Oxytocin Attenuates Amygdala Responses to Emotional Faces Regardless of Valence

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Background: Oxytocin is known to reduce anxiety and stress in social interactions as well as to modulate approach behavior. Recent studies suggest that the amygdala might be the primary neuronal basis for these effects.

Methods: In a functional magnetic resonance imaging study using a double-blind, placebo-controlled within-subject design, we measured neural responses to fearful, angry, and happy facial expressions after intranasal application of 24 IU oxytocin compared with placebo.

Results: Oxytocin reduced right-sided amygdala responses to all three face categories even when the emotional content of the presented face was not evaluated explicitly. Exploratory whole brain analysis revealed modulatory effects in prefrontal and temporal areas as well as in the brainstem.

Conclusions: Results suggest a modulatory role of oxytocin on amygdala responses to facial expressions irrespective of their valence. Reduction of amygdala activity to positive and negative stimuli might reflect reduced uncertainty about the predictive value of a social stimulus and thereby facilitates social approach behavior.

Key Words: Amygdala, emotion, facial expressions, functional magnetic resonance imaging, limbic system, neuropeptides, oxytocin, peptides

In rodents, the neuropeptide oxytocin improves social memory (1), decreases anxiety in social interactions (2), and plays an important role in affiliation behavior such as pair-bonding (3,4) and maternal care (5). In humans, oxytocin also seems to be a potent modulator in the processing of social stimuli. For example, oxytocin was found to suppress anxiety to psychosocial stress (6,7) and to induce a substantial increase in trust (8). In a recent study, we showed that a single dose of oxytocin promoted the ability to infer the affective mental states of others from subtle facial cues (9). Therefore, we sought to answer the question of whether the effects of oxytocin on complex social behavior can be traced back to the modulation of the processing of basic social cues, namely facial expressions, and have a significant impact on the neurofunctional correlates of facial emotion recognition.

Oxytocin shows significant binding in the human limbic system, including the amygdala (10–12). Experimental animal studies suggest that social memory effects of oxytocin are mediated by the amygdala (1,13). Therefore, the amygdala might play an important role in mediating the socio-affective effects of oxytocin.

It is well established that the amygdala is crucially involved in the processing of emotional stimuli (14) and the recognition of facial emotions (15). Facial fear and anger have consistently been shown to be associated with amygdala activity (16–18), even when facial expressions are processed without conscious awareness (19). However, amygdala activation has also been found in response to positive stimuli, especially to happy faces (20,21).

In humans, a first functional magnetic resonance imaging (fMRI) study indicated that oxytocin reduces amygdala responses to threatening non-social scenes and to angry and fearful faces (22), which might reflect a selective suppression to signals of threat. However, because oxytocin has been shown to exert substantial influence on rodents' social approach and affiliation behavior, it seems fruitful to explicitly investigate the effects of oxytocin on the perception of positive compared with negative social cues in humans. We hypothesized that oxytocin attenuates neural responses of the amygdala in response to cues of social threat, such as angry and fearful facial expressions and also modulates amygdala activation to happy facial expressions in an implicit facial affect recognition paradigm.

Methods and Materials

Subjects

Thirteen non-smoking healthy male volunteers (age, mean ± SD: 25.7 ± 2.9 years) participated in this study, all of them being free of psychotropic or endocrine medication. The study was approved by the institutional review board of the Medical Faculty of the University of Rostock. All participants gave written informed consent and were paid for participation.

Experimental Protocol

In a double-blind, placebo-controlled within-subject design, the experimental sessions were conducted with a 1-week interval. Oxytocin and placebo were administered intranasally (6,8,9,23). Forty-five minutes before the fMRI sessions, participants received 3 puffs of oxytocin per nostril (Syntocinon-Spray; Novartis, Basel, Switzerland; each puff with 4 IU oxytocin) or placebo (containing all ingredients except for the peptide). After positioning the participants in the scanner, three fMRI sessions were conducted within 75 min after drug administration.

All participants completed a multidimensional mood questionnaire (24) before and after drug administration to assess drug-induced mood effects. Pre-post δ scores were calculated to compare oxytocin and placebo sessions.

