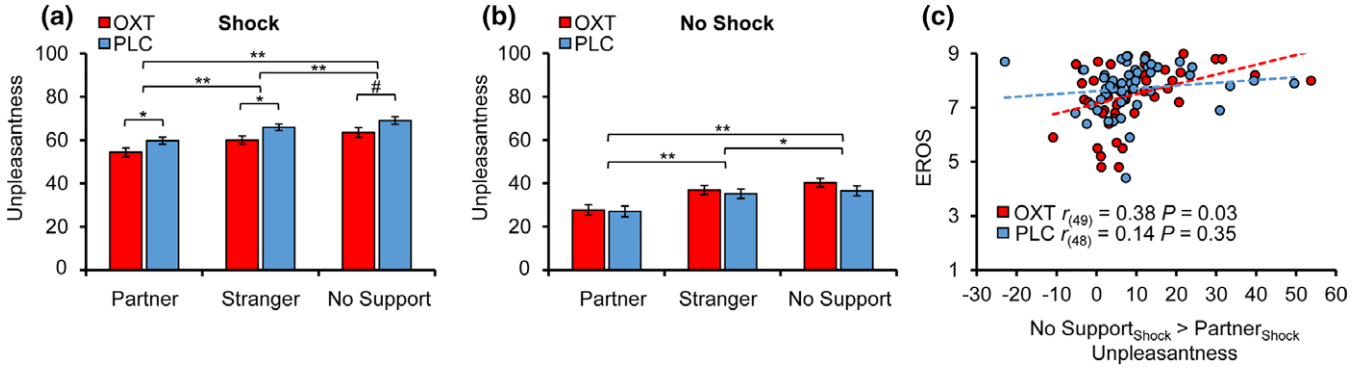

FIGURE 1 Intranasal oxytocin (OXT) compared with placebo (PLC) attenuated the unpleasantness of electric shocks irrespective of the social support condition (partner: $t_{(95)} = -2.05$, $p < .05$; stranger: $t_{(95)} = -2.45$, $p < .05$; no support: $t_{(95)} = -1.93$ $p = .06$) (a). There was no OXT effect on the unpleasantness ratings of the no shock trials (b). Receiving social support from the romantic partner was significantly more effective in reducing the unpleasantness of electric shocks than receiving social support from an unfamiliar person or receiving no support during the experiment across treatment groups (a; b). In the OXT group, a higher level of romantic love as assessed by the EROS scale was associated with a stronger social support effect by the partner (i.e., stronger decrease in unpleasantness compared with no support; (c) OXT: $r_{(49)} = 0.38$, $p < .05$; PLC: $r_{(48)} = 0.14$, $p = .35$). Error bars indicate the standard error of the mean (*SEM*). Abbreviations: EROS; subscale for romantic love of the Marburg attitude inventory of love styles; OXT, oxytocin; PLC, placebo. * $p < .05$, ** $p < .01$, # $p < .10$

The gPPI analysis for each subject was performed on the first level and included regressors for [Partner$_{Shock}$], [Partner$_{No\ Shock}$], [Stranger$_{Shock}$], [Stranger$_{No\ Shock}$], [No Support$_{Shock}$], and [No Support$_{No\ Shock}$].

3 | RESULTS

3.1 | Behavioral results

To investigate the modulatory effect of intranasal OXT, a mixed analysis of variance (ANOVA) with support type (partner, stranger, no support) and stimulus (shock, no shock) as within-subject factors, treatment (OXT, PLC) as a between-subject factor, and unpleasantness ratings as the dependent variable was performed. This ANOVA yielded main effects of stimulus ($F_{[1,95]} = 231.14$, $p < .01$, $\eta^2 = 0.71$) and support type ($F_{[2,190]} = 65.73$, $p < .01$, $\eta^2 = 0.41$). Brief electric shocks were rated (62.07 $\pm$ 11.97) as significantly more unpleasant than no shocks (33.90 $\pm$ 13.87). Receiving social support from the romantic partner significantly reduced the unpleasantness (42.18 $\pm$ 10.89) compared with support from the stranger (49.48 $\pm$ 9.70; $t_{[96]} = -9.10$, $p < .01$, $d = -0.70$) or no support (52.30 $\pm$ 10.58; $t_{[96]} = -9.17$, $p < .01$, $d = -0.94$). There was a weaker but still significant effect of stranger support compared with no support ($t_{[96]} = -3.62$, $p < .01$, $d = -0.28$).

