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Oxytocin Promotes Facial Emotion Recognition and Amygdala Reactivity in Adults with Asperger Syndrome

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The neuropeptide oxytocin has recently been shown to enhance eye gaze and emotion recognition in healthy men. Here, we report a randomized double-blind, placebo-controlled trial that examined the neural and behavioral effects of a single dose of intranasal oxytocin on emotion recognition in individuals with Asperger syndrome (AS), a clinical condition characterized by impaired eye gaze and facial emotion recognition. Using functional magnetic resonance imaging, we examined whether oxytocin would enhance emotion recognition from facial sections of the eye *vs* the mouth region and modulate regional activity in brain areas associated with face perception in both adults with AS, and a neurotypical control group. Intranasal administration of the neuropeptide oxytocin improved performance in a facial emotion recognition task in individuals with AS. This was linked to increased left amygdala reactivity in response to facial stimuli and increased activity in the neural network involved in social cognition. Our data suggest that the amygdala, together with functionally associated cortical areas mediate the positive effect of oxytocin on social cognitive functioning in AS.
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INTRODUCTION

The ability to infer socially relevant information such as emotions from facial expressions is fundamental to human social interaction. Impairments in the processing of faces, such as reduced attention to faces (Chawarska *et al*, 2010), diminished eye gaze (Klin *et al*, 2002), and deficits in recognition of emotions (Dawson *et al*, 2005; Harms *et al*, 2010) and other social information from faces (Adolphs *et al*, 2001) constitute typical social deficits in individuals with autism spectrum disorders (ASD). ASD is a cluster of pervasive developmental disorders comprising autism, Asperger's disorder (or Asperger syndrome; AS), and pervasive developmental disorder not otherwise specified. Functional imaging studies have provided evidence for alterations in the neural circuitry involved in the processing of social information in ASD, including in the amygdala (Dalton *et al*, 2005), the fusiform gyrus (Schultz *et al*, 2003), and the posterior superior temporal lobe (Pelphrey *et al*, 2005). Recently, it has been proposed that alterations in the central nervous oxytocin system might be associated with the social impairments characteristic of individuals with ASD (Carter, 2007).

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Oxytocin is a nine amino-acid neuropeptide that is fundamentally involved in the social behaviors of both rodents (Donaldson and Young, 2008) and humans (Meyer-Lindenberg *et al*, 2011). In healthy adults, oxytocin has been shown to reduce anxiety and endocrine responses to social stress (Chen *et al*, 2011; Heinrichs *et al*, 2003), to promote trusting behavior (Kosfeld *et al*, 2005), and to improve social memory (Guastella *et al*, 2008b; Rimmele *et al*, 2009). In regards to face processing, oxytocin has been shown to improve emotion recognition (Lischke *et al*, 2012a; Marsh *et al*, 2010) and the ability to infer the mental and emotional states of others from subtle facial cues (Domes *et al*, 2007b; Domes *et al*, 2012; Schulze *et al*, 2011), and to increase eye gaze to neutral and emotional human faces (Domes *et al*, 2013b; Gamer *et al*, 2010; Guastella *et al*, 2008a). On the neural level, recent electrophysiological research in animals (Viviani *et al*, 2011) and functional neuroimaging studies in humans (Baumgartner *et al*, 2008; Domes *et al*, 2007a; Domes *et al*, 2010; Gamer *et al*, 2010; Kirsch *et al*, 2005; Lischke *et al*, 2012b) suggest that the amygdala is a central region involved in the behavioral effects of oxytocin. In addition, whole brain analyses have revealed modulatory effects of oxytocin in prefrontal and temporal areas as well as in the brainstem (Zink and Meyer-Lindenberg, 2012).

Some genetic association studies suggest the involvement of structural variations of the oxytocin receptor gene in the development of ASD (Jacob *et al*, 2007; Lerer *et al*, 2007; Liu *et al*, 2010; Wermter *et al*, 2010; Wu *et al*, 2005), although the evidence is not consistent and a recent meta-analysis did

not find an overall effect for the two most frequently investigated single-nucleotide polymorphisms (rs53576 and rs2254298) in ASD (Bakermans-Kranenburg and van Ijzendoorn, 2013). Experimental studies have provided evidence that the administration of oxytocin might improve affective speech comprehension (Hollander *et al*, 2007), enhance emotion recognition, (Guastella *et al*, 2009) increase eye gaze and promote social interaction (Andari *et al*, 2010) in individuals with ASD, and increase responding of the amygdala to faces in an identity matching task (Domes *et al*, 2013a).

