

Effects of Intranasal Oxytocin on the Neural Basis of Face Processing in Autism Spectrum Disorder

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Background: Autism spectrum disorder (ASD) is associated with altered face processing and decreased activity in brain regions involved in face processing. The neuropeptide oxytocin has been shown to promote face processing and modulate brain activity in healthy adults. The present study examined the effects of oxytocin on the neural basis of face processing in adults with Asperger syndrome (AS).

Methods: A group of 14 individuals with AS and a group of 14 neurotypical control participants performed a face-matching and a house-matching task during functional magnetic resonance imaging. The effects of a single dose of 24 IU intranasally administered oxytocin were tested in a randomized, placebo-controlled, within-subject, cross-over design.

Results: Under placebo, the AS group showed decreased activity in the right amygdala, fusiform gyrus, and inferior occipital gyrus compared with the control group during face processing. After oxytocin treatment, right amygdala activity to facial stimuli increased in the AS group.

Conclusions: These findings indicate that oxytocin increases the saliency of social stimuli and in ASD and suggest that oxytocin might promote face processing and eye contact in individuals with ASD as prerequisites for neurotypical social interaction.

Key Words: Amygdala, autism, face processing, fMRI, oxytocin, social cognition

In humans, the face is a particular focus of attention in social interactions, starting soon after birth (1), with the eye region probably playing a crucial role in this spontaneous preference for faces (2–4). Early face preference is thought to be innate, and might be mainly driven by the configural appearance of faces (5,6).

Many individuals with autism spectrum disorder (ASD) show reduced preference for faces from their second year of life on (7). Studies with adults have demonstrated diminished eye gaze (8–10) and impaired facial emotion recognition (11,12) in persons with ASD. These typical deficits have been attributed to functional alterations in the neural circuitry involved in face processing (13), including the amygdala (8,14), the fusiform gyrus (8,15,16), and the posterior superior temporal lobe (17).

Initial studies in healthy humans show that oxytocin, a nine-amino acid neuropeptide, reduces anxiety and endocrine responses to social stress (18,19), modulates social memory (20–22), promotes trust in social interactions (23), improves the ability to infer the emotional or mental states of others from subtle facial cues (24–26), and increases eye gaze to neutral expressions (27) and emotional human facial expressions (28,29). Although the underlying neural mechanism remains to be fully

understood, recent neuroimaging studies suggest that oxytocin modulates amygdala responsiveness to emotional stimuli (29–33). In addition, whole-brain analyses have also revealed modulatory effects in prefrontal and temporal areas as well as in the brainstem (32–34).

The social impairments in ASD show parallels to the social deficits found in rodents with alterations of oxytocin (35). Thus, it has been argued that there might be a link between ASD and altered central nervous oxytocin functioning (36,37). Indeed, there is evidence for lower plasma levels of oxytocin in persons with ASD (38) and a possible role of genetic variations of the oxytocin receptor in the development of ASD (39–43). In addition, recent studies suggest that systemic infusions of oxytocin improve affective speech comprehension (44) and that intranasal oxytocin administration enhances emotion recognition (45) and increases eye gaze in face perception and promotes social interaction (46) in persons with ASD (47).

Notably, to date, no study has yet investigated the effect of oxytocin on brain activation pattern in the context of face processing in ASD. On the basis of the studies summarized above, we expected increased activity in the neural circuitry subserving face processing, in particular in the amygdala, fusiform gyrus, and superior temporal lobe after oxytocin treatment. To test this hypothesis, we tested the effect of a single intranasal dose of oxytocin on the ability to discriminate between faces with different identities. We presented photographs of faces and nonfacial objects to individuals with ASD and typically developing control participants while their regional brain activity was measured in the magnetic resonance imaging (MRI) scanner. In a randomized, placebo-controlled, double-blind, cross-over, within-subject design, during two different sessions all participants received a single intranasal dose of oxytocin or placebo before scanning.

