Oxytocin makes a face in memory familiar

Rimmele, U; Hediger, K; Heinrichs, M; Klaver, P
Oxytocin makes a face in memory familiar

Abstract

Social recognition is the basis of all social interactions. Here we show that in humans, the evolutionary highly conserved neuropeptide oxytocin, after intranasal administration, specifically improves recognition memory for faces, but not for nonsocial stimuli. With increased oxytocin levels, previously presented faces were more correctly assessed as 'known' whereas the ability of recollecting faces was unchanged. This pattern speaks for an immediate and selective effect of the peptide strengthening neuronal systems of social memory.
Social recognition is the basis of all social interactions. Here, we show that, in humans, the evolutionarily highly conserved neuropeptide oxytocin, after intranasal administration, specifically improves recognition memory for faces, but not for nonsocial stimuli. With increased oxytocin levels, previously presented faces were more correctly assessed as “known,” whereas the ability of recollecting faces was unchanged. This pattern speaks for an immediate and selective effect of the peptide strengthening neuronal systems of social memory.

Key words: oxytocin; social; face; recognition; memory; neuropeptide

Introduction
Across species, social recognition is the foundation on which all social relationships are built and maintained. The nonapeptide oxytocin is centrally involved in the regulation of basic social and reproductive behaviors, such as cohabitation, gestation, and breastfeeding, and in nonhuman mammals is crucial for social recognition (Carter, 1998, 2003; Ferguson et al., 2002; Winslow and Insel, 2004). In rodents, oxytocin enhances social recognition as indicated by decreased investigative behavior toward a conspecific rodent during a second encounter (Ferguson et al., 2002; Bielsky and Young, 2004). In oxytocin knock-out mice, social memory is impaired and can be fully restored by a single injection of oxytocin before an initial social encounter (Ferguson et al., 2002). Remarkably, oxytocin knock-out mice have no deficits in nonsocial memory (Ferguson et al., 2000), suggesting that oxytocin modulates only social but not nonsocial memory. The influence seems to be specific to encoding, because an injection of oxytocin before, but not after an initial social encounter restores social recognition in these mice (Ferguson et al., 2000).

In humans, the influence of oxytocin on social in comparison with nonsocial memory has not yet been investigated. However, there is emerging evidence that oxytocin facilitates social cognition and prosocial behavior also in humans (Heinrichs and Domes, 2008). Men treated with oxytocin performed better in inferring the affective state from the eye region of human faces (Domes et al., 2007a). Oxytocin also increases social behaviors like trust (Kosfeld et al., 2005; Baumgartner et al., 2008). In contrast, no consistent effects of oxytocin were found on learning of nonsocial stimuli (Fehm-Wolfsdorf and Born, 1991; Heinrichs et al., 2004). Here, we show that oxytocin selectively enhances memory encoding of faces in humans, but not of nonsocial stimuli.

Materials and Methods
Subjects. We studied 44 nonsmoking, healthy, heterosexual men without any psychiatric, neurological, and medical illness. Subjects were not on any medication and reported a normal sleep–wake cycle. The study was approved by the institutional review board of the University of Zurich. All subjects provided written informed consent and were paid for participation. Data from three subjects were excluded from analyses. One did not attend the second session, and two met criteria for a mental health disorder based on the Symptom-Checkliste SCL-90-R (Derogatis, 1983). Participants were instructed to abstain from beverages with caffeine or alcohol during experimental days and maintained a regular sleep–wake cycle the two nights before and during the study, with sleep between 10:00–11:30 P.M. and 7:00–8:30 A.M.

Social stimuli. A total of 120 grayscale Caucasian face stimuli (60 men; 60 women) was chosen from a pool of 780 faces that were selected from mainly four established databases: NimStim Face Stimulus Set (www.macbrain.org), Pictures of Facial Affect (Ekman and Friesen, 1971), International Affective Picture Set (Lang, 1999), Karolinska Directed Faces Database (KDEF) (www.ki.se/cns/news/AKDEF-e.html). All faces showed direct gaze and were presented in an elliptic mask on a black background. In a pilot study, a separate group of men (n = 50; 22.33 ± 0.63 years) had rated the faces on a 7 point scale on valence (1, very negative; 7, very positive) and arousal (1, not at all arousing; 7, very arousing). A total of 120 of the 780 faces was then chosen (40 negative; 40 neutral; 40 positive) for the main study. A total of 84 faces (28 negative; 28 neutral; 28 positive) served as encoding material and 36 faces as distractors (12 negative; 12 neutral; 12 positive).