On the basis of the results reported in neurotypical individuals and the initial findings on the beneficial effects of oxytocin on social cognition in ASD, we hypothesized that individuals with ASD would show increased emotion recognition performance following a single dose of intranasally administered oxytocin. Furthermore, we expected increased activity in the neural circuitry involved in facial emotion recognition following oxytocin treatment, in particular in the amygdala, the fusiform gyrus, and the superior temporal lobe. Given that individuals with ASD tend to disregard the relevance of the eye region in social communication (Klin *et al*, 2002), and are impaired in reading the 'language of the eyes' (Baron-Cohen *et al*, 2001), we expected that the effects of oxytocin would be pronounced for this particular social stimulus. To test these predictions, we conducted an experiment comparing the effects of oxytocin on emotion recognition from the eye as opposed to the mouth region while regional brain activity was measured with a magnetic resonance imaging (MRI) scanner.

MATERIALS AND METHODS

Participants

Participants were 14 adult males with Asperger's Disorder (or Asperger syndrome; AS) according to the DSM-IV and 14 healthy, typically developing, age-matched male controls (CON) (mean age $+/-$ SD; AS: $24.0 +/- 6.9$ years; CON: $23.6 +/- 5.4$ years; $t(26) = 0.17$; $P = 0.87$). Participants with AS were diagnosed by a trained and clinically experienced psychiatrist with the Autism Diagnostic Interview-Revised (ADI-R) (Lord *et al*, 1994), and Module 4 of the Autism Diagnostic Observation Schedule (ADOS-R) (Lord *et al*, 2000). All participants with AS met the cutoff score for Autistic Disorder in the ADOS-R. Using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) as an estimate of general intelligence, we did not find group differences in intellectual abilities (mean IQ $+/-$ SD AS: $122.4 +/- 24.1$; CON: $125.6 +/- 15.4$; $t(26) = 0.42$; $P = 0.60$). Additional information on demographic group characteristics is provided in Supplementary Table S1. All participants were not taking medication, had normal or corrected-to-normal vision, and reported no history of neurological, psychiatric (other than autism), or endocrine disorders. The present data were collected as part of a larger project on the neural effects of oxytocin in ASD. Data on face discrimination from the same project have been published previously (Domes *et al*, 2013a).

Procedure

Before the experimental sessions, all participants gave written informed consent and were screened for the presence of neurological, psychiatric, and somatic illness. Thereafter, participants completed a set of questionnaires (see Supplementary Methods) and were familiarized with the administration of the nasal spray, the imaging procedures, and the experimental procedure during scanning. Participants were instructed to abstain from smoking, caffeine, and analgesic medication on the scanning days.

Two experimental sessions were conducted in a randomized double-blind, placebo-controlled, within-subject, cross-over design. Forty-five minutes before the functional imaging sessions, participants self-administered three puffs per nostril of oxytocin (Syntocinon-Spray, Novartis, Switzerland; each puff with 4 IU oxytocin; total dose of 24 IU oxytocin) or placebo (containing all ingredients except for the peptide) under the supervision of the experimenter. To assess possible oxytocin-induced changes in mood, wakefulness, and calmness, participants completed a three-scale state questionnaire before substance administration and before entering the scanner (Steyer *et al*, 1997). The experiment lasted 3 h (45 min total scanning time). Participants received monetary compensation after completion of the study. All procedures were in accordance with the Declaration of Helsinki and were approved by the local ethics committee.