Methods and Materials

Participants

Fourteen adult male volunteers (mean age \pm SD: 24.0 \pm 6.9 years) with Asperger syndrome (AS) according to the DSM-IV and 14 healthy, neurotypical male control participants (NT) (mean

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age \pm SD: 24.3 ± 5.4 years) case-matched for age and total IQ were enrolled for participation through announcements on an institutional bulletin board and in the local newspaper. To rule out the confounding influence of mental retardation, we exclusively investigated individuals with AS. Diagnoses of the participants with AS were confirmed with the Autism Diagnostic Interview—Revised (ADI-R) (48) and the Autism Diagnostic Observation Schedule (ADOS) (49) administered by a trained and clinically experienced psychiatrist (E.K.). All participants met the cut-off scores for Autistic Disorder in the ADOS and on the subscales Reciprocal Social Interaction (RSI: mean = 20.6, SD = 5.6) and Communication (C: mean = 14.4, SD = 3.2) in the ADI-R. General intelligence as estimated with the Wechsler Abbreviated Scale of Intelligence (50) was on average above the normal range and did not differ between groups (mean \pm SD AS group: IQ = 122.4 ± 24.1 ; NT group: IQ = 125.6 ± 15.4 ; $t_{26} = .42$; $p = .603$). All participants were right-handed, free of any medication (including psychoactive), had normal or corrected-to-normal vision, and did not report a history of neurological or endocrine disease. All procedures were in accordance with the *Declaration of Helsinki* and were approved by the ethics committee of the medical faculty of the University of Rostock.

Procedure

Participants gave written informed consent before participation and were screened for the presence of neurological, psychiatric, and somatic illness. Subsequently, participants completed a set of questionnaires and were familiarized with the imaging procedures, the administration of the neuropeptide, and the stimuli during scanning. Participants were instructed to abstain from smoking, caffeine, and analgesic medication on the scanning days.

In a randomized double-blind, placebo-controlled, within-subject, cross-over design, two experimental sessions were conducted, separated by a 1-week interval. Each experimental session started with a screening of current somatic illness and

exclusion criteria for MRI. Oxytocin and placebo were administered intranasally 45 minutes before functional (f)MRI scanning (51). After a standardized protocol, participants self-administered three 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) under the supervision of the study coordinator. MRI scanning began with the functional scans followed by an anatomical scan for co-registration purposes during image analysis. Immediately before substance application and shortly before MRI scanning, the participants rated wakefulness, calmness, and mood on a three-scale state questionnaire (52). The total time of an experimental session was 3 hours, with approximately 45 minutes in the scanner. All participants received monetary compensation after completion of the study.

Face Discrimination Task

Black-and-white pictures of frontal and 45° averted neutral faces of 36 individuals (18 male/18 female) were taken from the Stirling Face Database (http://pics.psych.stir.ac.uk/2D_face_sets.htm). Pictures were edited to remove hair and clothing. Two sets of stimuli were created by either pairing direct and averted views of the same individual (same faces) or by pairing direct and averted views of different individuals (different faces). As a set of control stimuli, black-and-white pictures of different 36 houses (frontal and 45° views) were taken and combined in a similar way (same vs. different houses) (experimental design, Figure 1A). The resulting 48 stimuli were presented on a gray background for 4 sec with an inter-stimulus interval of 2.6 sec. During picture presentation, participants were asked to indicate as quickly as possible by a button press whether the two pictures of faces or houses depicted the same or different individuals or buildings (trial structure, Figure 1B). As a passive viewing baseline condition, 24 trials presenting pairs of gray areas matched for size and luminance to the faces/houses trials were included. Trials were presented in fully randomized order. The total time of the experiment was 8:20

