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The influence of oxytocin on volitional and emotional ambivalence

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Moral decisions and social relationships are often characterized by strong feelings of ambivalence which can be a catalyst for emotional distress and several health-related problems. The anterior cingulate cortex (ACC) has been identified as a key brain region in monitoring conflicting information, but the neurobiological substrates of ambivalence processing are still widely unknown. We have conducted two randomized, double-blind, placebo-controlled, functional magnetic resonance imaging experiments involving 70 healthy male volunteers to investigate the effects of the neuropeptide oxytocin (OXT) on neural and behavioral correlates of ambivalence. We chose moral decision-making and the imagery of partner infidelity as examples to probe volitional and emotional ambivalence. In both experiments, intranasal OXT diminished neural responses in the ACC to ambivalence. Under OXT, moral dilemma vignettes also elicited a reduced activation in the orbitofrontal cortex, and the imagery of partner infidelity was rated as less arousing. Interestingly, the OXT-induced differential activation in the ACC predicted the magnitude of arousal reduction. Taken together, our findings reveal an unprecedented role of OXT in causing a domain-general decrease of neural responses to ambivalence. By alleviating emotional distress, OXT may qualify as a treatment option for psychiatric disorders with heightened ambivalence sensitivity such as schizophrenia or obsessive-compulsive disorder.

Keywords: ambivalence; anterior cingulate cortex; fMRI; jealousy; moral; oxytocin

INTRODUCTION

Ambivalence, that is the experience of conflicting emotions or opposing thoughts, is a hallmark of countless situations in everyday life. At the root of his concept of tripartite, Bleuler (1908) differentiated between volitional, intellectual and emotional ambivalence. Moral decision-making can be considered as an instance of volitional ambivalence, since divergent moral values have to be evaluated. Intellectual ambivalence is related to philosophical skepticism, whereas emotional ambivalence describes a situation in which an individual simultaneously loves and hates another person.

Ambivalence can be the cause of emotional distress (van Harreveld *et al.*, 2009) and it may have detrimental influence on health-relevant processes. Ambivalent relationships are associated with coronary-artery calcification (Uchino *et al.*, 2014) and social support from an ambivalent friend is linked to greater cardiovascular reactivity during psychosocial stress (Gramer and Supp, 2014; Holt-Lunstad and Clark, 2014). The number of ambivalent network ties correlates with depression (Uchino *et al.*, 2001) and task-measured ambivalence is elevated in patients with schizophrenia (Docherty *et al.*, 2014). On the neural level, the evaluation of ambivalent target stimuli elicits activation in the anterior cingulate cortex (ACC) (Nohlen *et al.*, 2014), which is consistent with previous conflict-monitoring accounts of ACC function (Botvinick *et al.*, 1999). As it stands, not much is known concerning the neurobiological underpinnings of ambivalence.

The neuropeptide hormone oxytocin (OXT) is a key factor mediating relationship quality in human pair-bonds (Scheele *et al.*, 2012, 2013) and OXT has been found to enhance the buffering effect of social support on stress responsiveness (Heinrichs *et al.*, 2003). OXT also increases positive communication and reduces cortisol levels during an instructed couple conflict (Ditzen *et al.*, 2009). Interestingly, the ACC is a region of high OXT receptor (OXTR) density in the human brain (Boccia *et al.*, 2013) and adolescents with the minor CC-genotype of a OXTR polymorphism (rs237915) exhibited lower ACC activity in response to animated angry faces and were more resilient against the effect of stressful experiences (Loth *et al.*, 2014). Likewise, the intranasal administration of OXT reduces ACC activity during the pre-feedback period of a trust game (Baumgartner *et al.*, 2008). On the other hand, OXT can also facilitate the initial sensation of social stress and increase ACC activity (Eckstein *et al.*, 2014).

The present study was designed to directly investigate the modulatory effects of OXT on the neural processing of volitional and emotional ambivalence. In Experiment 1 (Exp. 1), we probed volitional ambivalence by measuring neural responses to moral dilemmas (Harrison *et al.*, 2012) in 48 healthy male volunteers after they had received intranasal OXT (24 IU) or placebo (PLC). These moral dilemmas primarily entailed difficult decisions about life and death trade-offs. In Experiment 2 (Exp. 2), we assessed emotional ambivalence in another sample of 22 healthy male participants with a task more proximate to OXT's bonding-related effects. We used description-based imagery of sexual and emotional infidelity of the participants' female partners (Takahashi *et al.*, 2006). Subsequently, the participants had to rate the arousal induced by the sentences depicting infidelity. Given the previous equivocal findings and the strong context-dependency of OXT effects (Preckel *et al.*, 2014), we expected that OXT would either alleviate or enhance the perceived ambivalence evident by an altered ACC response in both experiments or changed arousal ratings in Exp. 2.