Nonsocial stimuli. A total of 120 grayscale nonsocial stimuli (30 photographs of house fronts; 30 artificial objects that were photographs of art sculptures; 60 landscapes) served for assessment of nonsocial memory. Like the faces, they were presented in an elliptic mask on a black background. Twenty-one houses, 21 objects, and 42 landscapes were encoded, and 9 houses, 9 objects, and 18 landscapes served as distractors.

Design and procedure. A placebo-controlled, double-blind between-groups design was used, with 22 men included in the oxytocin group (age, 22.59 ± 0.57 years) and 19 men (22.53 ± 0.52 years) in the placebo group. Men were randomly assigned to the oxytocin or placebo arm. Oxytocin (24 IU) or saline was administered intranasally. All other details of the study were identical. Participants were randomly assigned to one of the two groups (n = 22 per group). For the oxytocin condition, oxytocin was delivered intranasally at 8:30 A.M., and for the placebo condition, saline was administered at the same time. Between sessions, participants were instructed to abstain from any foods or beverages containing caffeine or alcohol. No significant differences were found on demographic data (age, education, handedness) between participants in the oxytocin and placebo groups. In a pilot study, smoking status was not associated with recognition memory in a group of 22 healthy men; therefore, we did not exclude smokers from the present study.

Received Sept. 6, 2008; revised Nov. 12, 2008; accepted Nov. 24, 2008.
This work was supported by University of Zurich Young Investigator Research grants (Forschungskredit 2005; Forschungskredit 2006) (U.R.), U.R. was supported by Swiss National Science Foundation Grant PBZH11006 and by a grant from the Swiss Federal Institute of Sports. M.H. was supported by Swiss National Science Foundation Grant PP001-114788 and the Research Priority Program “Foundations of Human Social Behavior” at the University of Zurich. We thank Vera Dinkelacker for the face stimuli; Fabienne Marbacher, Manuel Schroeter, Corina Winzer, Milena van Dijk, and Claudia Zuccarella for their skilful assistance in data collection and analysis; and Elizabeth Phelps for helpful discussion on a previous version of this manuscript.
Correspondence should be addressed to Ulrike Rimmele, Department of Psychology, New York University, 6 Washington Place, Room 863, New York, NY 10003, E-mail: ur228@nyu.edu.
DOI:10.1523/JNEUROSCI.4260-08.2009
Copyright © 2009 Society for Neuroscience 0270-6474/29003-051510.00/0
group. Each volunteer in both groups participated in two experimental sessions taking place on 2 consecutive days. Sessions took place between 1:00 and 5:00 P.M. at the same time of day for each participant.

On day 1, two groups of healthy young men were administered intranasally with oxytocin (N = 22) and placebo (N = 19). Recent research has shown that intranasal administration of neuropeptides, such as vasopressin, enables direct access of the peptide to the central nervous compartment (Born et al., 2002), thus providing a useful method for assessing the effects of oxytocin on memory performance. On day 2, 24 h later, a surprise recognition memory test was administered to verify that they fully understood the difference between a “remember” and “know” judgment. After recognition testing, subjects rated all stimuli on a 7-point scale with regard to valence (1, very negative; 7, very positive).

Results

Rating of approachability during stimulus encoding

The oxytocin and placebo groups did not differ in their approachability ratings for faces (oxytocin, 3.56 ± 0.12; placebo, 3.64 ± 0.14) and nonsocial stimuli (oxytocin, 4.59 ± 0.12; placebo, 4.34 ± 0.12) during the encoding phase (values of \( p < 0.13 \)). In addition, no significant difference in rated approachability was observed between the treatment groups for faces sub-