Facial Emotion Recognition Task

Black-and-white photographs of four different individuals (two male, two female) displaying six basic facial emotions (anger, fear, disgust, happiness, sadness, and surprise) were taken from a standardized set of faces (Eckman and Friesen, 1976). Sections of the eye region and the mouth region were extracted from each picture. The resulting 48 pictures (24 eyes and 24 mouths) had a size of 390×150 pixels and were presented for 3 s at the center of a 800×600 pixel light grey screen. Facial stimuli were immediately followed by an emotional verbal label presented for 3 s. Half of the stimuli were presented followed by the correct label and half followed by an incorrect label. On each trial, participants were asked to indicate whether the label was correct or incorrect by pressing a button. Trials were presented with an inter-stimulus interval of 1.7 s. (trial structure—Figure 1a). In order to provide a baseline condition and to enhance design efficiency, 24 rest trials (a grey box comparable in luminescence and size to the facial sections) were presented randomly. The total time of the experiment was 9:40 min. Facial stimuli were presented with a pair of MRI-compatible LCD goggles (VisuaStim Digital, Resonance Technology, Northridge CA, USA) using Presentation 14.0 (Neurobehavioral Systems, Albany, CA, USA) allowing for response accuracy and latencies. Emotion recognition performance was analyzed based on two-high-threshold model discrimination indices p_r (Snodgrass and Corwin, 1988) for the eye and mouth condition by subtracting false alarm rates (FA) from hit rates (H): $P_r = H - FA$. Effects of oxytocin on response bias (ie, more or less liberal responding to targets in general) were assessed by calculating B_r: $B_r = FA/(1—(H - FA))$. A liberal bias results in $B_r > 0.5$ and a conservative bias is indicated by $B_r < 0.5$ (Snodgrass and Corwin, 1988).

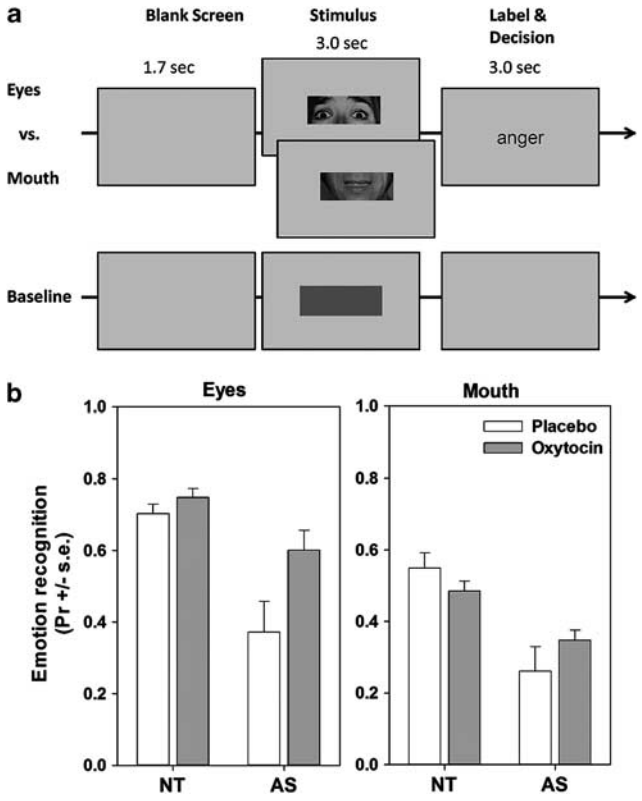

Figure 1 Experimental design and emotion recognition performance. (a) Trial structure and experimental conditions. (b) Effects of oxytocin on emotion recognition (discrimination index Pr) in individuals with Asperger syndrome (AS) and NT controls as a function of stimulus type (eyes *vs* mouth). In individuals with AS, oxytocin administration increased emotion recognition from the eye region, whereas this was not the case in NT controls.

Magnetic Resonance Imaging

Functional and structural images were acquired with a 1.5 Tesla Scanner (Siemens Avanto) equipped with high-speed gradients and the 12-channel standard Head Matrix Coil (Siemens, Erlangen, Germany). In order to reduce artifacts due to head motion, a vacuum cushion was used to stabilize the head, and participants were instructed to stay still during scanning. Following an anatomical scout for slice positioning, 214 volumes containing 36 interleaved axial slices (3 mm thickness with 1 mm gap) covering the whole brain were acquired using a T2*-sensitive echo-planar-imaging (EPI) sequence (Echo time (TE) = 40 ms, Repetition time (TR) = 2700 ms, Flip-angle = 90°, Field of View (FoV) = 214 × 214 mm, Matrix = 64 × 64). Following the functional scans, a structural image was acquired with a three-dimensional, T1-weighted, gradient-echo (MPRAGE) sequence (160 sagital slices, 1 mm slice thickness, TE = 3.9 ms, TR = 1500 ms, Flip-angle = 15°, FoV = 256 × 256 mm, Matrix = 256 × 256).