Furthermore, we found a significant interaction between stimulus and treatment ($F_{[1,95]} = 4.24$, $p < .05$, $\eta^2 = 0.04$). Post hoc *t*-tests revealed that OXT significantly attenuated the unpleasantness of the shock events irrespective of the current support condition (partner: $t_{(95)} = -2.05$, $p < .05$, $d = -0.41$; stranger: $t_{(95)} = -2.45$, $p < .05$, $d = -0.50$; no support: $t_{(95)} = -1.93$, $p = .06$, $d = -0.39$; cf. Figure 1a and Supporting Information Figure S4A) but had no significant effect on the perceived unpleasantness of the no shock events (partner: $t_{(95)} = 0.20$, $p = .84$, $d = 0.04$; stranger: $t_{(95)} = 0.58$, $p = .56$, $d = 0.12$; no support: $t_{(95)} = 1.24$, $p = .22$, $d = 0.25$; cf. Figure 1b and Supporting Information Figure S4B). An additional mixed ANOVA with sex as a second between-subject factor did not change the reported pattern of the behavioral results (cf. Supporting Information Results). Furthermore, the pain-attenuating effect of OXT did not differ between subjects with higher and lower levels of romantic love, assessed by the EROS scale (cf. Supporting Information Results). In summary, these results suggest an unspecific anti-nociceptive effect of OXT independent of the support condition.

Interestingly, an additional correlation analysis revealed a significant positive association between the subjects' level of romantic love and the support effect of the partner compared with no support on the experience of shocks only in the OXT group ($r_{[49]} = 0.38$, $p < .05$, cf. Figure 1c), but not in the PLC group ($r_{[48]} = 0.14$, $p = .35$). Thus, under OXT, participants with a higher level of romantic love showed a stronger decrease in the unpleasantness of shocks under partner support relative to no support.

3.2 | fMRI results

In the PLC group, brief electric shocks, relative to no shocks, produced widespread activations in pain-processing networks (Apkarian, Bushnell, Treede, & Zubieta, 2005; Jensen et al., 2016; Tracey & Mantyh, 2007) at the whole-brain level, including the insula, middle and anterior cingulate cortex, and the middle frontal gyrus (cf. Supporting Information Tables S1 and S2; Supporting Information Figure S1). Furthermore, shocks induced a significant activity increase in the bilateral AMY (peak MNI coordinates *x*, *y*, *z*: −18, 0, −12; $t_{[270]} = 3.94$, $p_{FWE} < .05$, $d = 0.29$; 20, 0, −12; $t_{[270]} = 4.00$, $p_{FWE} < .05$, $d = 0.30$). In a next step, we examined whether the neural responses to shocks compared with no shocks varied as a function of the current support condition under PLC. Receiving social support from either the romantic partner or the stranger compared with no support resulted in significantly diminished neural activity to shocks relative to no shocks in the left AI (−32, 14, 2; $t_{[270]} = 4.07$, $p_{FWE} < .05$, $d = 0.37$, cf. Figure 2a and Supporting Information Figure S5A). Additionally, receiving support from the romantic partner compared with stranger support and no support significantly increased neural activity in the right MFG

(40, 10, 36; $t_{[270]}$ = 4.90, p_{FWE} < .05, d = 0.63, cf. Figure 2b and Supporting Information Figure S5B). We detected no significant effect of partner or stranger support on VMPFC or AMY activity.

Intriguingly, compared with PLC, intranasal OXT significantly augmented the beneficial effect of partner support relative to no support in the left AI (i.e., diminished the response to shocks versus no shocks in the AI under partner support compared with no support; −30, 24, −8; $t_{[270]}$ = 3.55, p_{FWE} < .05, d = 0.62, cf. Figure 3a and Supporting Information Figure S6A). Furthermore, intranasal OXT significantly elevated the neural effect of partner support compared with no support in the right MFG (i.e., increased the response to shocks compared with no shocks under partner support relative to no support; 36, 18, 50; $t_{[270]}$ = 4.03, p_{FWE} < .05, d = −0.63, cf. Figure 3b and Supporting Information Figure S6B). OXT did not significantly modulate the effect of stranger support in the AI or MFG and had no effect on AMY and VMPFC activity (all ps > .05). The main effect of treatment across all conditions was not significant (p > .05), indicating that intranasal OXT did not have unspecific global effects on brain activation.