| Table 1. Memory performance after oxytocin and placebo for faces and nonsocial stimuli |
|---------------------------------|-----------------|-----------------|----------|----------|----------|----------|
|                                | Oxytocin Mean  | SEM             | Placebo Mean| SEM      | \( t \)   | \( p \)   |
| Faces                           |                |                 |            |          |          |          |
| Hit rate remember               | 0.46           | 0.04            | 0.40       | 0.04     | 1.001    | 0.322    |
| False alarm rate remember       | 0.09           | 0.02            | 0.08       | 0.02     | 0.299    | 0.767    |
| Hit rate know                   | 0.29           | 0.02            | 0.30       | 0.03     | -0.424   | 0.674    |
| False alarm rate know           | 0.20           | 0.02            | 0.26       | 0.03     | -2.010   | 0.049*   |
| Recollection                    | 0.37           | 0.04            | 0.32       | 0.03     | 1.035    | 0.307    |
| Familiarity                     | 0.33           | 0.03            | 0.22       | 0.03     | 2.504    | 0.017*   |
| Overall recognition             | 0.46           | 0.03            | 0.36       | 0.03     | 2.287    | 0.028*   |
| Nonsocial                       |                |                 |            |          |          |          |
| Hit rate remember               | 0.56           | 0.04            | 0.53       | 0.04     | 0.658    | 0.515    |
| False alarm rate remember       | 0.11           | 0.02            | 0.10       | 0.02     | 0.561    | 0.578    |
| Hit rate know                   | 0.22           | 0.03            | 0.25       | 0.02     | -0.822   | 0.416    |
| False alarm rate know           | 0.22           | 0.02            | 0.23       | 0.03     | -0.215   | 0.831    |
| Recollection                    | 0.45           | 0.04            | 0.43       | 0.04     | 0.461    | 0.648    |
| Familiarity                     | 0.24           | 0.03            | 0.27       | 0.02     | 0.859    | 0.396    |
| Overall recognition             | 0.44           | 0.04            | 0.44       | 0.03     | 0.015    | 0.973    |

Overall recognition memory = hit rate (remember + know) − false alarm rate (remember + know). Recollection = hit rate (remember) − false alarm rate (remember). Familiarity = (hit rate know/(1 − hit rate remember)) − (false alarm rate know/(1 − false alarm rate remember)).

The right two columns indicate results from pairwise statistical comparisons. * \( p < 0.05 \), significant differences between oxytocin and placebo in memory measures for faces, but not for nonsocial stimuli.
divided into negative (oxytocin, 2.46 ± 0.17; placebo, 2.47 ± 0.14), neutral (oxytocin, 3.90 ± 0.12; placebo, 4.16 ± 0.16), and positive (oxytocin, 4.31 ± 0.17; placebo, 4.29 ± 0.22) valence categories (all values of $p > 0.18$).

**Recognition of faces versus nonsocial stimuli**

Oxytocin differentially influenced overall recognition accuracy (hit rate – false alarm rate collapsed across remember and know responses) of social versus nonsocial stimuli (treatment by category interaction; $F_{(1,39)} = 4.90; p < 0.05$) (Fig. 1b; Table 1). Recognition accuracy for faces was superior in the oxytocin (0.46 ± 0.03) compared with the placebo group (0.36 ± 0.027; $t_{(39)} = 2.29; p < 0.05$), whereas recognition accuracy for the nonsocial stimuli was comparable in both groups ($p > 0.97$).

Analyses of recollection and familiarity revealed a more fine-grained picture of the oxytocin effect. Whereas oxytocin did not affect recollection (all values of $p > 0.42$) (Fig. 1c; Table 1), the peptide strikingly affected familiarity judgments, depending on whether the stimulus was a face or not (treatment by category interaction; $F_{(1,39)} = 14.32; p < 0.001$) (Fig. 1d; Table 1). Familiarity judgments of the faces were superior in the oxytocin (0.33 ± 0.03) than in the placebo group (0.22 ± 0.028; $t_{(39)} = 2.50; p < 0.05$). Specifically, subjects in the oxytocin group were less likely to give a know response to a new face (0.198 ± 0.02) than subjects in the placebo group (0.26 ± 0.03; $t_{(39)} = 2.03; p < 0.05$). For nonsocial stimuli, familiarity scores ($p > 0.39$) as well as number of false know responses ($p > 0.80$) were comparable between the treatment groups.