Image Preprocessing and Statistical Analyses

Preprocessing and statistical analyses were performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first five 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 individual anatomical image, segmentation, spatial normalization to the Montreal Neurological Institute (MNI) standard brain, and spatial smoothing (Gaussian kernel of 9 mm FWHM).

On the first-level, data for the two scanning sessions were compiled and treated as separate runs for each individual. We then modeled each event (eye *vs* mouth) of the two runs of a specific condition as box-car functions of 3 s duration starting with the onset of picture presentation convolved with a hemodynamic response function. In order to reduce slow drift artifacts, a high-pass filter with a cutoff period of 128 s was applied to the voxel time courses. Fixed-effects analysis was conducted by estimating regression coefficients for each condition using least squares within SPM8. Contrast estimates were then calculated for the following differential contrasts: eyes (oxytocin > placebo), mouth (oxytocin > placebo), and the reverse contrasts.

For second-level random-effects analyses, first-level contrasts were subject to a two-sample *t*-test, testing for oxytocin-induced effects during emotion recognition from the eyes and mouth stimuli within and between both groups. Region-of-interest (ROI) analysis for the amygdala was conducted using a sphere ROI of 5 mm radius around the peak voxel within the anatomical amygdala templates provided by the AAL database (Tzourio-Mazoyer *et al*, 2002). A small volume correction (SVC) for the statistical threshold of $P<0.05$ was applied for ROI analysis. Percent signal change (PSC) was extracted using rfxplot (Glascher, 2009) for the averaged signal from these ROI, and plotted to illustrate BOLD signal changes in response to facial stimuli in both drug conditions. Exploratory whole brain analysis was then conducted using an uncorrected statistical threshold of $P<0.001$ with a cluster extent threshold of $k \geqslant 10$. Coordinates of peak voxels within significant clusters are given in MNI space (Evans *et al*, 1993).

RESULTS

Effects of OT on Emotion Recognition

Participants with AS showed impaired overall emotion recognition performance compared with NT controls (main effect of group: $F_{1,26} = 20.68$; $P<0.001$), and emotions were easier to recognize from the eye compared with the mouth stimuli (main effect of stimulus category: $F_{1,26} = 39.94$; $P<0.001$). In the placebo condition, individuals with AS showed reduced recognition performance for eyes ($t_{26} = 3.70$; $P<0.01$) and for the mouth ($t_{26} = 3.59$; $P<0.01$) stimuli compared with NT controls. There was a trend for oxytocin to improve emotion recognition performance (main effect of drug condition: $F_{1,26} = 3.57$; $P = 0.07$), and a significant drug-by-stimulus interaction, reflecting stronger (and more consistent) effects of oxytocin for eyes compared with the mouth stimuli ($F_{1,26} = 5.95$; $P<0.05$). In addition, there was a significant drug-by-group interaction, suggesting stronger effects of oxytocin for participants with AS compared with NT controls ($F_{1,26} = 4.56$; $P<0.05$). In order to specify this interaction, separate 2-way ANOVAs for both groups were calculated: in participants with AS, oxytocin administration improved emotion recognition regardless of stimulus category (main effect of drug

condition: $F_{1,13} = 4.75$; $P < 0.05$; drug × stimulus interaction: $F_{1,13} = 2.50$; $P = 0.138$). In contrast, NT controls showed no overall improvement of emotion recognition following oxytocin administration (main effect of drug condition: $F_{1,13} = 0.10$; $P = 0.834$). Notably, the only significant pairwise comparison regarding the effect of oxytocin was found for emotion recognition from the eyes in participants with AS ($t_{13} = 2.32$; $P < 0.05$). (Figure 1b). Additional analyses on hit rates, false alarms rates, and response biases can be found in Table 1. To test for effects of oxytocin on wakefulness, calmness, and mood separate 3-way ANOVAs (group × drug × time) were calculated. There were no significant main effects of the drug condition, and no interaction effects involving the drug factor (all $P > 0.10$; Supplementary Table S2).