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Received December 7, 2006; revised March 6, 2007; accepted March 30, 2007.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2007.03.025

Implicit Facial Affect Recognition Paradigm

In a random block design pictures of facial affect were presented with different intensity levels (17). The faces depicted happy, fearful, or angry expressions (25). In each category pictures of 10 different actors were morphed in four intensity steps from 25% to 100% (Winmorph 2.0; http://debugmode.com/winmorph/) with an additional neutral category, resulting in 13 different conditions of valence and intensity. Within a specific condition the 10 pictures were presented for 2 sec each, resulting in blocks of 20-sec duration. The inter-block interval was 15 sec. The sequence of blocks was pseudo-randomized to circumvent sequential presentations of blocks with identical valence or intensity. The participant was asked to detect the gender of the particular picture presented. Three runs were presented with each run including all 13 conditions once.

Functional Imaging

Blood oxygenation level dependent functional images were acquired with a gradient-echo, echo planar imaging T2*-sensitive sequence on a 3T Scanner (Siemens Trio, Erlangen, Germany).

Details on imaging and statistical procedures can be found in Supplement 1. In short, volumes of 42 contiguous axial slices were obtained (2-mm thickness with 1-mm gap, repetition time 2.41 sec, echo time 25 msec, flip angle 90°, field of view 192 × 192 mm^2, matrix 64 × 64). After preprocessing, a first-level analysis was conducted, resulting in 13 contrast images that were subject to a second-level region of interest analysis (hypothesis-driven approach) with MARSBAR (http://marsbar.sourceforge.net) with predefined anatomical maps of the amygdala (26) and an exploratory random effects whole brain analysis with SPM2 (http://www.fil.ion.ucl.ac.uk/spm) with a threshold of $p < .001$ (uncorrected) and a cluster extend threshold of k = 10.

Results

The region of interest analyses revealed higher activation of the right amygdala in response to emotional faces as compared with neutral faces in the placebo condition, confirming previously reported results (17). More importantly, these effects were absent in the oxytocin compared with the placebo condition, regardless of the specific expression displayed. Accordingly, the direct comparisons between placebo > oxytocin for the three contrasts—angry > neutral, fearful > neutral, and happy > neutral—reached significance in the right amygdala (Table 1 and Figure 1). In addition, left-sided amygdala activity that occurred in the angry > neutral contrast under placebo did not reach statistical significance under oxytocin.

Table 2 summarizes data from whole brain analysis revealing enhanced activations under placebo compared with oxytocin in several frontal, temporal, and brainstem areas, whereas the oxytocin > placebo contrast revealed no significant cluster at a threshold of $p < .001$ (uncorrected).

Table 1. Effects of Drug Treatment on Activation in the Amygdala Using ROI Analyses

	Left Amygdala			Right Amygdala		
Contrast	Value	*t*	*p*	Value	*t*	*p*
PC						
Fearful-neutral	5.03	1.75	n.s.	5.13	2.17	<.05
Angry-neutral	5.91	2.33	<.05	8.03	2.62	<.01
Happy-neutral	3.11	1.21	n.s.	4.87	2.29	<.05
OT						
Fearful-neutral	3.12	1.33	n.s.	−1.87	−.97	n.s.
Angry-neutral	4.88	1.27	n.s.	.11	.03	n.s.
Happy-neutral	4.43	1.68	n.s.	−1.90	−.88	n.s.
PC > OT						
Fearful-neutral	1.91	.50	n.s.	7.00	2.22	<.05
Angry-neutral	1.02	.27	n.s.	7.93	2.56	<.01
Happy-neutral	−1.32	−.36	n.s.	6.77	2.24	<.05

$p < .05$, corrected for multiple comparison. PC, placebo; OT, oxytocin; ROI, region of interest.