**Influence of gender and valence on face recognition**

To explore whether the improved memory for faces after oxytocin was dependent on the gender of the face or its rated valence, ANOVAs were run including either an additional gender factor or a valence factor (negative; neutral; positive). Attention, as assessed by letter cancellation performance, increased from before substance administration (oxytocin, 29.0; placebo, 390.78) to the time after the period of stimulus encoding (oxytocin, 459.5 ± 36.4; placebo, 424.1 ± 33.7) ($F_{(1,39)} = 20.65; p < 0.001$), but did not differ between groups (all values of $p > 0.17$). Wakefulness did not change throughout the encoding session and also was not influenced by
oxytocin (all values of \( p > 0.19 \)). Negative affect, as assessed by the PANAS, decreased across the encoding session \( F_{(1,39)} = 8.16; p < 0.01 \), but the measure did not differ between oxytocin and placebo groups (all values of \( p > 0.27 \)). At recognition testing, again no differences between treatment groups were observed in all psychological measures (all values of \( p > 0.63 \)). When asked in the end of the second session, subjects were unable to correctly identify whether they had received an active agent or placebo (\( \chi^2 \) test; \( p > 0.25 \)).

**Discussion**

This is the first study to show that oxytocin improves recognition for faces, but not for nonsocial stimuli in humans. Our data indicate that a single dose of intranasally administered oxytocin 40 min before encoding causes a substantial improvement in the ability to recognize faces a day later, while leaving entirely unaffected the recognition of nonsocial stimuli. Our finding is consistent with previous observations suggesting a globally enhancing effect of oxytocin on processing of face stimuli (Guastella et al., 2008a,b; Savaskan et al., 2008). Most importantly, this result concurs with rodent studies that show oxytocin to be selectively essential for the establishment of memory of a conspecific, but not for learning of nonsocial information (Ferguson et al., 2000, 2002).

More specifically, the enhancing effect of oxytocin on recognition of faces versus nonsocial stimuli emerged for familiarity judgments, whereas recollection remained unaffected. The peptide strikingly improved familiarity judgments for faces, but not for nonsocial stimuli. This pattern shows that the advantage in social recognition after oxytocin expresses itself in a greater familiarity of previously encountered faces. Specifically, oxytocin lowered the detection threshold for faces. Indeed, the raw measure mainly affected was the false alarm rate for know responses, which was decreased after oxytocin administration, thereby distinctly improving the signal-to-noise ratio for discriminating new faces from old ones. Remarkably, recollection measures of face memory remained unaffected by oxytocin. Recollection reflects the conscious effortful retrieval of qualitative information of a study event, whereas familiarity judgments are based on a direct sensing of the memory strength (Yonelinas, 2002). Hence, the specific effect of oxytocin on familiarity of faces likely reflects an immediate strengthening of neuronal circuitry selectively representing social memories.

Additional analyses did not reveal any considerable influence of gender and valence of the face, or arousal on memory performance (all values of \( p > 0.21 \)). Thus, the enhancing effect of oxytocin on recognition and familiarity of faces is independent of whether the face is that of a man or a woman, and whether the face is experienced as negative, neutral, or positive, indicating that the social nature of the stimulus per se is relevant for the memory effect of the peptide regardless of its phenotypic appearance (Savaskan et al., 2008). Also, there was no difference between the oxytocin and placebo groups in any measure of attention, alertness, and mood at encoding or at recognition testing, which excludes that differences in recognition were confounded by effects of the peptide on these nonspecific functions.

Together, our data indicate that oxytocin in humans immediately strengthens the capability to correctly recognize and discriminate faces. The identification of an evolutionarily highly preserved hormone accounting for improved recognition of conspecifics not only in rodents, but also in humans, points to a similar mechanism of social recognition across species.