Moreover, we tested possible brain–behavior associations. The neural effect of partner support compared with stranger support in the right MFG positively correlated with the behavioral support effect in the OXT group. Put differently, higher neural activity in the right MFG in response to shocks under partner support was associated with a stronger decrease in the unpleasantness ratings of shocks under partner support (36, −8, 52; $t_{(44)}$ = 5.21, $r_{[46]}$ = 0.46, p < .01). This brain-behavior correlation was not significant in the PLC group ($r_{(46)}$ = 0.13, p = .38).

Finally, an analysis with the additional factor of sex did not show a significant interaction between the subjects' sex and treatment (all ps > .05). However, we found significant differences between female and male participants in the neural response to partner support selectively in the PLC group. At the whole brain level, female participants receiving partner support compared with those receiving no support showed increased neural activity to shocks versus no shocks in the left caudate nucleus (−18, 4, 24; k = 206, $t_{[88]}$ = 4.85, p_{FWE} < .05, d = 1.31), the left thalamus (−4, −16, 14; k = 127, $t_{[88]}$ = 4.67, p_{FWE} < .05, d = 1.22), and the calcarine fissure (30, −60, 4; k = 109, $t_{[88]}$ = 5.59, p_{FWE} < .05, d = 1.55). The ROI-based approach revealed that women receiving partner support also showed more pronounced activity in the right VMPFC compared with stranger support (10, 54, −12; $t_{[88]}$ = 3.74, p_{FWE} < .05, d = 0.86) and increased right VMPFC activity to stranger support relative to no support (6, 26, −14; $t_{[88]}$ = 3.62, p_{FWE} < .05, d = 1.00). Likewise, women exhibited increased activity in the left AMY in response to shocks versus no shocks for stranger support compared with no support (−24, 0, −14; $t_{[88]}$ = 3.82, p_{FWE} < .01, d = 1.42).

3.3 | Functional connectivity

We conducted a generalized psychophysiological interactions analysis to explore whether OXT influenced the functional coupling between brain regions involved in the processing of pain and social support. We found an OXT-induced increase in the functional connectivity between the right AI (seed region) and the right MFG under partner support relative to stranger support (26, 50, 34; $t_{[243]}$ = 4.21, p_{FWE} < .05, d = 0.70, cf. Figure 4a and Supporting Information Figure S7A).