ROI Analyses: OT Effects on Amygdala Reactivity

In participants with AS, analysis for amygdala activity showed increased responding of the left amygdala to both eye stimuli (x, y, and z: −18, −1, −23; t = 3.60, $k = 11$; $P(SVC) = 0.007$), as well as mouth stimuli (x, y, and z: −18, −1, −23; $t = 4.39$, $k = 11$; $P(SVC) = 0.0009$) following oxytocin treatment compared with placebo (contrast: $AS^{OXT > PLA}$). Similar effects were not observed in NT controls: there was neither an effect of oxytocin in the anatomical amygdala template during emotion recognition from the eyes nor from the mouth (Figure 2). In addition, no such effects were observed in the right amygdala or for the reverse contrast on both sides.

In order to test for linear associations between oxytocin-induced modulation of amygdala reactivity and emotion recognition performance, Pearson's correlations between the increase in PSC in the left amygdala (oxytocin—placebo) and the improvement in emotion recognition performance (averaged Pr for eyes and mouth stimuli) were calculated. In the AS group, we found a significant correlation ($r = 0.47$; $P < 0.05$, single-sided) between oxytocin-induced increase in amygdala reactivity and emotion recognition (averaged for the eye and mouth stimuli), this was not the case in the NT control group ($r = 0.14$; $P = 0.63$) Figure 3.

Table 1 Effects of Oxytocin On Hit Rates, False Alarm Rates, and Response Biases

	AS				NT			
	Oxytocin		Placebo		Oxytocin		Placebo	
	m	SD	m	SD	m	SD	m	SD
Eyes								
Hit rate	0.81	0.12	0.69	0.16	0.90	0.06	0.88	0.08
False alarms rate	0.21	0.13	0.32	0.21	0.15	0.08	0.18	0.07
Response bias	0.55	0.20	0.50	0.17	0.61	0.18	0.65	0.20
Mouth								
Hit rate	0.66	0.15	0.58	0.16	0.74	0.14	0.77	0.12
False alarms rate	0.31	0.11	0.26	0.25	0.26	0.12	0.22	0.12
Response bias	0.49	0.18	0.41	0.21	0.52	0.21	0.50	0.20

Abbreviation: AS, Asperger syndrome.

Effects of Drug Sequence

Sequence effects of drug administration were tested for both emotion recognition performance and functional b rain imaging. Including sequence of drug conditions as an additional factor in a four-way ANOVA did not reveal additional significant effects, indicating that the observed effects of oxytocin on emotion recognition performance were independent of whether oxytocin was given at the first scan or at the second.

In order to test for sequence effects of drug conditions on amygdala activity, we extracted PSC data from the left amygdala ROI and calculated a four-way ANOVA with the following factors: group, stimulus category, drug condition, and sequence of drug conditions. Except for the main effect of drug ($F(1,24) = 8.14$; $P = 0.009$), the drug × group ($F(1,24) = 4.68$; $P = 0.041$), and the drug × stimulus category interaction ($F(1,24) = 4.75$; $P = 0.039$), no other effect reached significance, indicating that the observed effect of

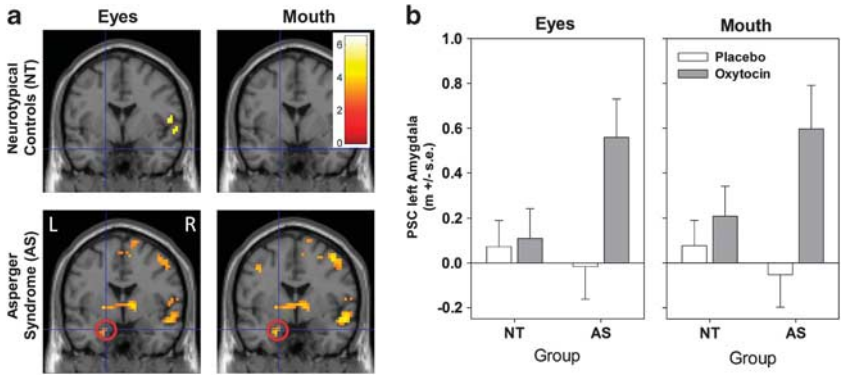

Figure 2 Effects of oxytocin on amygdala activity in individuals with Asperger syndrome (AS) and NT controls as a function of stimulus type (eyes *vs* mouth). (a) Oxytocin significantly increased the activation of the left amygdala (region-of-interest, ROI) in individuals with AS while viewing eyes (*x*, *y*, *z*: −18, −1, −23; $t = 3.60$, $k = 11$; P(small volume correction, SVC) = 0.007) and mouth stimuli (x, y, z: −18, −1, −23; $t = 4.39$, $k = 11$; $P(SVC) = 0.0009$). Statistical parametric maps are displayed with a threshold of $p(uncorr) < 0.005$; $k = 10$. (b) Percent signal change in the amygdala ROI (27 voxels) as a function of group, stimulus type, and drug condition. For individuals with AS, effects of oxytocin were comparable for eyes and mouth stimuli, whereas no such effect was observed in NT controls.

