Oxytocin Facilitates Approach Behavior to Positive Social Stimuli via Decreasing Anterior Insula Activity

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Abstract

Background: The neuropeptide oxytocin can extensively modulate human social behavior and affective processing, and its effects can be interpreted in terms of mediating approach-avoidance motivational processes. However, little is known about how oxytocin mediates approach-avoidance behavior and particularly the underlying neural mechanisms.

Methods: In a randomized, double-blind, between-subject design, the present pharmaco-fMRI study used an approach-avoidance paradigm to investigate oxytocin's effects on approach-avoidance behavior and associated neural mechanisms.

Results: Results revealed that oxytocin generally decreased activity in the right striatum irrespective of response (approach/avoidance) and social context, suggesting an inhibitory effect on motivational representation during both appetitive approach and aversive avoidance. Importantly, while on the behavioral level oxytocin selectively enhanced accuracy when approaching social positive stimuli, on the neural level it decreased left ventral and right dorsal anterior insula activity in response to social vs nonsocial positive stimuli compared with the placebo treatment. The left ventral anterior insula activity was negatively correlated with the corresponding accuracy difference scores in the oxytocin but not in the placebo group.

Conclusion: Given the role of the ventral anterior insula in emotional processing and the dorsal anterior insula in salience processing, the oxytocin-induced suppression of activity in these regions may indicate that oxytocin is acting to reduce interference from hyper-activity in core regions of the emotional and salience networks when approaching salient positive social stimuli and thereby to promote social interaction. Thus, oxytocin may be of potential therapeutic benefit for psychiatric disorders exhibiting avoidance of social stimuli.

Keywords: oxytocin, approach/avoidance behavior, anterior insula, positive social stimuli

Introduction

Across species, the hypothalamic neuropeptide oxytocin (OT) regulates social behavior, particularly bonding and maternal care (Striepens et al., 2011; Kendrick et al., 2018). During the last 2 decades, the number of studies examining oxytocinergic regulation of human behavior via intranasal administration of OT has steadily increased. While OT can facilitate appetitive approach behaviors, such as interpersonal trust and generosity (Kosfeld et al., 2005; Zak et al., 2007), pair bonding and maternal behavior (Strathearn et al., 2009; Scheele et al., 2012) and emotional empathy and face recognition (Hurlemann et al., 2010; Marsh et al., 2010), it can also promote aversive avoidance behavior by increasing envy and schadenfreude (Shamay-Tsoory

Significance Statement

The hypothalamic neuropeptide oxytocin (OT) plays an important role in modulating human social behavior. These effects can be interpreted in terms of OT's actions on basal approach-avoidance (AA) motivational processes, as proposed by the general AA hypothesis of OT (GAAO). However, few studies have evaluated the proposed OT effects on AA behavior and particularly the underlying neural mechanisms. Using neuroimaging combined with intranasal OT administration, the present study revealed that while OT selectively enhanced behavioral accuracy when approaching social positive stimuli, it decreased left ventral and right dorsal anterior insula (AI) activity in response to social vs nonsocial positive stimuli compared to the PLC treatment, with the left ventral AI activity being negatively correlated with the corresponding behavioral accuracy only in the OT group. These findings provide the first confirmatory evidence for the GAAO by demonstrating that OT facilitates human approach behavior to social positive stimuli via inhibiting AI activity.

et al., 2009), ethnocentrism (e.g., trust and empathy; De Dreu et al., 2010; Sheng et al., 2013), group-serving dishonesty (Shalvi and De Dreu, 2014), and noncooperation (Bartz et al., 2011; De Dreu et al., 2012).

To account for these complex and somewhat contradictory findings, Harari-Dahan and Bernstein (2014) proposed in their general approach-avoidance (AA) hypothesis of OT (GAAO) that the broad effects of OT on human behavior are mediated by its actions on basal AA motivational processes. More specifically, within this extended overarching framework, OT's complex behavioral effects are considered to be rooted in its modulation of the salience of personally relevant and emotionally evocative stimuli not necessarily restricted to social contexts (Harari-Dahan and Bernstein, 2014; cf. Kemp and Guastella, 2011 for the social-approach/withdrawal hypothesis and Shamay-Tsoory and Abu-Akel, 2016 for the social salience hypothesis). However, surprisingly few studies have experimentally evaluated the proposed effects of OT on AA behavior and particularly the underlying neural mechanisms.