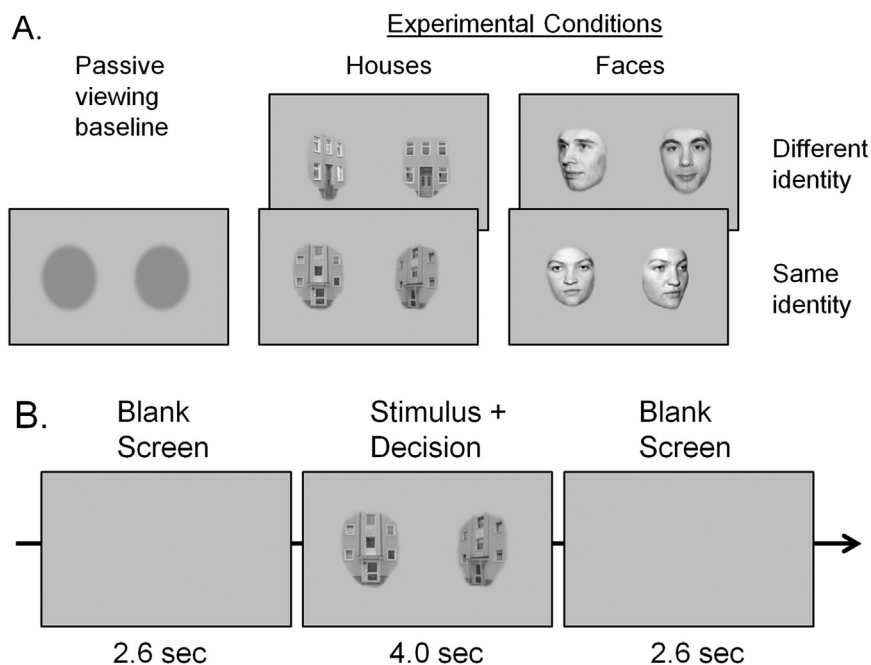


Figure 1. (A) Experimental conditions and sample stimuli. (B) Trial structure.

min. The experiment was presented with the use of Presentation 10.1 (Neurobehavioral Systems, Albany, California), allowing for the acquisition of response accuracy and latencies. To compare discrimination performance between the experimental conditions, we calculated the discrimination index p_r for face and house trials. The discrimination index p_r takes both hits (responding with “same” when the same individual was presented) and false alarm (responding with “different” when different individuals were presented) into account by subtracting the false alarm rate from the hit rate (53). Response latencies <300 msec and >4000 msec after stimulus onset were discarded (<5% overall) before averaging within each stimulus category.

Magnetic Resonance Imaging

Images were acquired with a 1.5-T Scanner (Siemens Avanto) equipped with high-speed gradients and the 12-channel standard Head Matrix Coil (Siemens, Erlangen, Germany). Thirty-six axial slices (3-mm thickness with 1-mm gap) covering the whole brain were acquired by means of a T2*-sensitive echo-planar-imaging sequence (echo time = 40 msec, repetition time = 2700 msec, flip angle = 90°, field of view = 214 × 214 mm, matrix = 64 × 64). A total of 181 volumes were acquired. Thereafter, a structural image was acquired by means of a three-dimensional, T1-weighted, gradient-echo (MPRAGE) sequence (160 sagittal slices, 1-mm slice thickness, echo time = 3.9 msec, repetition time = 1500 msec, flip angle = 15°, field of view = 256 × 256 mm, matrix = 256 × 256).

Image Preprocessing and First-Level Analysis

For both experiments, image preprocessing and statistical analysis was performed with the use of SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). The first four volumes of each functional series were discarded to reduce T1 saturation artifacts. Preprocessing included realignment of the images to the first image in the series, coregistration of the functional images and the anatomical image, correction of slice acquisition time, spatial normalization to the Montreal Neurological Institute standard brain, and spatial smoothing (gaussian kernel of 9-mm full-width half-maximum).

Data analysis began with modeling of each event of a specific condition as box-car functions convolved with a hemodynamic response function. To reduce slow drift artifacts, a high-pass filter with a cut-off period of 128 sec was applied to the voxel time courses. For the fixed-effects, first-level analysis regression coefficients for each condition were estimated by means of least squares within SPM8. Contrast estimates were calculated for the contrasts faces > control and houses > control to control for unspecific hemodynamic drug effects for second-level whole-brain analyses.

Second-Level Analysis

In a first step, the main effect of faces > houses was calculated in the total sample to reveal the neural circuitry specifically associated with face processing. As expected, we found increased activation during face discrimination in the following areas: left and right inferior occipital gyrus, precuneus, left and right amygdala, medial orbitofrontal gyrus, left and right fusiform gyrus, dorsomedial prefrontal gyrus, left inferior frontal gyrus, and right temporal pole [all p (familywise-error [FWE]-corrected) < .05] (Table 1 and Figure 2). These clusters were used for identification of regions of interest (ROIs) for the analysis of amygdala activity and as an inclusive mask for second-level analysis within areas specific for face discrimination.