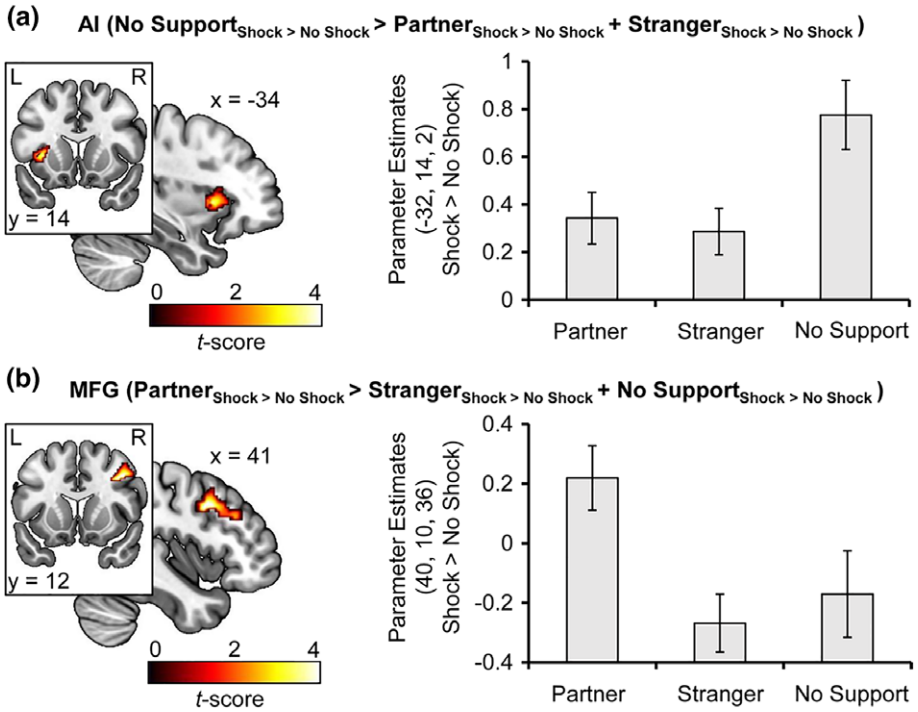

FIGURE 2 Under placebo, social support provided by both the partner and the stranger reduced responses to electric shocks in the left anterior insula (AI; a; peak MNI coordinates x, y, z: −32, 14, 2; $t_{[270]}$ = 4.07, p_{FWE} < .05, display threshold p < .05 uncorrected). Additionally, receiving social support from the romantic partner compared with the stranger and the no support conditions resulted in higher neural activity in the right middle frontal gyrus (MFG) in response to shocks relative to no shocks in the placebo group (b; peak MNI coordinates x, y, z: 40, 10, 36; $t_{[270]}$ = 4.90, p_{FWE} < .05, display threshold p < .05 uncorrected). Error bars indicate the standard error of the mean (*SEM*). Abbreviations: AI, anterior insula; L, left hemisphere; MFG, middle frontal gyrus; R, right hemisphere