MATERIALS AND METHODS

A detailed synopsis of all experimental procedures is provided in the Supplementary Information.

Subjects

Forty-eight healthy, non-smoking adult males (mean age ± s.d. = 24.6 ± 4.56 years) participated in Exp. 1 and 22 men (26.73 ± 3.60 years) volunteered in Exp. 2. Prior to the test sessions, the participants

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completed a comprehensive neuropsychological test battery and questionnaires assessing ethical ideology (Forsyth, 1980) and love styles (e.g. Eros, a committed romantic relationship) (Lee, 1988). All subjects were within a normal range of cognitive performance and there were no a priori differences between the OXT and PLC groups in Exp. 1 (Supplementary Tables S1 and S2). All subjects in Exp. 2 were in a romantic heterosexual relationship for more than 6 months (36 ± 25 months), were unmarried and had no children. Both experiments were approved by the Institutional Review Board of the Medical Faculty of the University of Bonn and carried out in compliance with the latest revision of the Declaration of Helsinki. Subjects were free of current and past physical or psychiatric illness, as assessed by medical history and a Mini-International Neuropsychiatric Interview.

Experimental design and fMRI tasks

For both experiments, we applied a randomized, PLC-controlled, double-blind design. Subjects were randomly assigned to either intranasal administration of OXT (24 IU; Syntocinon-Spray, Novartis; three puffs per nostril, each with 4 IU OXT) or PLC (sodium chloride solution), approximately 45 ± 10 min before the start of the fMRI.

We decided to use a between-subject design study for Exp. 1 to avoid the repetition of the same moral decisions. The task consisted of 24 non-dilemma story vignettes and 24 moral dilemma story vignettes taken from Harrison *et al.* (2012). Prior to the fMRI experiment, participants were familiarized with the vignettes and the corresponding stories. In the non-dilemma condition, participants had to recall each scenario and indicate the correct outcome by button press. In the moral dilemma condition, participants had to provide their own moral judgment by button press. For instance, the participants had to decide whether they want to endorse a utilitarian (e.g. suffocate your crying child to prevent the detection by enemy soldiers) or deontological action (e.g. remove your hand from the child's mouth). The paradigm featured a block design which included eight blocks of six moral dilemma or non-moral vignettes. Moral dilemmas and non-moral blocks were presented in an alternating order.

Exp. 2 consisted of a within-subject design study. The participants were confronted with three types of short sentences describing neutral actions of the partner or sexual and emotional infidelity. We used the same definition of sexual and emotional infidelity as Takahashi *et al.* (2006), with the former pertaining to a condition explicitly or implicitly indicating a sexual relationship or physical contact and the latter indicating diversion of the partner's emotional commitment to someone else. All sentences were written in German and started with 'My girlfriend.' The sentences were presented in six blocks for each of the three conditions. In each 24 s block, three different sentences were shown for 8 s each. The sequence of blocks was randomized, and blocks were separated from each other by a low-level baseline period of 20 s duration, in which a fixation cross was depicted in the center of the screen. The subjects were instructed to attentively read the sentences and to imagine the described situations. To assure attentive stimulus processing, subjects were asked to press a keypad button whenever a stimulus was presented (percent correct responses OXT 99.38 ± 2.03, PLC 98.65 ± 2.15, $P = 0.25$). After scanning, subjects were seated in front of a computer and were asked to rate arousal induced by the imagery of each sentence on a visual analog scale (ranging from 0, not arousing, to 100, most arousing). The sequence of the sentences was randomized. We decided to acquire arousal ratings after the fMRI sessions to avoid any confounding effect of the ratings (Taylor *et al.*, 2003) on the neural substrates of the mental imagery.

Acquisition and analysis of fMRI data

In Exp. 1, the MRI data were acquired with a Siemens Avanto MRI system (Siemens, Erlangen, Germany) operating at 1.5T. T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast were obtained (retention time (TR) = 3000 ms, echo time (TE) = 35 ms, matrix size: 64 × 64, pixel size: 3 mm × 3 mm × 3 mm, slice thickness = 3.0 mm, distance factor = 10%, field of view (FoV) = 192, flip angle = 90°, 36 axial slices). High-resolution anatomical images were acquired on the same scanner with a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1570 ms, TE = 3.42 ms, matrix size: 256 × 256, pixel size: 1 mm × 1 mm × 1 mm, slice thickness = 1.0 mm, FoV = 256, flip angle = 15, 160 sagital slices).