In a previous study that examined the effects of intranasal OT on human AA behavior, OT was found to accelerate both approach and avoidance behavior towards emotionally negative stimuli such as disgusted faces (Theodoridou et al., 2013; Harari-Dahan and Bernstein, 2017). Using similar paradigms, OT also facilitated approach towards angry faces with a direct gaze (Radke et al., 2013). Furthermore, in the context of pair bonding, OT was found to modulate interpersonal space by decreasing the preferred distance men in a romantic relationship kept between themselves and an unknown attractive woman (Scheele et al., 2012). However, these studies predominantly used emotional faces to investigate OT's actions on AA behavior and were thus unable to determine whether observed effects were driven by its well-established actions on increased attention and attraction to faces per se (Theodoridou et al., 2009; Domes et al., 2013; Shahrestani et al., 2013; Striepens et al., 2014; Xu et al., 2015). Moreover, the neural substrates mediating OT's effects on AA behavior also remain unclear, with initial evidence showing decreased amygdala activity only when approaching angry faces (Radke et al., 2017). Since this latter study also used facial stimuli, this again precludes any definitive conclusion as to whether findings simply reflect the well-documented anxiolytic effect of OT in decreasing amygdala responses to threatening facial expressions (Heinrichs et al., 2003; Kirsch et al., 2005) rather than specific effects on AA behavior.

The present study has therefore employed a face-independent AA task combined with fMRI to investigate OT's specific effects on AA behavior and the underlying neural mechanisms involved. Thus, social and nonsocial scenes rather than facial experimental stimuli were used to determine specific effects of OT on AA behavior per se to avoid its potential confounding effects on face processing. Participants were instructed to approach positive (appetitive approach) and avoid negative (aversive avoidance) stimuli during the AA task. In accordance with the GAAO that OT modulates salience of cues that are personally relevant and emotionally evocative but not necessarily specific to social contexts (Harari-Dahan and Bernstein, 2014), we hypothesized that OT would (1) facilitate approach behavior to positive stimuli, particularly more emotionally evocative social ones, and associated activity in the motivational and emotional salience core regions such as the striatum and anterior insula, and (2) decrease avoidance behavior via attenuating amygdala reactivity to negative stimuli, particularly more emotionally evocative negative social ones.

Methods And Materials

Participants and Treatment

A total of 83 healthy male students (mean age = 21.35 years, SD = 2.48) participated in a randomized, double-blind, between-subject experiment and were randomly assigned to receive either intranasal OT (40 IU; Oxytocin Spray, Sichuan Meike Pharmacy Co. Ltd, China) or placebo (PLC; same ingredients other than OT, i.e., sodium chloride and glycerin). To control for potential confounding effects from personality traits or mood states, subjects completed Chinese versions of validated psychometric questionnaires before treatment, including the Positive and Negative Affect Schedule (Watson et al., 1988), Autism Spectrum Quotient (Baron-Cohen et al., 2001), Empathy Quotient (Baron-Cohen and Wheelwright, 2004), and NEO 5-factor inventory (Costa and MacCrae, 1992). To further control for a potentially confounding influence of altered mood states, subjects were asked to complete the Positive and Negative Affect Schedule 3 times: after they first arrived (pretreatment), before MRI scanning (posttreatment), and finally after scanning (post-scan). Subjects received OT/PLC treatment in accordance with a standardized protocol (Guastella et al., 2013), and fMRI acquisition started 45 minutes after treatment. A total of 7 subjects were excluded due to technical issues during data acquisition (4 subjects) or excessive head movement (3 subjects). Thus, 39 subjects in the OT group and 37 subjects in the PLC group were included in the final analysis. In postscan interviews, subjects were unable to identify better than chance whether they had received OT or PLC (χ^2 = 0.21, P = .646). Written informed consent was obtained from all subjects before study inclusion. All procedures were in accordance with the latest version of the Declaration of Helsinki and approved by the ethical committee of University of Electronic Science and Technology of China.