ROIs for amygdala analysis were defined as spheres with a radius of 5 mm around the peak voxel of each significant cluster.

Table 1. Significant Cluster Showing Increased Activation During Discrimination of Faces Compared with Houses (Contrast: Faces > Houses) for the Whole Group of Participants ($n = 28$)

Region		Coordinates			Cluster k	t Value	p (FWE)
		x	y	z			
Inferior Occipital Gyrus	R	57	-66	6	543	10.21	<.001
Inferior Occipital Gyrus	L	-57	-60	9	475	9.45	<.001
Precuneus		0	-54	30	166	9.28	<.001
Amygdala	L	-27	-3	-18	66	7.65	<.001
Orbitofrontal Gyrus		0	51	-12	119	7.05	<.001
Amygdala	R	21	-3	-18	81	6.96	<.001
Fusiform Gyrus	R	45	-42	-21	27	6.70	<.001
Fusiform Gyrus	L	-45	-42	-21	17	5.86	.001
Mid Temporal Gyrus	R	57	-9	-21	24	5.62	.002
Dorsomedial Prefrontal Cortex	R	3	54	21	68	5.56	.002
Inferior Prefrontal Cortex	L	-48	36	-3	14	5.16	.010
Cuneus	R	6	-84	24	27	5.13	.011
Temporal Pole	R	36	9	-36	11	5.08	.013

All voxels are significant at $p < .05$ (FWE-corrected). Coordinates of peak voxels are given in Montreal Neurological Institute space; k = cluster size.

FWE, family-wise error; L, left; R, right.

Percent signal change data were extracted by means of *rfxplot* (<http://rfxplot.sourceforge.net/>) (54) from these predefined amygdala ROIs in each stimulus condition (faces and houses) against an implicit baseline and were subject to two separate 2 (group) × 2 (drug) × 2 (stimuli) analysis of variance (ANOVA) for left and right amygdala in IBM SPSS Statistics (Version 20.0). Post hoc single comparisons were done with Student t test.

Following a hypothesis-driven approach, second-level analysis in SPM was restricted to the areas specific for face discrimination to investigate oxytocin-induced modulation of brain activity beyond the amygdala. Inclusive masks covering the regions shown in Table 1 and Figure 2 were used for subsequent analysis. Whole-brain random-effects analyses included a three-way general linear model ANOVA (group × drug × stimulus) and follow-up two-way general linear model ANOVAs for each study group with the factors “stimulus” (first-level contrast of faces and houses against the control condition, see above) and “drug.” The threshold for significance for the analysis of within-subject drug-induced modulations of brain activity was set at $p < .05$, small volume corrected (SVC) for multiple comparisons within spheres of 5-mm radius around the peak voxels.

Results

Task Performance

Performance in discrimination of faces and houses were calculated with a 2 (condition) × 2 (drug) × 2 (group) ANOVA. Houses were more difficult to discriminate ($F_{1,26} = 117.07$; $p < .001$) in the total sample, and individuals with AS showed impaired performance for faces compared with NT controls, whereas this was not the case for houses, as indicated by a significant group × condition interaction ($F_{1,26} = 4.25$; $p < .05$).