In Exp. 2, a Siemens Trio MRI system (Siemens, Erlangen, Germany) operating at 3T was used to obtain T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent contrast (TR = 3000 ms, TE = 35 ms, matrix size: 64 × 64, pixel size: 3 mm × 3 mm × 3 mm, slice thickness = 3.0 mm, distance factor = 10%, FoV = 192, flip angle = 90°, 36 axial slices). In addition, high-resolution anatomical images were acquired on the same scanner using a T1-weighted 3D MPRAGE sequence (imaging parameters: TR = 1570 ms, TE = 3.42 ms, matrix size: 256 × 256, pixel size: 1 mm × 1 mm × 1 mm, slice thickness = 1.0 mm, FoV = 256, flip angle = 15°, 160 sagital slices).

The MRI data were preprocessed and analyzed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7 (The MathWorks Inc., Natick, MA). The first five volumes of each functional time series were discarded to allow for T1 equilibration. Images were corrected for head movement between scans by an affine registration. For realignment, images were initially realigned to the first image of the time-series and subsequently realigned to the mean of all images. For spatial normalization, the mean EPI image of each subject was normalized to the current Montreal Neurological Institute (MNI) template (Evans *et al.*, 1992; Holmes *et al.*, 1998) using the unified segmentation function in SPM8. This algorithm combines image registration, tissue classification and bias correction within the same generative model. In Exp. 1, all images were thereby transformed into standard stereotaxic space and resampled at 3 mm × 3 mm × 3 mm voxel size. The normalized images were spatially smoothed using an 8 mm full width at half maximum Gaussian kernel. In Exp. 2, all images were resampled at 2 mm × 2 mm × 2 mm voxel size and spatially smoothed using a 6 mm full width at half maximum Gaussian kernel. Raw time series were detrended by the application of a high-pass filter (cut-off period, 128 s). A two-level random effects approach based on the general linear model as implemented in SPM8 was used for statistical analyses for both experiments.

On the first level in Exp. 1, the two conditions ('moral' and 'non-moral') of the block design were defined and modeled by a boxcar function convolved with a hemodynamic response function. The movement parameters were included as confounds in the design matrix. Each experimental condition was compared relative with the low level baseline and differences between each condition were computed separately for the OXT and PLC group. To examine the effects of OXT in Exp. 1, parameter estimates of all contrasts were used to perform two-sample *t*-tests on the second level with a significance threshold of $P < 0.05$ corrected for multiple comparisons (family-wise error [FWE]).

On the first level in Exp. 2, six conditions ('$\text{Sexual}_{\text{OXT}}$,' '$\text{Neutral}_{\text{OXT}}$,' '$\text{Emotional}_{\text{OXT}}$,' '$\text{Sexual}_{\text{PLC}}$,' '$\text{Neutral}_{\text{PLC}}$' and '$\text{Emotional}_{\text{PLC}}$') were modeled by a boxcar function convolved with a hemodynamic response function. The movement parameters were included as confounds in the design matrix. Each condition was compared relative with the low level baseline and non-specific effects of OXT were

analyzed by comparing all items with the low level baseline. Differences between each condition were computed separately for the OXT and PLC sessions and we built the contrasts [$Sexual_{OXT} > Sexual_{PLC}$], [$Neutral_{OXT} > Neutral_{PLC}$] and [$Emotional_{OXT} > Emotional_{PLC}$] to specifically examine the modulatory effects of OXT. Parameter estimates for each contrast were subjected to one-sample *t*-tests on the second level for the whole brain with a significance threshold of $P < 0.05$ corrected for multiple comparisons (FWE). Based on the previous finding that patients with obsessive-compulsive disorder (OCD) exhibit an increased neural response to moral task vignettes in the orbitofrontal cortex (OFC) (Harrison *et al.*, 2012), we used 6 mm spheres as regions of interest (ROI) centered at the coordinates of the reported maximum value for the OFC (MNI *x*, *y*, *z*: ±4, 38, −20). Given the strong OXT effect on ambivalence-related activation of the ACC in Exp. 1, we used an anatomically defined ROI of the ACC in Exp. 2. The ACC ROI was defined using the Wake Forest University (WFU) Pickatlas (Version 3.0), which provides a method for generating ROI masks based on the Talairach Daemon (TD) database (Maldjian *et al.*, 2003). ROI-based two-sample (Exp. 1) or one-sample (Exp. 2) *t*-tests were computed with a threshold of $P < 0.05$ and FWE-corrected for multiple comparisons based on the size of the ROI. Anatomical classification was done using the WFU Pickatlas, automatic anatomic labeling (aal) or TD labels (Lancaster *et al.*, 2000; Maldjian *et al.*, 2003). In order to further examine the specific OXT effect, the parameter estimates were extracted from the activated clusters in the ACC, OFC, the posterior cingulate cortex and the precuneus using the MarsBaR toolbox (Brett *et al.*, 2002) (see also http://marsbar.sourceforge.net/) with a sphere size of 6 mm.