The AA Task

In a revised AA task (Chen and Bargh, 1999), participants were instructed to make approach responses to positive social or nonsocial stimuli (e.g., happy friends meeting or beautiful landscapes) and avoidance responses to social or nonsocial negative stimuli (e.g., victims or environmental pollution). In a prestudy, we selected 620 pictures mostly from the International Affective Picture System (Lang et al., 2008) and additionally from the Internet that were rated in terms of valence and arousal (9-point Likert scale) by an independent sample of 34 healthy volunteers (18 males). Based on this data, a total of 112 stimuli (28 pictures per category, positive vs negative and social vs nonsocial) were selected: social positive (valence: mean±SD=2.36±0.27; arousal: 6.27±0.35), social negative (valence: 2.47±0.26; arousal: 6.65±0.46), nonsocial positive (valence: 1.68±0.39; arousal: 6.25±0.42), and nonsocial negative (valence: 1.87±0.55; arousal: 6.10±0.70). Note that the valence rating scores were transformed to the distance from the neutral midpoint of the 9-point scale. Each picture was presented for 3 seconds at a 624- × 468-pixel resolution followed by a jittered inter-stimulus interval of 2 to 6 seconds. Subjects were instructed to pull the positive stimuli towards their body by pressing the "down" key and push the negative stimuli away from their body by pressing the "up" key successively via a response pad during the 3-second presentation. To realistically convey approach and avoidance of the stimuli for the subjects, each pulling-associated button press would enlarge the picture by 100×75 pixels while each pushing response would decrease the size of the picture by 100×75 pixels. All subjects preformed 10 practice trials before entering the scanner and were instructed to respond as fast and accurately as possible during the experiment.

Image Acquisition and Data Analysis

Images were collected using a 3 Tesla, GE Discovery MR750 system (General Electric Medical System, Milwaukee, WI). During each fMRI scan, a time series of volumes was acquired using a T2*-weighted echo-planar pulse sequence (repetition time: 2000 ms; echo time: 30 ms; number of slices: 39; slice thickness: 4 mm; gap: 1 mm; field of view: 240×240 mm; resolution: 64×64; flip angle: 90°). To control for any anatomic abnormalities and increase normalization accuracy during preprocessing, additional T1-weighted images were acquired obliquely with a 3-dimensional spoiled gradient echo pulse sequence (repetition time: 6 milliseconds; echo time: 2 milliseconds; flip angle: 9°; field of view: 256×256 mm; acquisition matrix: 256×256; number of slices: 156; slice thickness: 1 mm).

Images were processed using SPM8 (Wellcome Department of Cognitive Neurology, London; https://www.fil.ion.ucl.ac.uk/spm/software/spm8/) (Friston et al., 1994). The first 5 functional images were deleted to achieve magnet-steady images, and the remaining images were realigned to correct for head movement based on a 6-parameter rigid body algorithm. After co-registering the mean functional image and the T1 image, the T1 image was segmented to determine the parameters for normalizing the functional images to Montreal Neurological Institute (MNI) space. These normalized images were finally spatially smoothed using a Gaussian kernel (8 mm full-width at half maximum).

The first-level design matrix included 4 condition-specific regressors (social positive/negative, nonsocial positive/negative) convolved with the canonical hemodynamic response function and the 6 head-motion parameters as nuisance regressors. Contrast images for each stimulus condition, all positive and all negative were created separately. On the second level, group differences were analyzed using 2-sample t tests. Interactions were tested using an ANOVA model implemented in a flexible factorial design. Based on our region-specific hypotheses, the analysis focused on core regions involved in salience processing (Menon, 2015; Uddin, 2015) and appetitive/approach (social/nonsocial reward) and withdrawal/avoidance (punishment/threat) motivational processes (Izuma et al., 2008; Delgado et al., 2008, 2009; Rademacher et al., 2010; Schlund and Cataldo, 2010; Palminteri et al., 2012), that is, the amygdala, the AI, and the striatum. Importantly, these regions strongly overlap with the network mediating the social cognitive and affective effects of intranasal OT (Kirsch et al., 2005; Wigton et al., 2015; Shamay-Tsoory and Abu-Akel, 2016; Kendrick et al., 2018; Yao et al., 2018). Regions-of-interest (ROIs) were anatomically defined using the Automated Anatomic Labeling atlas (Tzourio-Mazoyer et al., 2002). Within the unilateral a priori ROIs, a threshold of $P<.05$ family-wise error (FWE) peak-level correction was set for multiple comparisons using small volume correction (SVC). Parameter estimates used for plotting and brain behavior associations analysis were extracted for each subject from a 6-mm sphere centered on the peak voxel within corresponding ROIs. For additional exploratory whole-brain analyses, a threshold of $P_{FWE}<.05$ corrected at peak level was used and only clusters >10 voxels are reported.