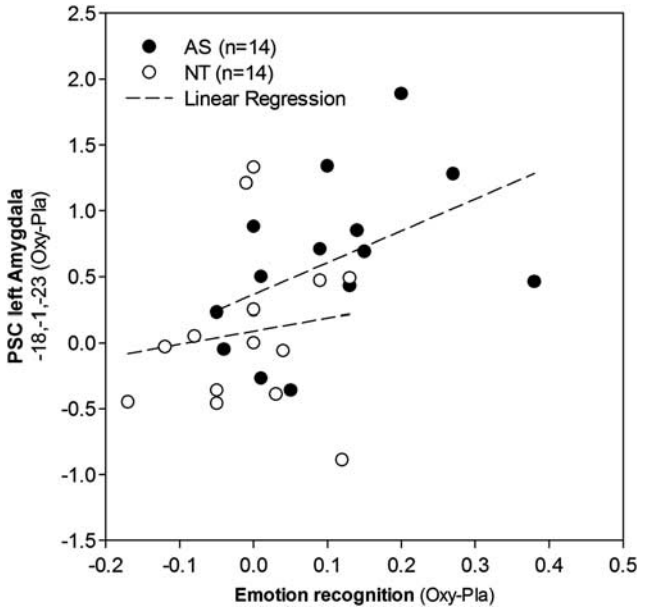

Figure 3 Linear association between oxytocin-induced modulation of left amygdala reactivity to facial stimuli and emotion recognition performance. In the Asperger syndrome (AS group), oxytocin-induced increase in amygdala reactivity predicted the improvement in emotion recognition ($r = 0.47$; $P < 0.05$, single-sided), whereas this was not the case in the NT control group ($r = 0.14$; $P = 0.63$).

oxytocin was independent of whether oxytocin was administered at the first scan or at the second.

Whole Brain Analysis

Whole brain analysis was conducted to explore oxytocin-induced modulations of regional brain activity during facial emotion recognition beyond the predefined ROI in the amygdala. In participants with AS, we found significantly increased activation in the temporal pole, superior temporal cortex, inferior frontal gyrus, Supplementary Motor Area, cerebellum, and superior parietal lobe following oxytocin administration compared with placebo (contrast: $AS^{OXT>PLA}$) for both eye stimuli and mouth stimuli. Using the same combined statistical and extend threshold ($p_{uncorrected} < 0.001$ and $k > 10$) there were only two significant clusters in NT controls showing increased activation following oxytocin administration compared with placebo (contrast: $NT^{OXT>PLA}$): the inferior frontal gyrus (for eye stimuli) and the fusiform gyrus (for mouth stimuli). Contrasting these effects explicitly (contrast: $AS^{OXT>PLA} > NT^{OXT>PLA}$) revealed only two clusters: one in the ventro-lateral prefrontal cortex and one in the cerebellum. In both groups, the reverse contrasts ($AS^{PLA>OXT}$ and $NT^{PLA>OXT}$) did not reveal significant clusters, indicating that regional brain activity in response to facial stimuli was not attenuated under oxytocin compared with placebo. A complete list of activated clusters is given in Table 2.

DISCUSSION

In accordance with our hypothesis, and in line with previous research in adolescents with ASD (Guastella *et al*, 2009), a single dose of intranasally administered oxytocin improved performance on a basic emotion recognition task in adults with AS, and to a lesser extent in neurotypical controls. This effect was more pronounced for the inference of emotions from the eye region compared with the mouth region, and could not be explained by enhanced response latencies or a drug-induced response bias toward more liberal answering.