RESULTS

Experiment 1

Behavioral results

OXT had no significant effect on the rejection rate of moral dilemmas (mean % rejected OXT = 54.83 ± 12.31, PLC = 53.44 ± 18.83, $t_{(37.39)} = 0.30$, $P = 0.77$, $d = 0.09$). Furthermore, a repeated-measures analysis of variance (ANOVA) with treatment as between-subject factor (OXT *vs* PLC), morality (moral dilemma *vs* non-moral vignettes) as within-subject variable and reaction time (RT) as a dependent variable yielded a main effect of morality ($F_{(1,36)} = 97.2$, $P < 0.001$, $\eta^2 = 0.73$), but no further significant main or interaction effects. The RT for moral dilemma decisions (2.96 ± 0.31 s) was significantly longer than the RT for responses in the non-moral condition (2.54 ± 0.27 s). In a next step, we conducted a repeated measures ANOVA with RT as dependent variable, decision (accepted *vs* rejected) as within-subject factor and treatment as a between-subject variable. We found no main effects, but we did observe a trend for an interaction of treatment and decision ($F_{(1,37)} = 3.28$, $P = 0.08$, $\eta^2 = 0.08$). Post-hoc paired *t*-tests revealed that participants in the OXT group accepted moral dilemmas significantly faster than they rejected them ($t_{(19)} = -2.25$, $P = 0.04$, $d = 0.11$), whereas there was no difference in the PLC group ($P = 0.73$).

fMRI results

Under PLC, the evaluation of moral dilemmas, compared with the non-dilemma condition, elicited broad activations in a moral decision-making network including the medial-frontal lobe, the cingulate cortex, the temporal lobe and the angular gyrus (cf. Supplementary Table S3) (Greene *et al.*, 2001; Heekeren *et al.*, 2005). As expected, there were no significant activations for the contrast 'non-dilemma > dilemma.' The OXT treatment reduced the neural responses to ambivalent moral dilemmas ('moral > non-moral') in the ACC (MNI *x*, *y*, *z*: 12, 41, 1, $t_{(46)} = 5.35$, $P_{FWE} < 0.01$; cf. Figure 1A), the posterior cingulate cortex (MNI *x*, *y*, *z*: 0, −46, 31, $t_{(46)} = 4.31$, $P_{FWE} = 0.02$), the precuneus (MNI *x*, *y*, *z*: 0, −58, 37, $t_{(46)} = 3.68$, $P_{FWE} = 0.02$) and the medial cingulate cortex (MNI *x*, *y*, *z*: 9, −43, 34, $t_{(46)} = 3.61$, $P_{FWE} = 0.02$). Interestingly, a ROI-based analysis revealed that the OXT group also exhibited decreased activation in the OFC for the contrast moral > non-moral (MNI *x*, *y*, *z*: 0, 35, −20, $t_{(46)} = 2.97$, $P_{FWE} = 0.03$; cf. Figure 1B).