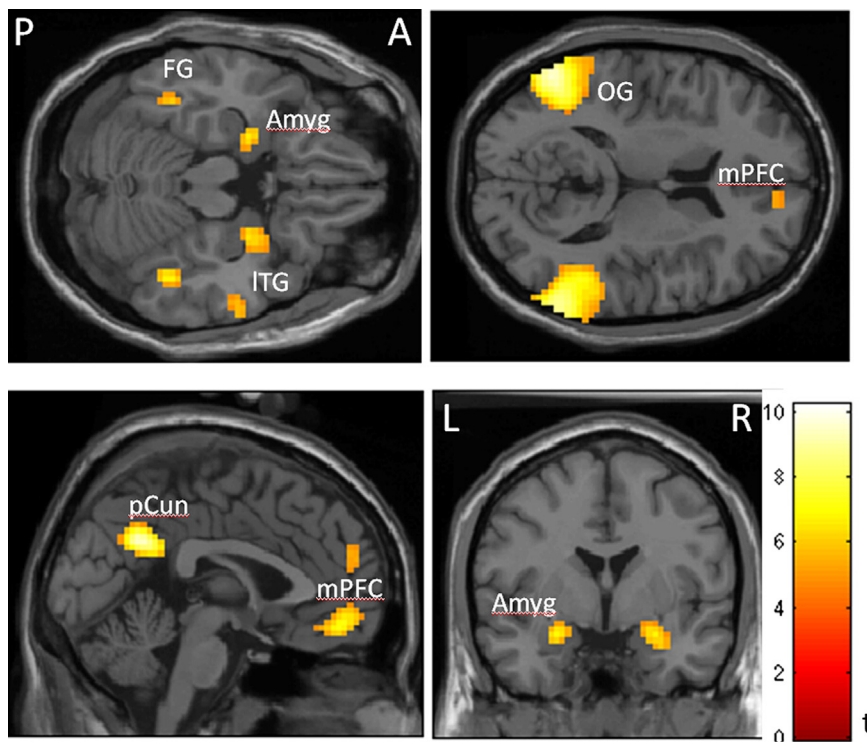


Figure 2. Significant clusters showing increased activation in the bilateral fusiform gyrus (FG), amygdala (Amyg), occipital gyrus (OG), lateral temporal gyrus (ITG), medial prefrontal cortex (mPFC), and precuneus (pCun) during the discrimination of faces compared with houses in the whole group of participants ($n = 28$). (contrast: faces > houses). T-map with a threshold of $p < .05$ (familywise-error-corrected). L, left; R, right.

However, there was neither a significant main effect of oxytocin nor a significant interaction of drug with group, condition, or both (all $p > .05$). Thus, oxytocin had no effect on task

performance in either group. The three-way ANOVA of response latencies revealed increased response time to houses as compared with faces ($F_{1,26} = 16.68$; $p < .001$). Again, individuals with

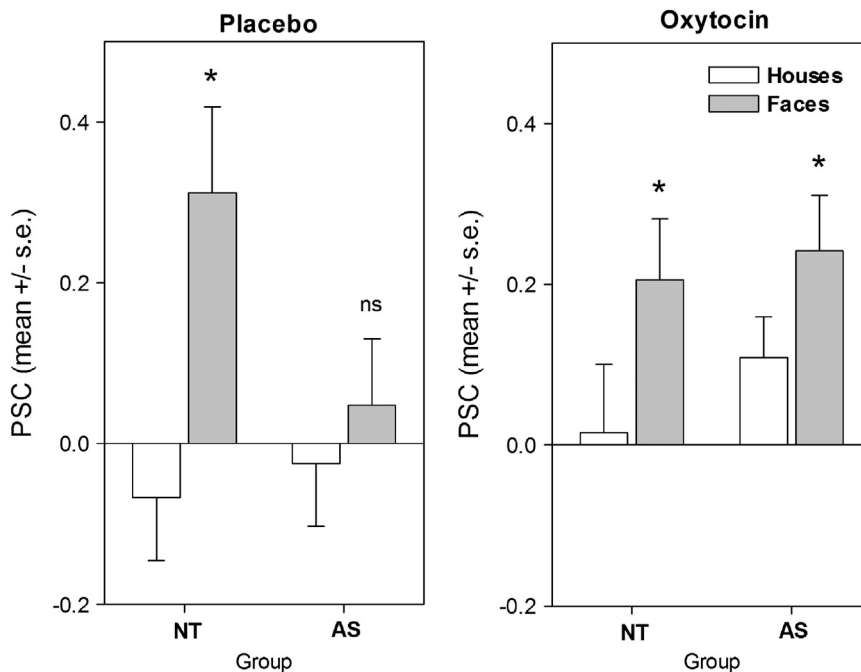


Figure 3. Region of interest analyses of amygdala activity. Differential activation during face and house discrimination within the right amygdala ($x, y, z: 21, -3, -18$) for individuals with Asperger syndrome (AS) and neurotypical (NT) controls. Bars depicted mean percent signal change (PSC) compared with the control stimuli. Error bars represent the standard error of mean. *Significant difference for paired t test; $p < .05$ (two-tailed). ns, not significant.