Autistic individuals often disregard the relevance of social information from the eye region (Klin *et al*, 2002) and show difficulties in interpreting social information from the eyes (Baron-Cohen *et al*, 2001). Improved emotion recognition from the eye region found in the present study is consistent with recent studies showing enhanced gaze to the eye region after intranasal oxytocin administration in healthy volunteers (Andari *et al*, 2010; Domes *et al*, 2013b; Gamer *et al*, 2010). Taken together, these studies suggest that oxytocin-induced enhancement of attention to the eye region (Andari *et al*, 2010) might be the mediating factor for the beneficial effect on emotion recognition in autistic individuals.

At the neural level, oxytocin administration specifically increased amygdala reactivity to facial stimuli in the AS group. Participants with AS showed increased activations in the left amygdala, regardless of whether eye or mouth stimuli were shown. No such effect was observed in NT controls. The implication of the amygdala in mediating emotion recognition performance is supported by the positive correlation between increased amygdala activation and emotion recognition performance in the AS group observed in the present study. Numerous studies have provided evidence that amygdala activity is associated with fear and emotion processing, face perception, affective learning, and more broadly with the motivational relevance and salience of the stimuli presented (for a recent review: Adolphs, 2010). Thus, increased responding of the amygdala following oxytocin administration in the present study might reflect increased allocation of cognitive resources to the presented stimuli, and might therefore represent part of the neural basis for increased emotion recognition performance. The evidence regarding amygdala activity during face perception in adults with ASD is inconsistent, and includes studies both showing elevated (Dalton *et al*, 2005; Kleinhans *et al*, 2009; Monk *et al*, 2010; Tottenham *et al*, 2013; Weng *et al*, 2011) and reduced amygdala reactivity (Ashwin *et al*, 2007; Bookheimer *et al*, 2008; Corbett *et al*, 2009; Hadjikhani *et al*, 2007; Kleinhans *et al*, 2011; Perlman *et al*, 2011). Although increased amygdala reactivity has been interpreted as reflecting increased fear or ambiguity in relation to the stimuli presented (eg, Dalton *et al*, 2005), the finding of reduced amygdala reactivity was previously linked to impaired attention, salience or motivational relevance of facial stimuli in ASD (eg, Bookheimer *et al*, 2008). In the present study, amygdala reactivity to facial stimuli appeared to be comparable between the AS group and NT controls under placebo. Although the present study does not provide unambiguous evidence for increased salience rather than increased fear during facial emotion processing following oxytocin treatment in the AS group, the notion of increased salience rather than increased fear would predict increased emotion recognition performance, which was indeed the case in the present study. In addition, amygdala reactivity has been shown to be positively

Table 2 Whole Brain Analysis for the Effects of Oxytocin On Brain Activity During Emotion Recognition from the (A) Eyes or (B) the Mouth Relative to Baseline

Region		Coordinates			Cluster k	*T*-value
		x	y	z		
A. Eyes						
Asperger: OXT > PLA						
Temporal pole	R	39	17	−32	34	6.50*
Cerebellum	L	−18	−34	−26	123	5.36
Supp. motor area	R	12	11	58	36	5.35
Sup. temporal sulcus	R	60	−52	7	74	5.11
Inf. frontal gyrus	R	57	17	25	17	4.50
Dorso-lateral PFC	R	30	−22	70	15	4.33
Thalamus	R	12	−1	4	11	4.25
Supp. motor area	L	−3	5	58	10	4.03
Sup. temporal gyrus	L	−60	−16	16	10	3.95
Dorso-latral PFC	R	39	8	37	23	3.91
Sup. temporal gyrus	R	54	−4	−11	11	3.88
Sup. parietal lobe	L	−24	−61	61	10	3.87
Neurotypical controls: OXT > PLA						
Inf. frontal gyrus	R	54	−4	10	11	4.36
AS > NT: OXT > PLA						
Ventro-lateral PFC	L	−36	53	19	11	4.69
Cerebellum	L	−18	−34	−26	20	4.31
NT > AS: OXT > PLA						
No significant cluster						
B. Mouth						
Asperger: OXT > PLA						
Temporal pole	R	42	17	−32	33	6.37*
Anterior insula	R	30	22	4	20	5.29
Sup. temporal gyrus	R	54	−4	−11	60	5.25
Cerebellum	L	−18	−34	−26	59	5.24
Supp. motor area	R	12	11	58	24	5.04
Sup. temporal sulcus	R	51	−49	10	68	4.89
Inf. frontal gyrus	R	54	17	25	41	4.86
Post. cingulate	L	−3	−25	31	16	4.57
No label	L	0	2	4	31	4.57
Post. cingulate	R	18	−37	43	19	4.48
Dorso-lateral PFC	R	42	−1	55	18	4.43
Brainstem	L	−3	−22	−16	11	4.42
Sup. temporal sulcus	L	−45	−55	4	11	4.36
Thalamus	R	6	−16	7	10	4.27
Sup. parietal lobe	L	−24	−61	61	21	4.24
Precentral gyrus	L	−39	2	43	11	4.20
Sup. parietal lobe	R	33	−46	58	19	4.19
Anterior insula	L	−45	14	1	10	4.16
Precentral gyrus	R	30	−22	70	12	4.16
Dorso-lateral PFC	R	39	8	37	32	4.13
Anterior cingulate	R	12	−43	−23	11	4.13
Neurotypical controls: OXT > PLA						
Fusiform gyrus	R	39	−40	−26	10	3.86
AS > NT: OXT > PLA						
No significant cluster						
NT > AS: OXT > PLA						
No significant cluster						