Experiment 2

Behavioral results

A repeated-measures ANOVA with treatment (OXT *vs* PLC) and type (emotional, neutral and sexual) as within-subject variables and arousal ratings as dependent variable yielded a main effect of type ($F_{(1.24,26.07)} = 240.17$, $P < 0.01$, $\eta^2 = 0.92$), a main effect of treatment ($F_{(1,21)} = 5.10$, $P = 0.04$, $\eta^2 = 0.20$) and a trend for an interaction of type and treatment ($F_{(1.47,30.95)} = 2.67$, $P = 0.099$, $\eta^2 = 0.11$; Figure 2A). The imagery of both sexual and emotional infidelity elicited stronger arousal than neutral sentences ($t_{(21)} = 17.99$, $P < 0.01$, $d = 5.31$ and $t_{(21)} = 14.46$, $P < 0.01$, $d = 4.37$). Consistent with previous findings in men (Buss *et al.*, 1992), the description of sexual infidelity was perceived as more arousing than emotional infidelity ($t_{(21)} = 4.74$, $P < 0.01$, $d = 0.52$). Post-hoc *t*-tests revealed that OXT diminished arousal ratings for sexual ($t_{(21)} = 2.30$, $P = 0.03$, $d = 0.22$) and emotional infidelity ($t_{(21)} = 2.29$, $P = 0.03$, $d = 0.28$), but had no effect on the neutral category ($t_{(21)} = 0.31$, $P = 0.76$, $d = 0.04$). Participants with higher scores on a questionnaire measurement of romantic love, Eros, were more likely to rate both emotional (PLC: $r = 0.46$, $P = 0.03$; Figure 2A; OXT: $r = 0.34$, $P = 0.13$) and sexual infidelity (PLC: $r = 0.43$, $P = 0.048$; OXT: $r = 0.40$, $P = 0.07$) as more arousing, but there was no correlation for neutral items (PLC: $r = -0.17$, $P = 0.45$; OXT: $r = -0.004$, $P = 0.99$). Furthermore, OXT did not influence subjective anxiety, mood ratings or attention (cf. Supplementary Table S4).

fMRI results

At the whole-brain level, the imagery of sexual infidelity under PLC treatment, compared with the neutral condition, produced widespread activations in a fronto-temporal network including the middle and medial frontal gyrus, ACC and middle and superior temporal gyrus (cf. Supplementary Table S5). As expected, there were no significant activations for the contrast 'neutral > sexual,' but, surprisingly, the neutral condition elicited a stronger activation than did emotional infidelity. Neutral imagery of the partner, compared with emotional infidelity, produced activation in the inferior parietal lobule, cingulate cortex, middle and superior frontal gyrus, occipital gyrus, pallidum and insula (cf. Supplementary Table S5).

Importantly, a diminished neural response in the cingulate cortex to sexual infidelity was evident after OXT treatment (MNI *x*, *y*, *z*: −2, 30, −8, $t_{(21)} = 4.38$, $P_{FWE} = 0.04$; Figure 2B). This OXT effect in the ACC positively correlated with the behavioral OXT effect on arousal ratings of sexual infidelity (MNI *x*, *y*, *z*: 0, 10, 30, $t_{(21)} = 5.06$, $P_{FWE} = 0.01$; MNI *x*, *y*, *z*: 0, 20, 30, $t_{(21)} = 4.92$, $P_{FWE} = 0.02$; MNI *x*, *y*, *z*: −2, 38, 12, $t_{(21)} = 4.68$, $P_{FWE} = 0.03$; Figure 2C).

DISCUSSION

In the present study, we aimed at elucidating the modulatory influence of OXT on the neural processing of volitional and emotional ambivalence. The OXT treatment reduced ACC activation during both moral decision-making (Exp. 1) and the imagery of sexual infidelity (Exp. 2). In addition, OXT diminished activation in the ventromedial prefrontal cortex in response to moral evaluations. On the behavioral level, these neural effects were paralleled by the accelerated acceptance compared with the rejection of moral dilemmas in the OXT, but not the PLC