Table 2. Group Differences Showing Decreased Activation During Discrimination of Faces Compared with Houses (Contrast: Faces > Houses) for Individuals with Asperger Syndrome Compared with Neurotypical Control Participants

		Coordinates			Cluster <i>k</i>	<i>t</i> Value	<i>p</i> _{uncorrected}
		x	y	z			
Placebo + Oxytocin: NT > AS (Faces > Houses)							
Inferior occipital gyrus	R	51	-78	-6	57	3.91	<.001
Fusiform gyrus	R	42	-45	-18	16	3.73	<.001
Medial prefrontal cortex	L	-9	54	39	11	3.39	<.001
Precuneus	L	-3	-54	36	16	2.85	<.003
Placebo Condition: NT > AS (Faces > Houses)							
Fusiform gyrus	R	42	-45	-18	38	3.67	<.001
Inferior occipital gyrus	R	51	-78	-6	69	3.63	<.001
Amygdala	R	27	3	-18	27	3.32	.001
Oxytocin Condition: NT > AS (Faces > Houses)							
Medial prefrontal cortex	L	-6	51	36	13	3.62	<.001
Precuneus	L	-3	-57	36	17	3.09	.001

All voxels are significant at $p < .005$ and $k > 10$. Coordinates of peak voxels are given in Montreal Neurological Institute space; k = cluster size.

AS, Asperger syndrome; L, left; NT, neurotypical controls; R, right.

AS showed specifically increased response latencies to faces as compared with houses ($F_{1,26} = 4.92$; $p < .05$). However, response latencies were not affected by oxytocin administration (all $p > .05$). Descriptive statistics may be found in Table S2 in Supplement 1.

ROI Analysis of Amygdala Activity

For left amygdala activity, there was no main effect of drug as well as no interaction effect involving drug. However, for right amygdala activity, the three-way interaction of group \times drug \times condition was significant ($F_{1,26} = 4.552$; $p < .05$), indicating that the effect of oxytocin differentially influenced face processing in the AS and control groups. Subsequent paired t tests revealed that under placebo, individuals with AS showed no differential amygdala activity to faces and houses ($t_{13} = 0.84$; $p = .417$), whereas NT controls showed markedly higher amygdala responses to faces compared with houses ($t_{13} = 5.73$; $p < .001$). After oxytocin treatment, both groups, AS and NT controls, showed stronger activation of the amygdala in response to faces as compared with houses (AS: $t_{13} = 3.22$; $p = .007$; NT: $t_{13} = 2.96$; $p = .011$) (Figure 3).

Effects within the Face-Processing Network

Within the face-processing network, individuals with AS showed attenuated activation of right inferior occipital gyrus, right fusiform gyrus, left medial prefrontal cortex, and left precuneus (contrast: NT [faces > houses] > AS [faces > houses]) when averaging over placebo and oxytocin condition (Table 2). However, when calculating the same contrast for both drug conditions separately, individuals with AS showed decreased right amygdala activity specifically in the placebo condition (Table 2).

The effect of oxytocin on face processing was tested by contrasting the oxytocin and placebo conditions for the contrast of faces > houses in both groups (three-way interaction) to

reveal areas within the face-processing network showing increased activity following oxytocin treatment. There was only one cluster in the right anterior amygdala (x, y, z ; 27, 6, -18; $k = 40$; $t = 2.43$; $p_{SVC} < .05$) within the face-processing network showing a significant three-way interaction. No other region appeared to be differentially modulated by oxytocin.

To further explore the effect for oxytocin found in the amygdala, we calculated two-way interaction contrasts for each group separately. For this contrast (oxytocin [faces > houses] > placebo [faces > houses]) the AS group showed increased activity within the right posterior amygdala (x, y, z ; 24, -9, -18; $k = 23$; $t = 2.55$; $p_{SVC} < .05$) (Figure 4A). No other cluster in this contrast reached significance within the face-processing network. For the control group, there were no significant clusters.