Results

Questionnaires

Two-sample t tests on questionnaires measuring mood, autistic traits, empathy, and personality traits revealed no significant differences between the treatment groups (Ps>.136; supplementary Table 1).

Behavioral Results

For response times, a repeated-measures ANOVA was performed with social context (social vs nonsocial) and response type (approach vs avoidance) as within-subject factors and treatment (OT vs PLC) as between-subject factor. This revealed a significant main effect of response type (F(1, 74)=250.46, $P<.001$), with subjects being significantly faster to approach positive than to avoid negative stimuli (1617.33±176.84 vs 1776.95±184.28). The interaction between social context and response was also significant (F(1, 74)=19.04, $P<.001$), with posthoc tests reavealing that subjects were faster to approach social compared with nonsocial positive stimuli (1600.86±172.73 vs 1633.79±180.49) but slower to avoid social than nonsocial negative stimuli (1784.72±181.76 vs 1769.18±187.65). There were no other significant effects ($P>.106$).

In terms of response accuracy (RA), there was a significant main effect of social context (F(1, 74)=15.75, $P<.001$), with a higher accuracy for social compared with nonsocial stimuli (95.4%±5.7% vs 93.7%±5.4%). The main effect of response type was also significant (F(1, 74)=109.59, $P<.001$), with a higher accuracy for approaching positive than avoiding negative stimuli (97.5%±3.4% vs 91.7%±5.8%). While the interaction between social context, response type, and treatment was not significant (F(1, 74)=0.76, $P=.385$), an exploratory pairwise comparison revealed a significantly higher RA only for social ($P=.031$) but not nonsocial positive stimuli ($P=.568$) in the OT relative to the PLC group (Figure 1). The interaction between social context and response type was marginally significant (F(1, 74)=3.18, $P=.079$),

suggesting a trend of higher accuracy to social vs nonsocial stimuli for positive ($P < .001$; 98.8%±2.1% vs 96.2%±4.0%) but not negative stimuli ($P = .280$; 92.1%±6.1% vs 91.3%±5.6%). There were no other significant effects ($P > .361$). Given the slightly higher valence scores for social compared with nonsocial positive stimuli, to clarify whether the valence difference would confound the significant OT's effects, we further conducted a correlation analysis between valence scores for individual pictures by independent raters and RA for social and nonsocial positive stimuli in the experimental subjects and found no significant associations either for social (Pearson $r = 0.061$, $df = 28$, $P = .759$) or nonsocial positive stimuli (Pearson $r = -0.044$, $df = 28$, $P = .823$). Thus, the magnitude of the positive valence score for the individual pictures did not influence response accuracy.

fMRI Results

We first examined unspecific effects of treatment (OT vs PLC) independent of response type and social context using a 2-sample *t* test. This revealed decreased right striatum activity (MNI = 22,
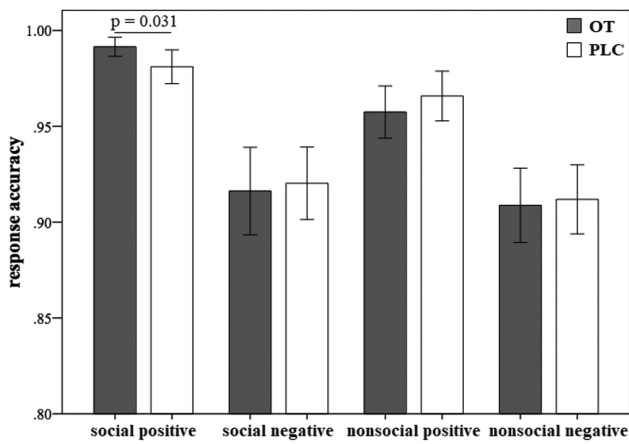

Figure 1. Response accuracy in response to each condition in the oxytocin and placebo groups. Error bars show standard errors.

2, 8, $t = 4.05$, $P_{FWE} = .025$ SVC, voxels = 48; Figure 2A) in the OT compared with the PLC group (OT $_{all\ conditions}$ < PLC $_{all\ conditions}$).