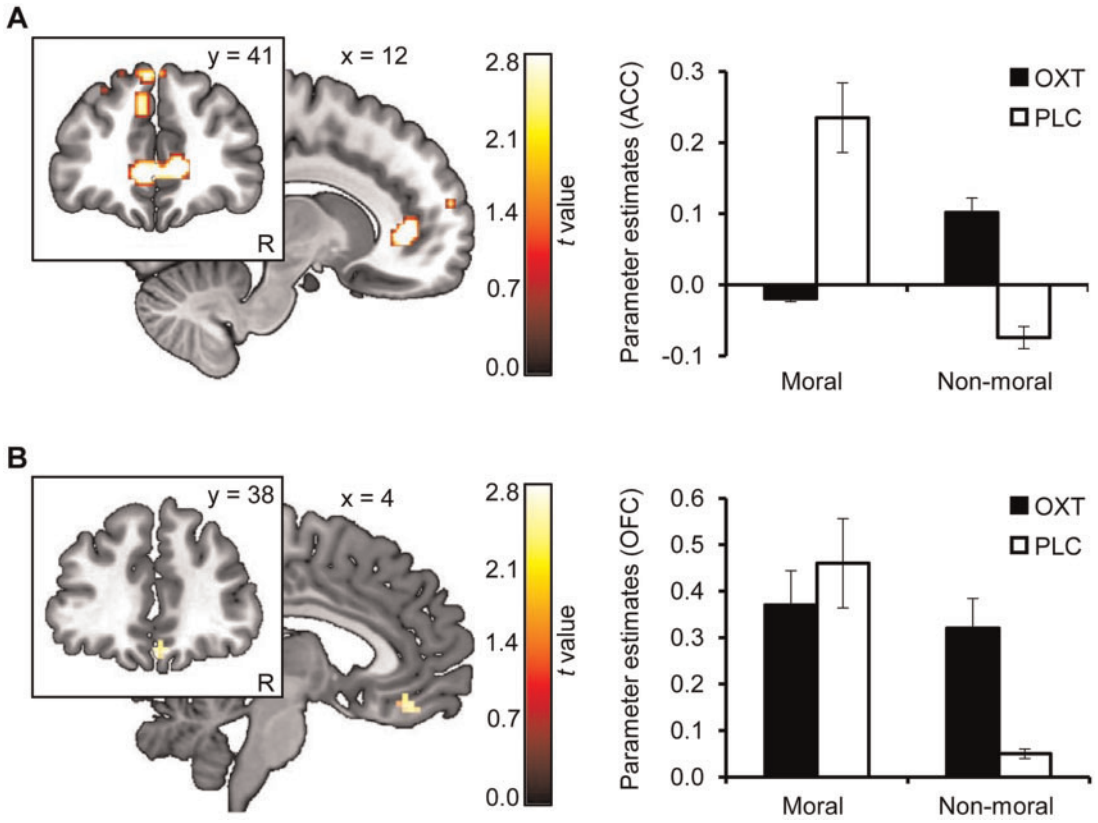

Fig. 1 Oxytocin (OXT) effects on moral decision-making (Experiment 1). OXT compared with placebo (PLC) significantly reduced brain activity in the anterior cingulate cortex (**A**) and orbitofrontal cortex (**B**) during the evaluation of moral dilemmas. Error bars indicate the standard error of the mean (SEM). Abbreviations: ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; OXT, oxytocin; PLC, placebo.

group (Exp. 1), and by decreased arousal ratings of imagined infidelity (Exp. 2). Importantly, a stronger reduction of ACC activity was associated with an enhanced decrement of arousal, thus indicating that the ACC recruitment reflects the psychological response to ambivalence.

Consistent with our previous findings, the OXT treatment had no effect on the endorsement of utilitarian or deontological options (Scheele *et al.*, 2014b). However, during the evaluation of moral dilemmas compared with non-dilemma scenarios, OXT suppressed activity in the cingulate cortex and precuneus, which have been identified as regions distinguishing difficult from easy personal moral judgments (Greene *et al.*, 2004). We have recently shown that OXT can induce a self-referential processing bias in moral decision-making (Scheele *et al.*, 2014b) and greater self-congruence may subsequently produce a diminished sense of volitional ambivalence. Current neurobiological concepts of human morality (Koenigs *et al.*, 2007; Shenhav and Greene, 2010) further emphasize the function of the ventromedial prefrontal cortex and OFC for producing moral emotions such as guilt or shame. In fact, patients with OCD display a moral hyper-sensitivity which has been linked to increased engagement of these brain regions (Harrison *et al.*, 2012). It is currently still elusive to what extent OXT is involved in the pathogenesis of OCD. An early case study reported anti-obsessive effects of an intranasal OXT treatment (Ansseau *et al.*, 1987), but two small clinical trials (den Boer and Westenberg, 1992; Epperson *et al.*, 1996) failed to detect significant improvements. Cerebrospinal fluid measurements of OXT levels in OCD patients are inconsistent (Leckman *et al.*, 1994; Altemus *et al.*, 1999). Nevertheless, anti-obsessive effects of serotonin reuptake inhibitors may be partly exerted through oxytocinergic mechanisms (Humble *et al.*, 2013) and our results suggest that an OXT treatment could be particularly beneficial for a subtype of OCD patients with moral-related compulsions.