Abbreviation: MNI, Montreal Neurological Institute; PFC, prefrontal cortex.
Coordinates are given in MNI space for peak voxels within clusters with a threshold of $P<0.001$ (uncorr.) and an extend threshold of $k=10$; *P(FWE-corrected) <0.05.

associated with eye gaze in ASD (eg, Dalton *et al*, 2005), and thus might code for the salience of this particular facial region. However, as we had no eye-tracking data in the present study, future experiments are needed to test the proposed mediating role of visual attention for the observed behavioral and neural effects of oxytocin in ASD.

The whole brain analysis revealed significantly increased activity in the temporal pole after oxytocin treatment in individuals with AS. The temporal pole has been associated with inferring the mental state of others (Frith and Singer, 2008), thus potentially representing another candidate region for mediating the positive effects of oxytocin on emotion recognition. In addition, we found increased reactivity to facial stimuli in the superior temporal gyrus, the anterior insula, the inferior frontal lobe, and the Supplementary Motor Area after oxytocin treatment in the AS group. These regions have previously been implicated in face processing (Atkinson and Adolphs, 2011), cognitive and affective empathy (Shamay-Tsoory, 2011), facial mimicry and imitation (Carr *et al*, 2003), and might thus represent a part of the neural circuitry underlying facial emotion recognition in the present study. It should be noted that most of the exploratory whole brain results have to be interpreted with caution, as most of the effects did not survive a family-wise error correction for multiple testing. In addition, although there were no comparable oxytocin effects in NT controls, future studies employing bigger sample sizes are needed to directly compare the neural effects of oxytocin in typically developing individuals and those with ASD.

To our knowledge, this is the first study showing beneficial effects of intranasal oxytocin on facial emotion recognition in high functioning adults with AS. We provide evidence that the behavioral effect of intranasal oxytocin is pronounced for the processing of eye stimuli. The present results further suggest that intranasal oxytocin enhances the salience of emotional facial stimuli in ASD, which is in line with previous results using neutral faces (Andari *et al*, 2010; Domes *et al*, 2013a). The observation that oxytocin modulated the activity in a distributed network of brain regions involved in social cognitive functioning suggests that the effects of oxytocin in social cognition extend beyond a simple modulation of emotional arousal at the level of the amygdala. As oxytocin did not change wakefulness, calmness, and mood over the course of our study, it is unlikely that the effects are due to a general modulation of arousal. Future studies should explicitly test for the specificity of the observed effects for social stimuli as compared with non-social stimuli, and also incorporate clinical control groups with impairments in social cognitive functioning (eg, social anxiety disorder), in order to clarify the specificity of findings with regard to the diagnostic group.

Oxytocin-induced facilitation of emotion recognition and eye contact might be a crucial prerequisite for social approach behavior and intact social cognitive functioning. The present findings are in line with the results of a study with adolescents (Guastella *et al*, 2009) and suggest that intranasal oxytocin might help to improve a specific deficit in emotion recognition in ASD, ie, shaping motivation and attention for the most informative aspects of social stimuli (Andari *et al*, 2010).

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