For the reverse contrast indicating oxytocin-induced reduction of activity to face processing as compared with processing of houses (placebo [faces > houses] > oxytocin [faces > houses]), there was no significant cluster in the AS group. However, NT controls showed decreased differential activation to facial compared with house stimuli in the right anterior amygdala after oxytocin treatment (x, y, z ; 24, 6, -18; $k = 38$; $t = 2.88$; $p_{SVC} < .05$) (Figure 4B). No other cluster for this contrast reached significance within the face-processing network in either group.

Discussion

To our knowledge, this is the first study to report increased activity in the amygdala after oxytocin administration in individuals with ASD in the context of face processing. In the present study, we controlled for nonspecific effects by comparing oxytocin-induced changes in neural activity with a condition with nonsocial stimuli. Overall, the face-matching paradigm used in the present study robustly activated the network involved in face processing consistent with previous studies (55). Increased amygdala activation has been found in similar neutral face-matching paradigms (56) and has been reported in a number of studies comparing amygdala responses with faces with other nonfacial categories (57). In the placebo condition, the AS group showed attenuated activity in parts of the face-processing network, namely, the right fusiform gyrus, the right inferior occipital gyrus, and the right amygdala, which is in line with a number of studies reporting decreased activity in these areas in ASD (14–16,58–60). After oxytocin treatment, NT controls showed decreased activity in the right anterior amygdala, which replicates the results of previous studies in healthy men, which showed attenuated amygdala activity after oxytocin treatment in response to emotional facial expressions (32,33,61). In contrast to the NT group, oxytocin resulted in increased right posterior amygdala responding to social as compared to nonsocial stimuli in ASD. Broadly speaking, the amygdala has been associated with processing of emotional stimuli (62), threat-related stimuli in particular (63), face processing (13), and vigilance for salient stimuli (64,65). The present results suggest that the amygdala is robustly activated by nonemotional neutral social stimuli and thus might reflect the social salience of the visual stimulus rather than its emotional valence. Increased amygdala activity after oxytocin treatment in the AS group is likely to reflect increased salience of the faces presented (66) or increased allocation of attentional resources in the processing of these social stimuli (67), as compared with the nonsocial stimuli.

There is another line of evidence that points to the possibility that oxytocin might have modulated visual scanning of faces.