Jealousy is often the consequence of assumed partner infidelity and constitutes a risk factor for domestic violence (Kingham and Gordon, 2004). In addition, delusional jealousy, also called Othello's syndrome, frequently occurs from neurological disorders (Graff-Radford *et al.*, 2012). In contrast to Takahashi *et al.* (2006), we did observe significant activations during the imagery of sexual infidelity in the cingulate cortex and frontal regions, but not in the amygdala or hippocampus. This discrepancy and the diminished neural responses in the emotional condition could result from intercultural differences between a European and an Asian sample, but it is more likely to reflect distinct features in bonding-related sample characteristics such as the clearly longer relationship duration in our study (36 months *vs* 15 months in the study of Takahashi *et al.* [2006]; cf. Supplementary Table S6). Romantic relationships evolve over time and the first phase of 'being in love' is characterized by high passion and intimacy usually lasting approximately half a year. During the second phase of a relationship, 'passional love,' feelings of euphoria and excitation decrease and in the third phase, 'companionate love,' the relationship becomes friendship-like (de Boer *et al.*, 2012). In the present study, the participants were in the second phase and future studies are warranted to elucidate whether OXT exerts similar effects on jealousy processing during the first and third phases of a relationship.

The ACC has been previously found to signal distress due to exclusion from an opposite-sex player in a cyberball game, suggesting that the social attachment system recruits the ACC to promote social connectedness (Eisenberger *et al.*, 2003). Aside from reducing ACC activity during the pre-feedback period of a trust game (Baumgartner *et al.*,