Next, we examined treatment effects and interactions between treatment and social context on appetitive approach and aversive avoidance separately. For appetitive approach, decreased activity in the right striatum (MNI = 20, 2, 6, $t = 3.96$, $P_{FWE} = .031$ SVC, voxels = 29) and the left dorsal AI (MNI = -38, 12, 6, $t = 3.52$, $P_{FWE} = .040$ SVC, voxels = 11; Figure 2B) was found in the OT compared with the PLC group (OT $_{all\ positive}$ < PLC $_{all\ positive}$). Examining the interaction between treatment and social context (OT $_{social\ positive > nonsocial\ positive}$ < PLC $_{social\ positive > nonsocial\ positive}$) during approach behavior revealed significant interaction effects in the left ventral AI (MNI = -42, 6, -6, $t = 3.57$, $P_{FWE} = .022$ SVC, voxels = 14; Figure 3A) and the right dorsal AI (MNI = 48, 12, 2, $t = 3.40$, $P_{FWE} = .036$ SVC, voxels = 7; Figure 3B), suggesting that OT decreased activity in these regions during approach of social relative to nonsocial positive stimuli.

With respect to aversive avoidance, OT decreased activity in the right striatum (MNI = 24, 2, 10, $t = 4.31$, $P_{FWE} = .011$ SVC, voxels = 58) and the right amygdala (MNI = 28, -4, -18, $t = 3.34$, $P_{FWE} = .025$ SVC, voxels = 2; Figure 2C) irrespective of social context (OT $_{all\ negative}$ < PLC $_{all\ negative}$). Examination of interaction effects between treatment and social context during avoidance behavior (OT $_{social\ negative > nonsocial\ negative}$ < PLC $_{social\ negative > nonsocial\ negative}$) revealed no significant effects ($P_{FWE} < .05$ SVC). There were also no other significant effects in the a priori ROIs ($P_{FWE} < .05$ SVC). For completeness, additional effects beyond the a priori ROIs on the whole-brain level are reported in supplementary Table 2 ($P_{FWE} < .05$).

Brain Behavior Associations

Correlation analyses between extracted parameter estimates from the left ventral and the right dorsal AI (social positive > nonsocial positive) and RA difference scores (social positive – nonsocial positive) were conducted separately to explore associations between OT-induced modulation on neural responses and corresponding behavioral indices. Results showed a significant negative correlation between activity in the left ventral AI (MNI = -42, 6, -6) and RA difference scores in the OT (Pearson $r = -0.346$, $df = 39$, $P = .031$; Figure 3A) but not in the PLC group
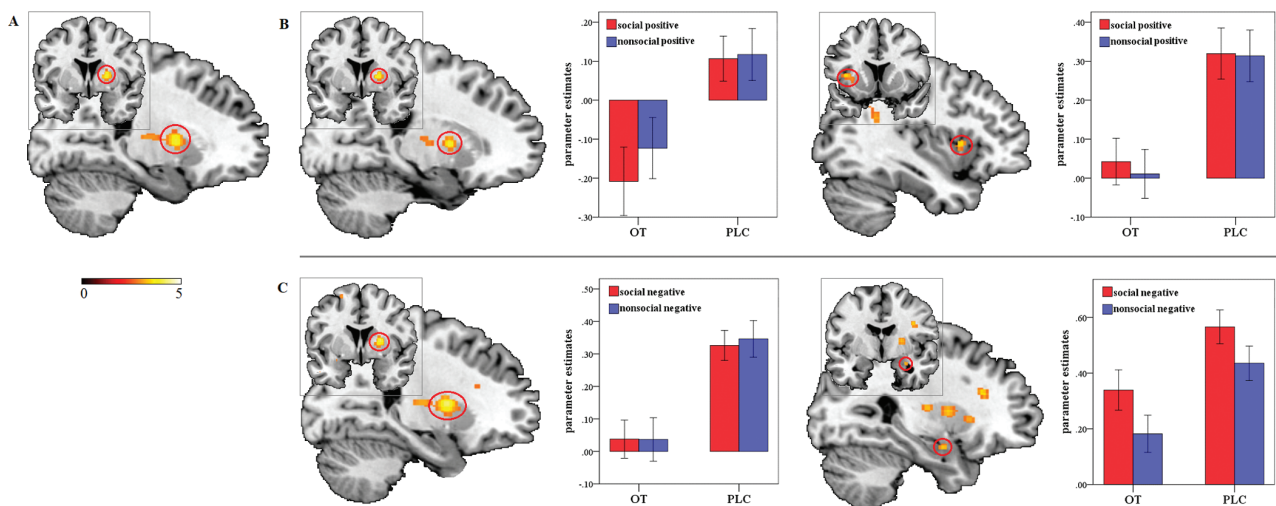