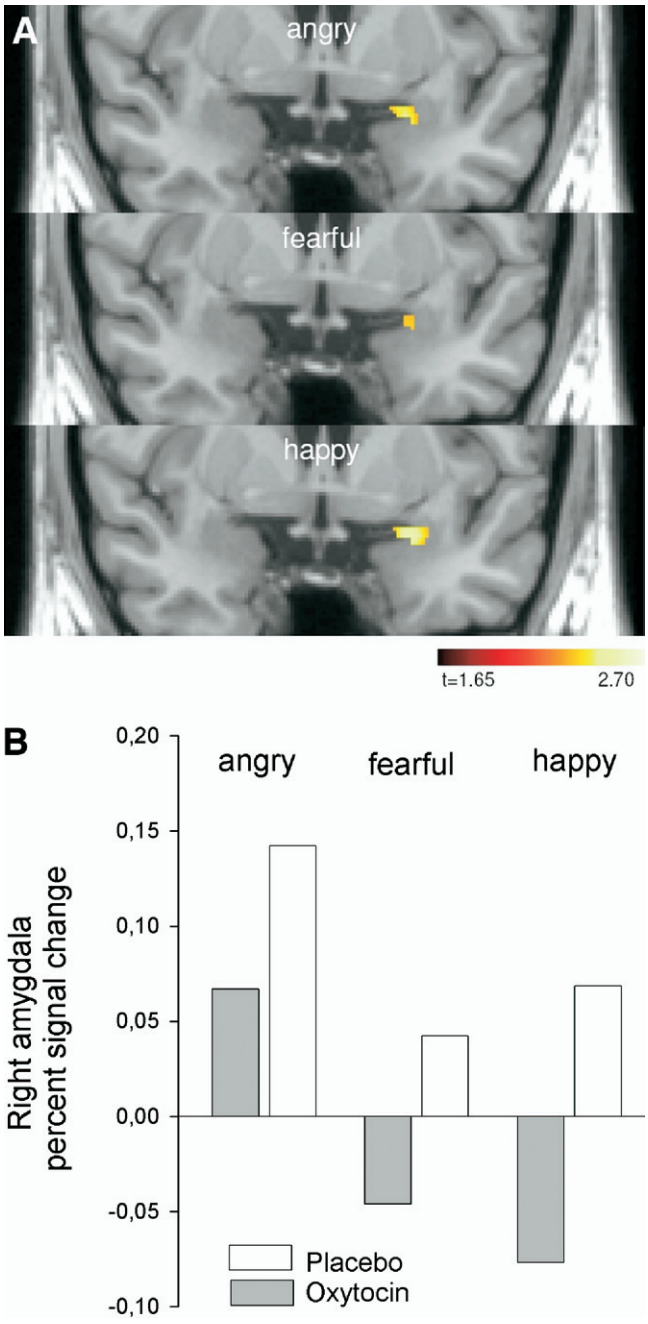

Figure 1. (A) Statistical parametric map of the region-of-interest analyses for the amygdala (y = 4). Significantly higher activation was found after placebo compared with oxytocin treatment in the right amygdala for differential contrasts of emotional versus neutral faces. **(B)** Percent signal change for the three contrasts in the right amygdala for placebo and oxytocin sessions.

Table 2. Whole Brain Analysis

	Coordinates				
	x	y	z	k	t
PC > OT: Fearful-Neutral					
Paracentral gyrus L BA5	−15	−36	60	28	3.64
Frontal medial lobe L BA8	−36	21	51	17	3.38
Medulla L	−3	−48	−39	15	3.58
Anterior cerebellum/culmen	0	−48	−12	81	3.51
Inferior temporal lobe L BA20	−57	0	−36	28	3.53
Medial temporal lobe L BA19	−57	−69	15	13	3.38
PC > OT: Angry-Neutral					
Thalamus/pulvinar L	−24	−21	6	34	4.13
Postcentral gyrus L BA3	−18	−33	57	15	3.54
Precentral gyrus R BA4	39	−18	45	12	3.40
PC > OT: Happy-Neutral					
Inferior temporal lobe L BA38	−39	3	−36	27	3.54
Inferior temporal lobe R BA38	30	6	−48	11	3.52
Paracentral gyrus L BA5	−18	−36	51	12	3.41
Medial temporal lobe L BA19	−57	−66	15	14	3.37

Significant clusters (k > 10) of placebo > oxytocin contrast with a threshold of $p < .001$ (uncorrected). Reported activations are significant at $p < .001$ (uncorrected) with an extend threshold of k = 10. Coordinates are reported relative to the anterior–commisure in the Montreal Neurologic Institute space. BA, Brodmann area; L, left; OT, oxytocin; PC, placebo; R, right.