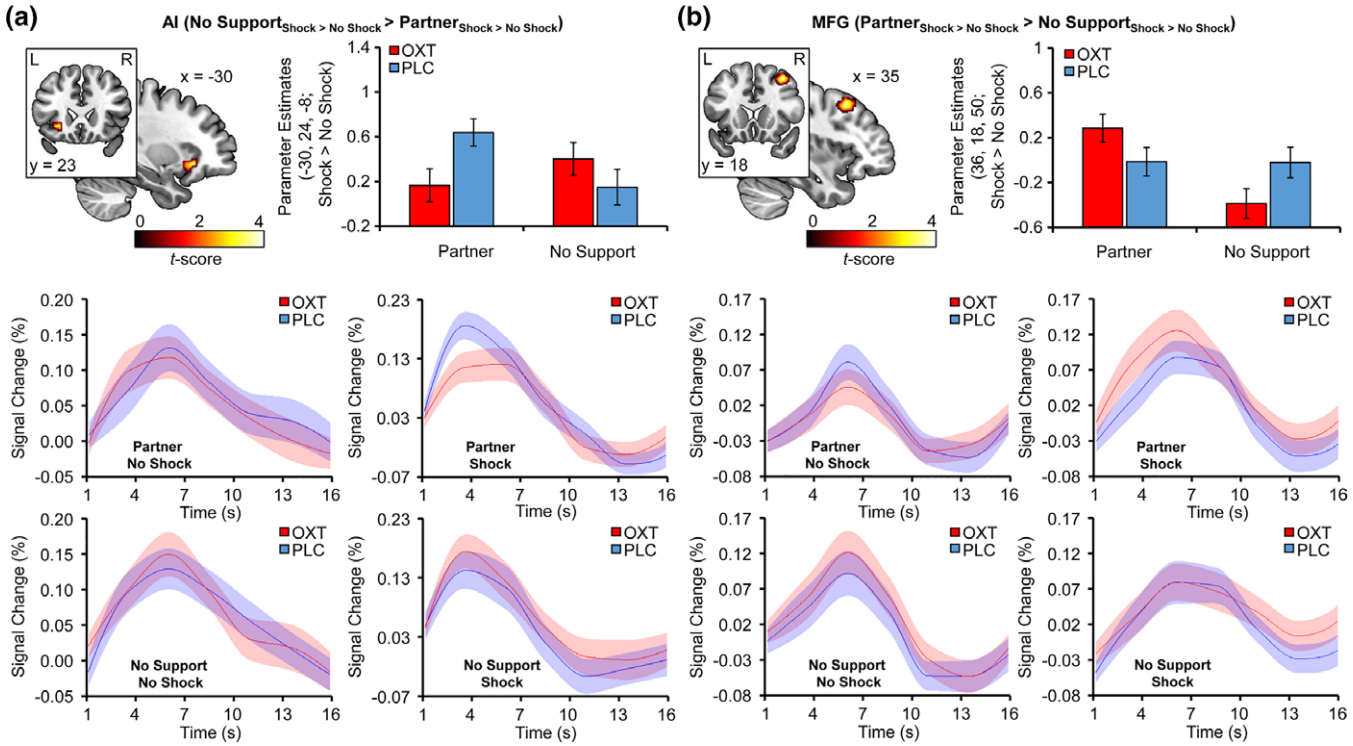

FIGURE 3 Intranasal oxytocin (OXT) significantly augmented the beneficial effect of partner support relative to no support in the left anterior insula (AI; i.e., stronger decrease in AI response to shocks relative to no shocks under partner support compared with no support; a: peak MNI coordinates x, y, z: −30, 24, −8; $t_{(270)}$ = 3.55, p_{FWE} < .05, display threshold p < .05 uncorrected). Furthermore, intranasal OXT enhanced the neural effect of partner support in the right middle frontal gyrus (MFG), evident in an increased response to shocks compared with no shocks under partner support relative to no support after OXT treatment (b; peak MNI coordinates *x*, *y*, *z*: 36, 18, 50; $t_{(270)}$ = 4.03, p_{FWE} < .05, display threshold p < .05 uncorrected). Error bars the shaded areas indicate the standard error of the mean (*SEM*). Abbreviations: AI, anterior insula; L, left hemisphere; MFG, middle frontal gyrus; OXT, oxytocin; PLC, placebo; R, right hemisphere

Furthermore, we observed enhanced functional coupling between the right MFG (seed region) and the left AMY under OXT treatment (−30, −4, −14; $t_{[264]}$ = 3.13, p_{FWE} < .05, d = 0.51, cf. Figure 4b and Supporting Information Figure S7B). Interestingly, this OXT effect was specific to partner support. We did not observe significant changes for stranger support.

4 | DISCUSSION

The aim of this study was to decipher the OXT-dependent mechanisms that mediate the effects of social support on the processing of experimental pain in romantic couples. Our findings in the PLC group mirrored the previously reported pain-relieving effects of social support provided by the romantic partner (Coan et al., 2006; Eisenberger et al., 2011; Younger et al., 2010). On a subjective level, receiving support from the romantic partner was more effective in reducing the unpleasantness of shocks compared with support from a stranger and no support. On the neural level, both partner and stranger support reduced pain-related neural activity in the AI, a region that integrates information about the salience of an incoming stimulus for the individual's internal body state (Wiech et al., 2010). Accordingly, social interactions may serve as a calm model (Brown et al., 2003) and may reduce the unpleasantness of pain by diminishing the salience of noxious stimuli (Krahe, Springer, Weinman, & Fotopoulou, 2013). Notably, only partner support, but not stranger support, induced an increase in neural responses to electric shocks in the MFG, a region that plays a key role in top-down cognitive control over emotions (Ochsner & Gross, 2005). Interestingly, using the prefrontal cortex as a target region for repetitive transcranial magnetic stimulation (rTMS) elicits analgesic effects in patients and healthy volunteers (Moisset, de Andrade, & Bouhassira, 2016). Prefrontal cortex rTMS might alter the experience of pain via top-down modulatory effects on limbic and brainstem regions (Craggs, Price, Verne, Perlstein, & Robinson, 2007; Lorenz, Minoshima, & Casey, 2003). Hence, our findings indicate that the stronger beneficial effects of partner support may be caused by a dual mode of action involving a decrease in AI activity, and concomitantly an increase in PFC activity.

Interestingly, we did not observe an effect of partner or stranger handholding on VMPFC activity under PLC. Eisenberger et al. (2011) used partner photographs as a symbol of an attachment figure and found increased VMPFC activity. Thus, recruitment of the VMPFC may not be required in the case of more salient safety signals such as handholding. Additionally, differences in VMPFC activity may be driven by sex effects. Eisenberger et al. (2011) analyzed data from female subjects and our data showed higher VMPFC activity in female compared with male participants under partner and stranger support in the PLC group. Women show greater pain sensitivity (Riley,