Figure 2. (A) Decreased right striatum activity in the oxytocin (OT) compared with the placebo (PLC) group. (B) Decreased activity in the right striatum and the left dorsal anterior insula (AI) in the OT compared with the PLC group during appetitive approach. (C) Decreased activity in the right striatum and the right amygdala in the OT compared with the PLC group during aversive avoidance. Statistic maps were displayed with a $P < .005$ uncorrected threshold. Error bars show standard errors.
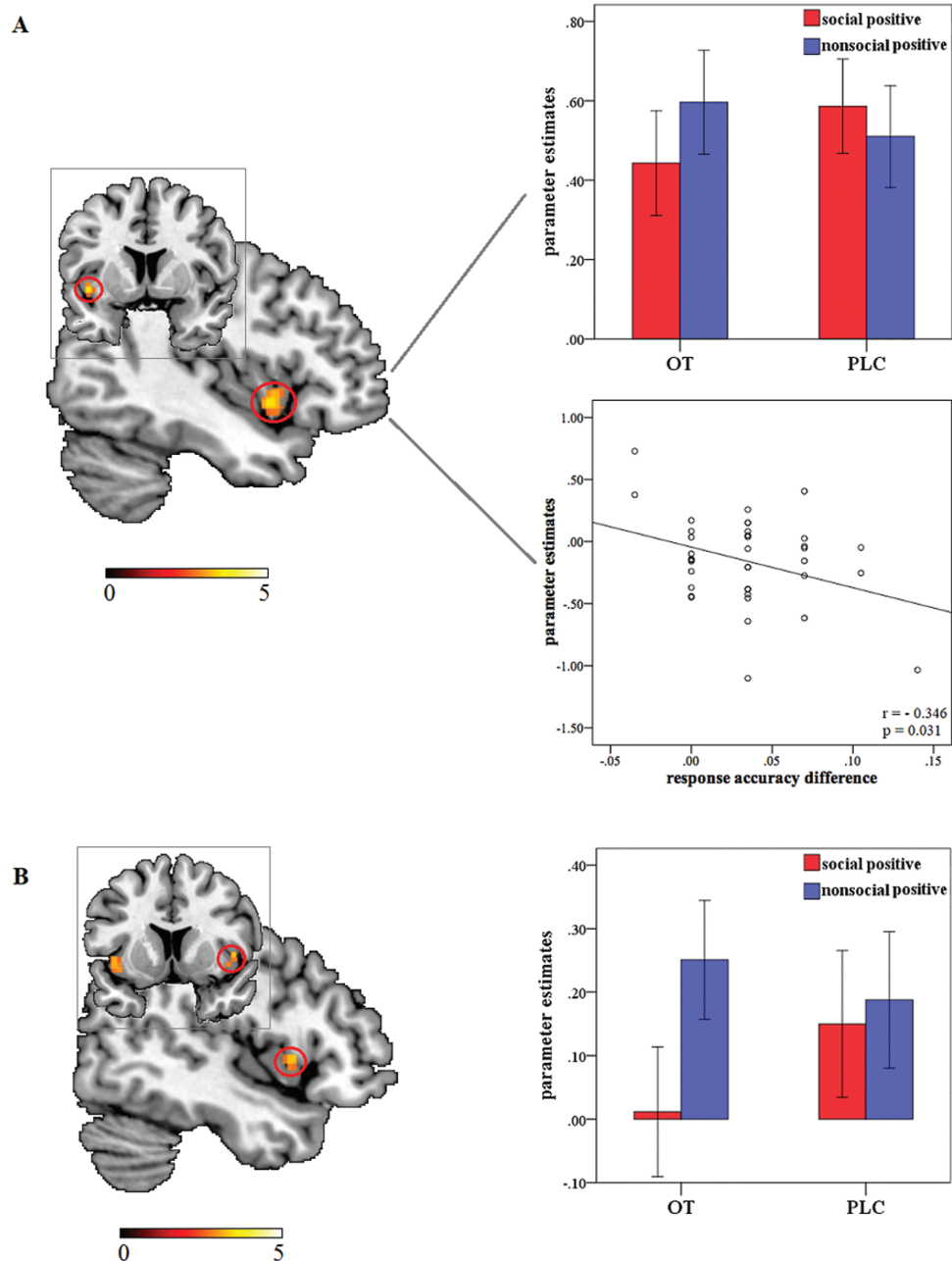
Figure 3. Oxytocin (OT) decreased the left ventral anterior insula (AI) (A) and the right dorsal AI (B) activity in response to social relative to nonsocial positive stimuli (OT $_{\text{social positive>nonsocial positive}}$ <placebo [PLC] $_{\text{social positive>nonsocial positive}}$). Statistic maps were displayed with a P<.005 uncorrected threshold. Error bars show standard errors.