In rodents, oxytocin is essential in the medial amygdala for establishing a social memory (Ferguson et al., 2002). Olfactory cues of a conspecific are conveyed via the main and accessory olfactory pathways to the medial amygdala where oxytocin acts to modulate encoding of the memory for the initial social encounter (Ferguson et al., 2002). The medial amygdala projects to the bed nucleus of the stria terminalis and via the lateral septum to the hippocampus, which is most crucial for storage and retrieval of many types of memories. After a social exposure, oxytocin knock-out mice show hypoactivation of the medial amygdala and several downstream projections of this nucleus (Ferguson et al., 2001). Interestingly, these mice simultaneously show a massive hyperactivation of other brain areas including the hippocampus and somatosensory cortex, which possibly reflects the recruitment of alternative pathways for processing social cues. Oxytocin administered into the medial amygdala of knock-out mice before an initial social encounter fully restores social recognition (Ferguson et al., 2001). Conversely, an oxytocin receptor antagonist administered to the medial amygdala of wild-type mice impairs social recognition. These findings show that the activation of oxytocin receptors in the medial amygdala is both necessary and sufficient for the successful formation of a social memory in mice.

In humans, faces constitute the primary social cue. The processing of faces relative to other visual stimuli recruits a distributed neural system in the human brain (Haxby et al., 2000). In particular, among other regions, numerous neuroimaging studies identified the amygdala, the superior temporal sulcus (STS), and a region in the fusiform gyrus, the fusiform face area (FFA), to be critically involved in face processing (Sergent et al., 1992; Haxby et al., 1994; Kanwisher et al., 1997; McCarthy et al., 1997) (for review, see Haxby et al., 2000; Adolphs, 2002; Vuilleumier, 2007). It has been proposed that the fusiform face area processes invariant aspects of faces and thus contributes to face identity perception, whereas the STS and the amygdala are more important for the processing of variable aspects of faces, such as eye gaze and emotional expression. However, these regions do not act separately from each other, but rather interact with each other, in particular the amygdala and the FFA (Vuilleumier, 2007).

The neuronal mechanisms mediating the effects of oxytocin on human face memories cannot be inferred from the present data. Expression of oxytocin receptors has been revealed in various brain regions, particularly in the amygdala and hippocampus (Insel and Shapiro, 1992; Gimml and Fahrenholz, 2001; Landgraf and Neumann, 2004; Huber et al., 2005), but also in different regions of the neocortex (Insel et al., 1991; Gimml and Fahrenholz, 2001). Recent functional magnetic resonance imaging studies indicated a specific modulation of amygdalar activity during face processing after administration of oxytocin (Kirsch et al., 2005; Domes et al., 2007b; Petrovic et al., 2008). Of note, one of these studies revealed oxytocin-induced blood oxygen level-dependent signal changes also in the fusiform gyrus (Petrovic et al., 2008). Both amygdala and fusiform gyrus are involved in the acquisition of familiarity for faces (Kosaka et al., 2003). In previous experiments using the same face presentation as well as dose and timing of oxytocin as in the present study, we found that oxytocin administered before face encoding reduces activity in the amygdala (Domes et al., 2007b). This effect, like the enhancing effect of oxytocin on face familiarity in the present study, was independent on the valence or arousal value of the faces. Given that the amygdala contributes to emotion perception in faces, whereas face identity is mediated via the FFA (Adolphs, 2002; Vuilleumier, 2007), the independence on valence and arousal so consistently observed for the effects of oxytocin suggests a primary role for the FFA (rather than amygdala) in mediating the
enhanced facial familiarity after oxytocin, revealed in here. The focus of the effect of the peptide on familiarity rather than recollection of faces likewise suggests that oxytocin predominantly acts at the neocortical level of the face encoding circuitry. In combination, our observations argue for the view that the enhanced familiarity judgments for faces encoded under the influence of oxytocin involve both an action on the amygdala as well as the fusiform face area, with perhaps a leading role for the influence on the fusiform gyrus.

In summary, the findings of our study show a crucial function of oxytocin in the early processing of the most basic class of social stimuli (i.e., faces). Similar to animal studies, we find that oxytocin strengthens the encoding of conspecifics and is essential for the identification and recognition of individual conspecifics. Social recognition is an essential prerequisite of more complex social behaviors. Many animal and a few human studies have shown that oxytocin is involved in the regulation of complex social behaviors, such as trust, pair bonding, or parental care. In the light of our basic findings, oxytocin appears to provide an effective approach for selectively influencing and ameliorating the foundation of basic social competences in humans, especially in disease conditions.

References