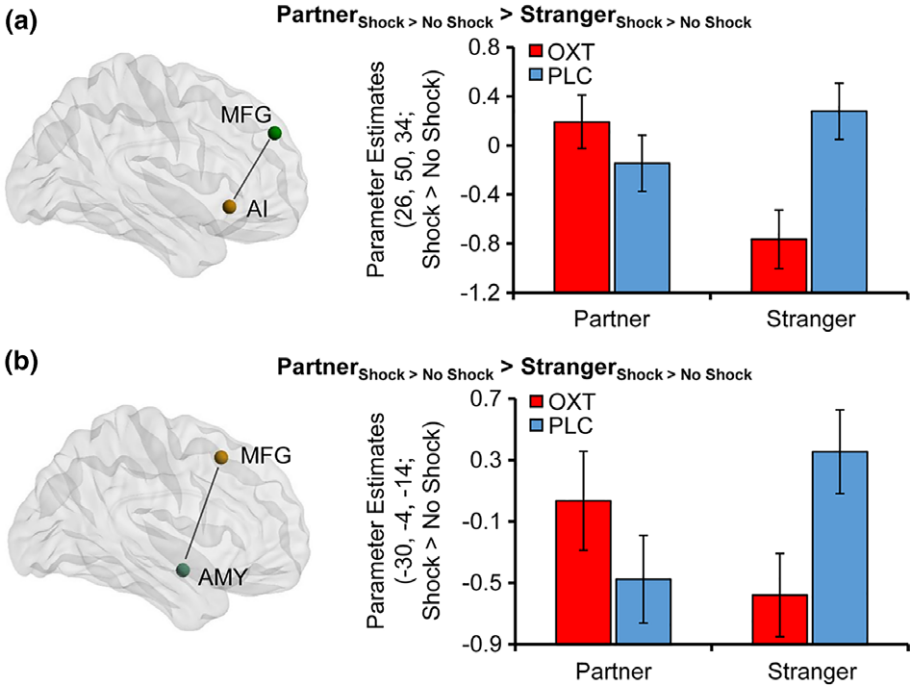

FIGURE 4 Intranasal oxytocin (OXT) significantly enhanced the functional coupling of the right anterior insula (AI) as seed region to the right middle frontal gyrus (MFG) during partner support versus stranger support (a; peak MNI coordinates *x*, *y*, *z*: 26, 50, 34; $t_{[243]} = 4.21$, $p_{FWE} < .05$). OXT also increased the functional coupling of the right MFG as seed region to the left amygdala (AMY) during partner support relative to stranger support (**b;** peak MNI coordinates x, y, z: −30, −4, −14; $t_{[264]} = 3.13$, $p_{FWE} < .05$). Seed regions are color-coded in brown. Error bars indicate the standard error of the mean (*SEM*). Abbreviations: AI, anterior insula; AMY, amygdala; MFG, middle frontal gyrus; OXT, oxytocin; PLC, placebo

Robinson, Wise, Myers, & Fillingim, 1998) and more attention to pain (Keogh & Herdenfeldt, 2002) relative to men, which may explain the additional recruitment of the VMPFC in female subjects. There is accumulating evidence that steroid hormones influence nociceptive processing (Maurer, Lissounov, Knezevic, Candido, & Knezevic, 2016) and may thus modulate the beneficial effect of social support on experimentally induced pain. Future studies are warranted to examine whether the neurobiological underpinnings of social support vary as a function of hormonal levels associated with different phases of the menstrual cycle.

Importantly, the observed OXT-induced reduction of the unpleasantness ratings of shocks provides further support for the analgesic effects of OXT (Eckstein et al., 2016; Paloyelis et al., 2016; Rash & Campbell, 2014; Zunhammer, Geis, Busch, Greenlee, & Eichhammer, 2015). Contrary to our first hypothesis, this effect was independent of the support conditions suggesting that OXT did not alter the subjective experience of social support. In previous studies, the additive effect of intranasal OXT has been more pronounced in endocrine responses rather than in subjective ratings (Heinrichs et al., 2003). In line with our second hypothesis, OXT specifically augmented the positive effects of romantic partner support by further diminishing neural activity in the AI and simultaneously increasing neural activity in the MFG and the functional connectivity between these regions. Mechanistically, the stronger reduction of AI activity to electric shocks under partner support after the administration of intranasal OXT may reflect anti-nociceptive effects of OXT that have been recently reported in human and animal studies (Rash, Aguirre-Camacho, & Campbell, 2014). Of note, we observed a unilateral effect of OXT on AI activity under partner support. The asymmetry of the electric shock administration in the fMRI paradigm may have contributed to the asymmetry of the neural effects. However, the reported left lateral OXT effects on AI activity are in line with recent meta-analytic findings showing the most robust OXT effects on left insular cortex activity (Wigton et al., 2015).