Oxytocin had no effect on self-reported calmness, wakefulness, or mood (all $p > .50$). Performance in gender detection was nearly perfect (99.6% correct responses) and was not affected by drug administration ($p > .50$).

Discussion

This is the first study to show that a single dose of oxytocin attenuates right-sided amygdala responses to emotional faces, irrespective of the stimuli valence. This effect seemed not to be limited to the explicit processing of stimulus valence, because an implicit recognition paradigm was applied. These results are in line with a previously reported study that used an explicit matching paradigm of negative faces and aversive scenes (22). Our data extend these results, because the modulatory effect was found not to be limited to negative emotions but was also observed when happy faces were presented.

The result of reduced responding of the amygdala to angry and fearful faces corroborates the stress-reducing and anxiolytic effects of oxytocin found in previous studies in rodents (2,27) and humans (6). The suppression of amygdala activity to happy faces might be interpreted in terms of oxytocin reducing arousal to affective social stimuli in general. Accordingly, it has been argued that the amygdala mediates arousal and vigilance to emotionally relevant stimuli and broadly responds to ambiguity (14), uncertainty (28), and emotionally laden stimuli in general (20,21) rather than being specific for the detection of threat.

After this notion, one might speculate that attenuation of amygdala responses to both positive and negative stimuli in this study reflects reduced uncertainty about the predictive value of a social stimulus (28), which in turn might motivate the individual to initiate social approach behavior (6,8). Although not being conclusive, we have recently shown that oxytocin promotes social cognition (i.e., facilitates inferences regarding the affective mental state from subtle social cues) (9). It should be noted that our interpretation contradicts studies that argued that the amygdala promotes social cognition (1) by enhancing salience and attention to socially relevant cues (29). Therefore, our interpretation is a hypothesis for future research rather than a conclusion that can be drawn from the present data.

The modulatory effect of oxytocin within the brainstem suggested by the whole brain analysis is in accordance with a previously reported reduced amygdala–brainstem coupling after oxytocin treatment (22). The oxytocin effects found in the superior temporal lobe and the temporal poles concur with current concepts of face processing, which postulate that temporal areas are involved in the evaluation of the changeable aspects of faces, including facial expressions (30). However, interpretations have to be made with caution, because the statistical threshold of $p < .001$ (uncorrected) that we used for the whole brain analysis was fairly liberal.

The present results support the idea that exogenously administered oxytocin suppresses amygdala responses to emotionally laden social cues independent of their valence. Although Kirsch *et al.* (22) have shown that oxytocin induces suppression of amygdala activity not only in relation to social but also to non-social stimuli, the question of specificity of oxytocin effects has to be more thoroughly investigated and extended to further details of the stimuli (e.g., by studying the differential effects on ambiguous, uncertain as opposed to unambiguous, familiar stimuli). Another interesting question is whether oxytocin is relevant for the development of psychiatric conditions that involve social dysfunction and alterations of amygdala reactivity (e.g., autism [31], borderline personality disorder [32], and social phobia [33]) as well as how far genetic factors like serotonin transporter (5-HTT)-Promotor gene polymorphism might influence the results.

Imaging sessions were performed at Neuroimage Nord in Hamburg. The study was supported by grants from the Swiss National Science Foundation (Grant No. PP001-114788) and the Research Priority Program "Foundations of Human Social Behavior" of the University of Zurich (to MH).

We thank Katrin Mueller and Friederike Walde for assistance with data collection and Stefanie Brassen for helpful suggestions on data analysis.

The authors reported no biomedical financial interest or potential conflicts of interest.

Supplementary material cited in this article is available online.

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