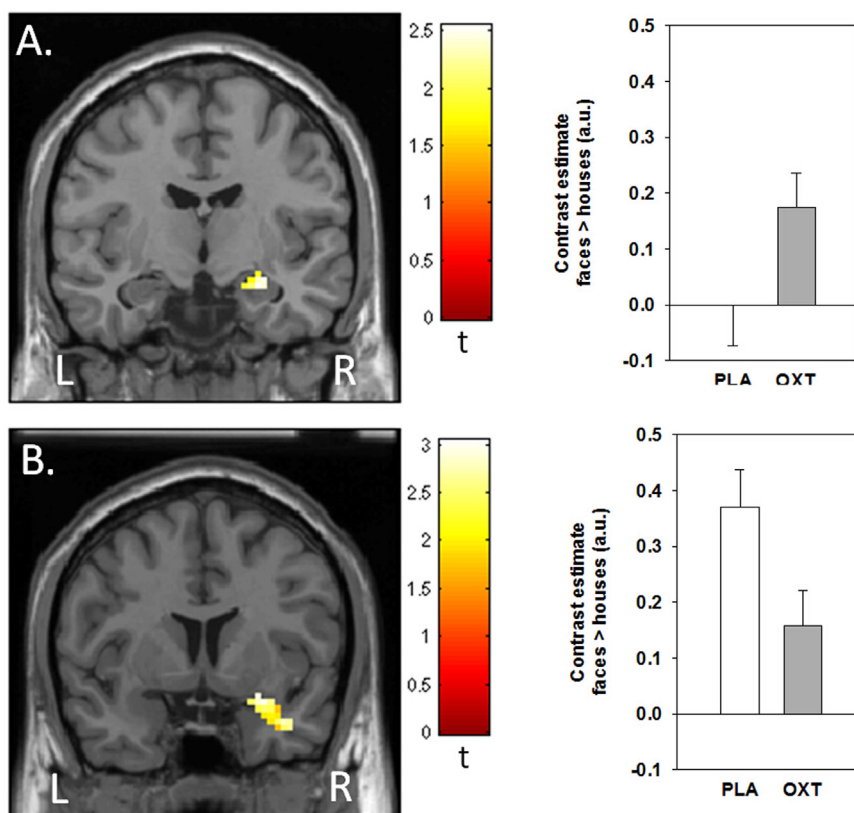


Figure 4. Effects of oxytocin on right amygdala activity. **(A)** Individuals with Asperger syndrome showed increased activation to faces compared with houses (contrast: OXT [faces > houses] > PLA [faces > houses]) in the posterior amygdala ($x, y, z: 24, -9, -18$), whereas **(B)** neurotypical controls showed decreased differential activation to faces compared with houses after oxytocin treatment in the anterior amygdala ($x, y, z: 24, 6, -18$) (contrast: PLA [faces > houses] > OXT [faces > houses]). T-maps were thresholded at $p < .05$ (uncorrected) for illustration purposes. a.u., arbitrary units; L, left; OXT, oxytocin; PLA, placebo; R, right.

Studies in healthy male participants have shown that oxytocin promotes eye gaze (27,28). Decreased eye gaze is a prominent behavioral sign of ASD (9), and it has been shown that increased eye gaze is associated with increased amygdala activity in ASD (8). More specifically, a recent study has provided the first evidence that oxytocin promotes gazing time toward the eye region in ASD (46). Hence, increased eye gaze after oxytocin treatment might have been associated with increased amygdala activity in the present study. Future studies using eye-tracking during functional imaging are thus needed to further examine this hypothesis. An alternative explanation refers to the possibility that participants with AS perceived the facial stimuli more negatively after oxytocin treatment. Although participants did not report any effect of the experimental procedure on arousal or mood, this question remains unanswered with the current data. Nevertheless, to further investigate this hypothesis, future studies should more thoroughly measure subjective emotional responses to the stimuli presented.

As summarized in the introduction, a number of studies have shown that oxytocin promotes social cognitive function in NT controls as well as in individuals with ASD, at least in the context of mental state attribution or emotion recognition. Because there were no effects of oxytocin on face identity matching performance of neutral faces in the present study, the observed effects on amygdala reactivity are not simply the result of altered performance or differential task difficulty. It should be noted as a limitation that in the present study, we did not explicitly

differentiate between oxytocin-induced modulation of brain activity during correct and incorrect trials of the matching task. This question of performance-related modulation of brain activity could be investigated in follow-up studies with the use of performance-sensitive tasks.

After recent theoretical concepts were introduced regarding the role of the amygdala in social cognition, its contribution might be best described as coding for a stimulus's saliency or relevance and thus coordinating the function of distributed cortical networks for the in-depth evaluation of the biological significance of the stimulus (62,65). In line with this view, it has been put forward that decreased fusiform gyrus activity repeatedly reported in ASD might be a developmental consequence of early dysfunction of the amygdala and thus reduced saliency of facial stimuli in ASD (68). In the placebo condition, participants with AS showed decreased activity in the right amygdala as well as primary and secondary visual cortices compared to controls. However, the effect of oxytocin appeared to be selective for amygdala activity.

These results might have far-reaching implications for our understanding of the neuropeptidergic modulation of social perception and its neural basis. They further strengthen the view that the amygdala mediates the behavioral effects of oxytocin on face processing and possibly more broadly on social cognition. Notably, the present result of increased amygdala activity to neutral faces in ASD extend previous studies on the amygdala dampening effects of oxytocin in healthy males and thus suggest

that oxytocin is not solely involved in the suppression of fear and stress but may also fine-tune the neural representation of social saliency and thus exert adaptive effects on social cognitive functioning. Furthermore, the present results provide new insights in how the central oxytocin system might be involved in altered social perception reported in ASD. Although previous studies have shown that a single dose of oxytocin promotes social cognitive functioning in ASD (44–46) and might also have beneficial effects over 6 weeks of daily administration (69), large-scale controlled clinical trials are still lacking. Nevertheless, the present study provides the first evidence for short-term positive effects of a single dose of oxytocin on amygdala reactivity to social stimuli in a small sample of individuals with ASD and thus might stimulate clinical trials on the effectiveness of oxytocin as an adjunctive treatment option in the context of social skills training in ASD.

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