Additionally, an OXT-induced increase in activity in the PFC, where OXT receptors are highly expressed (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013), may reflect enhanced top–down cognitive control that has been previously observed in the context of food craving behavior (Striepens et al., 2016) and fear extinction (Eckstein et al., 2015). Notably, in the OXT group, MFG activity negatively correlated with the unpleasantness of shocks under partner support. Given the enhanced functional coupling between the MFG and AI and AMY under OXT, our data indicate that the MFG modulates the perceived unpleasantness of noxious stimuli via the AI and AMY (Lorenz et al., 2003). Interestingly, the anti-nociceptive effect of OXT was linked to the functional coupling of the AI and AMY (cf. Supporting Information Figures S2 and S7C).

Notably, OXT had no significant effect on the neural substrates of stranger support and the beneficial effect of partner support under OXT was more pronounced in subjects with a higher level of romantic love. Importantly, the more pronounced OXT effect on the beneficial effects of partner support in subjects with a higher level of romantic love could not be ascribed to baseline differences in the endogenous OXT concentration between subjects with higher and lower levels of romantic love (cf. Supporting Information Results).

This finding raises the question of whether OXT has similar effects on romantic partner support in cases of less positive

relationship quality and in different stages of romantic relationships. Our results corroborate recent conceptualizations that OXT plays a crucial role in the maintenance of romantic relationships (Hurlemann & Scheele, 2016), for example, by specifically increasing the hedonic value of a romantic partner's touch (Kreuder et al., 2017). Interestingly, social touch between romantic partners during the experience of pain strengthens inter-partner brain-to-brain coupling in the alpha/mu-band, and this brain-to-brain coupling enhances touch-related analgesia and empathic accuracy (Goldstein, Weissman-Fogel, Dumas, & Shamay-Tsoory, 2018). Given that intranasal OXT augments alpha-band inter-brain neural oscillations during a social coordination task (Mu, Guo, & Han, 2016), we hypothesize that OXT also modulates brain-to-brain coupling between romantic partners. Instead of establishing de novo bonding, OXT seems to strengthen *a priori* existing predispositions (Hurlemann & Scheele, 2016). The trust-enhancing effect (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Van IJzendoorn & Bakermans-Kranenburg, 2012) may be stronger if a positive relationship already exists between the supportive other and the support recipient (Bartz et al., 2011). On that note, OXT may be more effective as adjunct treatment of psychotherapy if a collaborative therapeutic alliance between the patient and the therapist has been established before the OXT treatment commences.

Intriguingly, our findings lead to the hypothesis that impaired OXT signaling may exacerbate the sequelae of lower-than-normal social support. Neglect during early childhood and adverse early bonding experiences result in long-lasting changes in the endogenous OXT system (Heim et al., 2009; Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005), and experiences with the caregiver early in life have a profound impact on the individual's subsequent perception of social bonds as a source of safety in case of need (Mikulincer & Shaver, 2012). Insecure attachment between the child and caregiver is paralleled by decreased responsiveness to social support (Ditzen et al., 2008), and early victimization is associated with lower levels of perceived social support from attachment figures (Hill, Kaplan, French, & Johnson, 2010). Accordingly, by disrupting OXT-dependent mechanisms, early maltreatment may render individuals vulnerable to future stress-related disorders because they benefit less from social support.

The present study has some limitations. First, to rigorously control potential confounders, the same experimenter held the subject's hand in the partner and the stranger support conditions Therefore, individual handholding preferences of the romantic couples (e.g., pressure, caressing) were not modeled. It seems likely that the social support effects would have been even more pronounced in a naturalistic setting. Second, the experimenter was blinded to the drug (OXT vs. PLC), but our cover story did not allow blinding of the condition (partner support, stranger support, no support). Thus, unconscious minimal variations in handholding cannot be entirely excluded. Importantly, our results cannot be attributed to unspecific effects of OXT on mood or anxiety (cf. Supporting Information Table S3).

5 | CONCLUSION

Overall, our findings provide new insights into the neurochemical mechanisms underlying the beneficial effects of social support on the experience of pain. The neuropeptide OXT may promote social support in romantic couples by a dual mechanism of combining anti-nociceptive effects with increases in the salience of and trust toward attachment figures.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.K. and D.S. designed the experiments; A.K., L.W., and M.W. conducted the experiments; A.K., L.W., M.W., and D.S. analyzed the data. All authors contributed to writing the article. All authors read and approved the manuscript in its current version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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