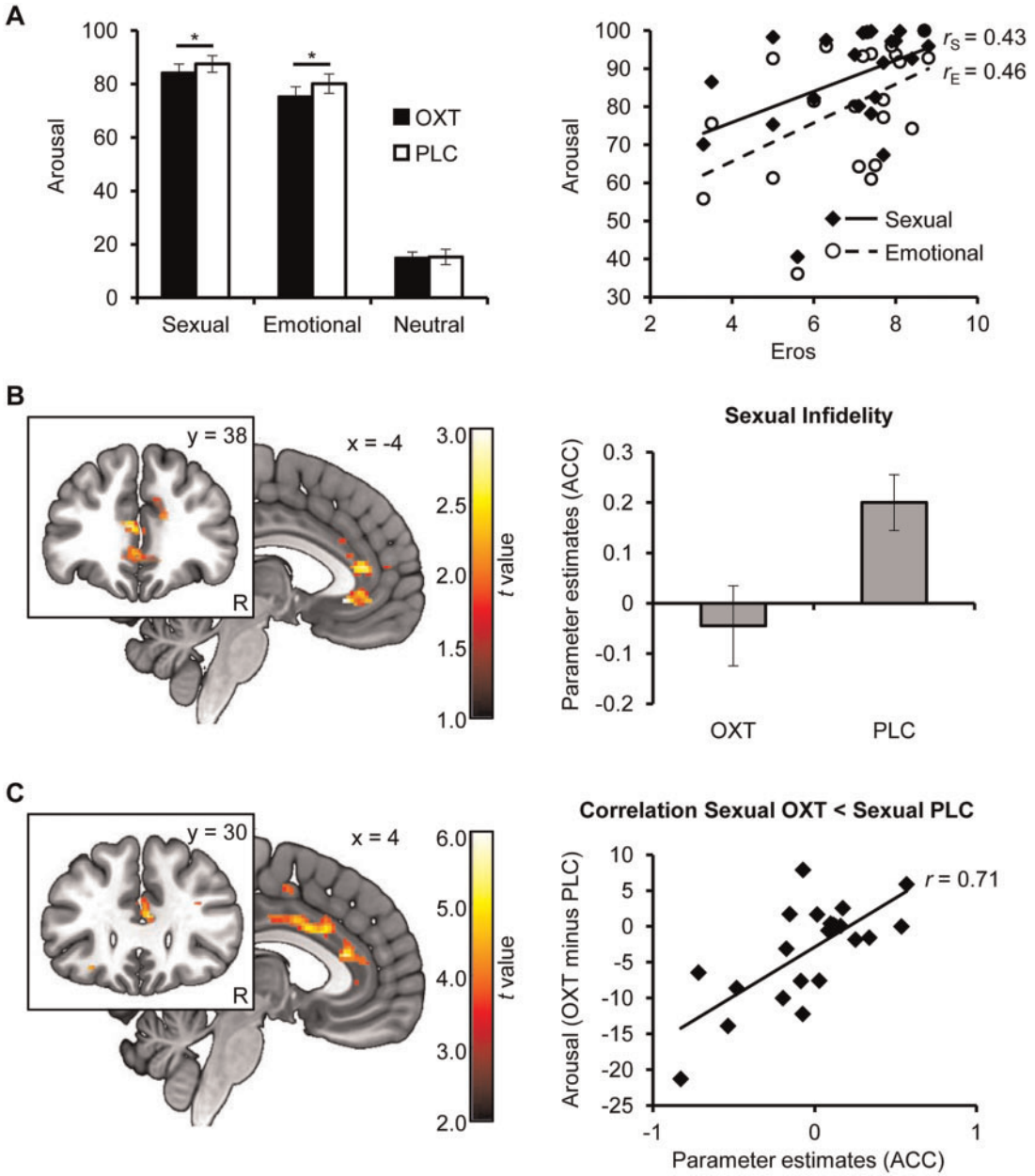

Fig. 2 Oxytocin (OXT) effects on imagery of infidelity (Experiment 2). OXT significantly decreased arousal ratings of sentences describing sexual as well as emotional partner infidelity and these ratings positively correlated with Eros (a romantic love style) (**A**). OXT diminished the neural response to imagery of sexual infidelity in the anterior cingulate cortex (ACC) (**B**) and this OXT effect on ACC activity predicted the behavioral OXT effect on arousal ratings of sexual infidelity (**C**). Abbreviations: ACC, anterior cingulate cortex; OXT, oxytocin; PLC, placebo; $^*P < 0.05$.

2008), OXT also abolishes the negative evaluation of aversely conditioned faces by attenuating ACC and amygdala response (Petrovic *et al.*, 2008). The absence of an amygdala downregulation in the present study corroborates the results of Petrovic *et al.* (2008), who reported that the amygdala modulation varies as a function of task features.

The intriguing findings of reduced arousal ratings of and ACC responses to the imagery of sexual infidelity along with our previous finding of increased activity in reward-associated brain regions after OXT treatment (Scheele *et al.*, 2013) indicate that OXT may decrease emotional ambivalence by promoting and strengthening the pair-bond representation. Our results therefore complement the interactionist component process model (Bartz *et al.*, 2011; Scheele *et al.*, 2014a), which posits that social OXT effects are contingent upon contextual and interindividual factors. In ambivalent situations, OXT may bias an individual toward favoring a prosocial interpretation of conflicting emotions or cognitions.

In accordance with Bleuler's (1908) description of ambivalence as a core symptom of schizophrenia, several recent studies document elevated levels of relationship-associated or task-measured ambivalence in patients with schizophrenia (Tremeau *et al.*, 2009; Antonius *et al.*, 2013; Docherty *et al.*, 2014). Since an exploratory meta-analysis of four randomized controlled trials investigating OXT's influence on psychosis found only weak treatment effects (Gumley *et al.*, 2014), the promise of OXT seems to instead lie more in augmentation of therapies to alleviate ambivalence-related symptoms. Given that OXT

is known to increase the willingness to socially share one's emotion (Lane *et al.*, 2013), we predict that OXT would enhance the therapeutic effect of ambivalence-tailored treatment protocols.

A limitation to the present study is that we tested exclusively male participants. Future studies are warranted to unravel possible sexual-dimorphic effects of OXT (Preckel *et al.*, 2014) on neural and behavioral substrates of ambivalence. Furthermore, the block design in Exp. 1 precluded a differential analysis of the moral dilemmas pertaining to the extent of potential self-benefit which can moderate behavioral OXT effects (Scheele *et al.*, 2014b). In Exp. 2, we did not collect electrodermal responses as an arousal-associated index of sympathetic activity and we cannot exclude the possibility that the repeated presentation of the sentences during the fMRI and the subsequent behavioral task influenced our results. Nevertheless, the selective effect profile of OXT speaks against a strong impact of novelty. OXT specifically reduced the arousal induced by the imagery of sexual and emotional infidelity, but it had no effect on arousal ratings of neutral sentences which were also presented twice. Furthermore, there were no differences between the arousal ratings of the first and second session irrespective of the treatment (cf. Supplementary Information).

Taken together, we provide here first evidence that the neuropeptide hormone OXT can reduce volitional and emotional ambivalence in the domains of moral decision-making and imagery of partner infidelity. Our findings can help to inform the design of future clinical trials examining the therapeutic potential of an OXT treatment for psychiatric disorders with altered ambivalence processing such as schizophrenia or OCD.

AUTHOR'S CONTRIBUTION

K.P. and D.S. contributed equally to this work (shared 1st authorship). K.P., D.S. and R.H. designed the experiments; K.P., D.S. and M.E. conducted the experiments; K.P., D.S. and R.H. analyzed the data; K.P., D.S., M.E., W.M. and R.H. wrote the paper.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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