(Pearson r=0.039, df=37; P=.818). The correlation difference between groups was tested using the Fisher z-transformation test and revealed a marginally significant difference between the OT and PLC groups (Fishers z-score=-1.672, P=.094).

Discussion

The present study investigated OT's effects on AA behavior and corresponding neural mechanisms using emotional scenes and specifically examined whether the effects generalize across social and nonsocial contexts. On the neural level, a significant main effect of treatment was observed in the right striatum, with OT generally decreasing activity in this region irrespective of response type and social context. Furthermore, separate examination of appetitive approach and aversive avoidance revealed that while OT specifically decreased the left dorsal AI activity during approaching positive stimuli, it decreased right amygdala activity during avoidance of negative stimuli. Additionally, exploring the role of social context revealed evidence for a selective enhancement effect of OT on RA when approaching social relative to nonsocial positive stimuli. This behavioral effect was accompanied by decreased left ventral and right dorsal AI activity in response to social vs nonsocial positive stimuli in the OT compared with the PLC group, with the relative difference in left ventral AI activity and RA for social vs nonsocial positive stimuli exhibiting a negative association following OT. By contrast, during aversive avoidance, no evidence for the social specificity of OT was observed. These

findings provide support for the GAAO by showing that OT modulates activation of motivational and emotional salience core regions during both approach to positive and avoidance to negative stimuli across social and nonsocial contexts and that OT specifically facilitates approach behavior to more personally relevant and emotionally evocative stimuli, namely positive social stimuli, via inhibiting AI activity.

Examination of unspecific OT effects on AA behavior revealed significantly decreased activity in the right striatum following OT across both response type and social contexts. The striatum has been strongly involved in both approach (social/nonsocial reward) and avoidance (punishment/threat)-motivated behavior (Izuma et al., 2008; Delgado et al., 2008, 2009; Rademacher et al., 2010; Palminteri et al., 2012). Thus, OT may inhibit motivational representation both during appetitive approach and aversive avoidance. Furthermore, OT additionally decreased left dorsal AI activity during approach to positive stimuli across social and nonsocial contexts. As a core hub of the salience network (Menon, 2015; Uddin, 2015), the reduced dorsal AI activity may thus reflect an OT-evoked decrease in the salience of positive stimuli when subjects approached them.

The observed inhibitory effects of OT on striatum and AI activity seem to conflict with both the proposal that it enhances the salience of social cues (Shamay-Tsoory and Abu-Akel, 2016) and some previous findings that OT-induced alterations on human social behavior are associated with increased activity in the striatum and AI (Baumgartner et al., 2008; Strathearn et al., 2009; Striepens et al., 2011; Yao et al., 2018). Given that OT effects on social behavior are often highly context and person dependent (Bartz et al., 2011), this inconsistency could be due to different paradigms and contexts used in these previous studies. In previous studies, subjects were asked to passively process certain stimuli, whereas the present study using an AA task required subjects to actively approach or avoid them.

It is notable that OT also decreased activation of the left ventral and right dorsal AI during approaching social relative to nonsocial positive stimuli. Given the role of the ventral AI in emotional processing (Nieuwenhuys, 2012; Uddin, 2015; Wager and Barrett, 2017) and the dorsal AI in salience processing (Menon, 2015; Uddin, 2015), these attenuated AI activities may indicate a more robust inhibitory effect of OT on decreasing both the emotional and salience processing of social positive stimuli that are more personally relevant and emotionally evocative (Harari-Dahan and Bernstein, 2014). Consistent with previous observations that OT can enhance processing of positive facial emotion (Guastella et al., 2008; Marsh et al., 2010; Domes et al., 2013; Xu et al., 2015), the present study found evidence that OT may specifically facilitate RA during approaching social but not nonsocial positive stimuli. Thus, the oxytocinergic downregulation of AI activation may act to attenuate interference caused by hyperactivation of the AI when subjects approach external social positive stimuli, resulting in enhanced accuracy of social information processing and facilitation of social interaction. This assumption is further supported by the presence of a significant negative correlation between the left ventral AI activity and the RA difference between social and nonsocial positive stimuli following OT but not PLC administration. However, it should be noted that the difference in brain-behavior correlation between groups was only marginally significant, and thus inferences regarding this effect of OT need to be drawn with caution.

Additionally, OT was found to decrease amygdala activity during avoidance responses to negative stimuli independent of social context. This finding is in line with the anxiolytic action of OT via inhibiting amygdala responses to threatening stimuli (Kirsch et al., 2005; Petrovic et al., 2008). Based on the GAAO (Harari-Dahan and Bernstein, 2014), the absence of a social-specific effect of OT on avoiding negative stimuli suggests that threatening social and nonsocial stimuli may be comparable in terms of personal relevance and emotional evocation, perhaps due to the high survival relevance of threating events during evolution (Woody and Szechtman, 2011).

Given that we found no significant personality and mood difference between OT and PLC groups, this argues against confounding effects of pretreatment between-group differences on the observed effects of OT. However, individual differences in personality traits have been shown to mediate approach and avoidance behavior, as proposed by the (revised) Reinforcement Sensitivity Theory (Gray and McNaughton, 2000; Corr, 2004). More specifically, previous studies have demonstrated associations between the functional organization of the salience network, particularly the AI, and its interactions with anxiety-related traits such as harm avoidance (Baur et al., 2013; Markett et al., 2013, 2016). Thus, future studies should consider examining the role of individual differences in personality traits on AA behavior and their potential modulatory effects on the effects of OT in this domain. Moreover, within this context, the present findings may lend support for potential therapeutic benefits of OT for psychiatric disorders such as social anxiety and autism exhibiting altered approach/avoidance towards social stimuli (Heuer et al., 2007; Davis et al., 2010; Roelofs et al., 2010; Tanaka and Sung, 2016).

There are several limitations in the present study. Firstly, considering that organisms have primarily evolved mechanisms to approach stimuli associated with positive outcomes and to avoid those associated with aversive ones, we only asked subjects to approach positive and avoid negative stimuli. Effects of OT on approaching negative and avoiding positive stimuli thus remain to be determined. Secondly, we used only male subjects to avoid possible confounding effects from menstrual cycle; thus, the present conclusions are limited to males and sex differences remain to be explored. Thirdly, another potential limitation is that we cannot completely exclude the possibility of a complex interaction involving differences in social and nonsocial stimuli valence and OT effects on response accuracy during approach behavior. However, for positive valence stimuli, we found no association between individual picture valence and response accuracy for either social or nonsocial stimuli, suggesting that valence differences are unlikely to have had a major impact on our results. Finally, we do not know if the effects we observed with a 40-IU dose of OT may also be observed with lower doses. A previous study has revealed a dose-dependent effect of OT (12, 24, and 48 IU), with the 24-IU dose being most effective in inhibiting amygdala activity during negative emotional processing (Spengler et al., 2017). However, in 2 previous studies from our group, we reported evidence for comparable effects of 24- and 40-IU doses on both behavioral and neural changes in the context of empathy and self-processing in humans (Zhao et al., 2017; Geng et al., 2018).

In conclusion, the present study provides first evidence for the GAAO by demonstrating that while OT inhibits motivational representations both during appetitive approach and aversive avoidance, it facilitates human approach behavior to more general positive social stimuli via inhibiting AI activity. This inhibitory effect of OT may reduce interference from emotion-facilitated hyperactivation of core regions of the emotional and salience networks when approaching external social salient

positive stimuli and consequently be of benefit in promoting social interaction.

Supplementary Materials

Acknowledgments

Statement of Interest

None.

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