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Oxytocin attenuates feelings of hostility depending on emotional context and individuals' characteristics

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In humans, oxytocin (OT) enhances prosocial behaviour. However, it is still unclear how the prosocial effects of OT are modulated by emotional features and/or individuals' characteristics. In a placebo-controlled design, we tested 20 healthy male volunteers to investigate these behavioural and neurophysiological modulations using magnetoencephalography. As an index of the individuals' characteristics, we used the empathy quotient (EQ), the autism spectrum quotient (AQ), and the systemising quotient (SQ). Only during the perception of another person's angry face was a higher SQ a significant predictor of OT-induced prosocial change, both in the behavioural and neurophysiological indicators. In addition, a lower EQ was only a significant predictor of OT-induced prosocial changes in the neurophysiological indicators during the perception of angry faces. Both on the behavioural and the neurophysiological level, the effects of OT were specific for anger and correlated with a higher SQ.

Humans are social creatures, and prosocial behaviour is crucial for the interaction of individuals with their environment. Oxytocin (OT) has attracted attention regarding the neurological basis of prosocial behaviours that facilitate interpersonal relationships (e.g., perceptions of trustworthiness, attractiveness and approachability). OT is a hormone that is primarily synthesised in the central nervous system and plays an important role in the regulation of the development of prosocial behaviour and in various reproductive effects, such as parturition and lactation[1]. In animal models, OT is essential for social interactions[2,3], and these animal studies have led to a number of human studies to investigate the mechanisms of this prosocial effect[4–16]. Intriguingly, recent human studies have shown that the administration of OT facilitates temporary attachment between strangers, increasing trust, reciprocity, generosity[13–15], and positively modulate sociality[1,10–12,17,18]. In addition, the amygdala is rich in OT receptors[19,20], and OT acts as an anxiolytic by reducing activity in the amygdala[21]. This anxiolytic-like effect may contribute to human prosocial behaviour by reducing anxiety in personal relations[11].

Although the above-mentioned studies suggest the potential of OT to facilitate sociality, a minority of published studies indicated the opposite result, i.e., antisocial effects, such as increased feelings of envy[22], mistrust[23], attachment insecurity[24], or outgroup derogation[25]. Thus, a recent review suggested that the positive effects of OT on sociality may depend on context or individual factors[26]. With regard to OT's effect on prosociality, no previous study has demonstrated either how contextual and individual differences factors modulate the effects of OT on neural responses to social stimuli or how the neural effects of OT parallel its nuanced prosocial behavioural effects. This is the first study that addresses the individual-dependent effects of OT on prosocial behaviour.

There is accumulating evidence that OT has critical implications for autism spectrum disorder (ASD), in which deficits in social behaviour are common[27]. For example, children with autism have lower plasma OT levels compared with age-matched controls[28], and polymorphisms of multiple OT-related genes are associated with ASD[4,29]. Thus, ASD is a good candidate for treatment with OT, and several symptoms of ASD can be ameliorated by OT administration[5,30]. Considering the association between OT and ASD, we speculated that individuals with autistic-like traits would benefit from OT. Traits of ASD have been characterised using the following three

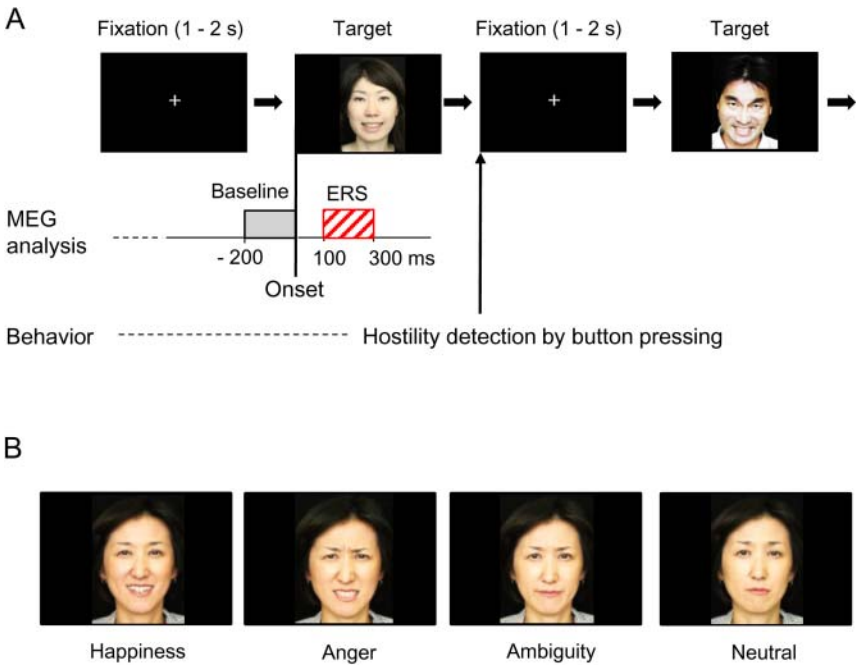

Figure 1 | Task paradigm. A, Each trial started with a fixation cross presented for a random duration of 1000–2000 ms (1000, 1200, 1400, 1600, 1800, and 2000 ms). After the fixation cross, the face of a stranger was presented. The participants then replied whether they detected hostility in the face by pressing the button held in the right or left hand. The next trial was started immediately after pressing the button. A total of 148 pictures were presented in random order, and the total time of the task was approximately 7–10 min. All faces showed direct gaze and were presented on a black background. We defined the periods of interest as 200-ms windows starting 100 ms after onset of stimulus. B, Representative facial pictures of four different facial expressions (happiness, anger, ambiguity, and neutrality). ERS, event-related synchronisation.

dimensions[31–33]: the empathy quotient (EQ)[33], the autism spectrum quotient (AQ)[31], and the systemising quotient (SQ)[32]. These three dimensions can be used to assess milder variants of autistic-like traits (i.e., low EQ, high AQ and high SQ) in typically developing individuals[34–36]. Empathy is an essential part of normal social functioning that allows us to understand the intentions of others, predict their behaviour, and experience an emotion triggered by their emotion. EQ is a self-report questionnaire for use with adults of normal intelligence that focuses purely on this domain[33]. Systemising is the drive to analyse the variables in a system and derive the underlying rules that govern the behaviour of a system. The SQ is a self-report questionnaire for use with adults of normal intelligence that focuses purely on this domain across the range of different system classes[32].

Magnetoencephalography (MEG) is a neurophysiological technique that records the magnetic sources generated from simultaneous firing of groups of pyramidal cells[37]. Unlike indirect measures such as functional magnetic resonance imaging (fMRI), which records aspects of blood flow, MEG directly records neuronal activity and thus records real-time neural activity. In addition, MEG provides not only excellent temporal resolution (on the order of milliseconds) but also good spatial resolution with appropriate source modelling methods. Recent advantageous source analysis methods based on the adoptive beamformer approach[38] enable the estimation of source current power changes in an arbitrarily chosen voxel (e.g., amygdala) within the whole brain at high resolution. Using such methods, recent studies demonstrated that gamma band (30 – 50 Hz) event-related synchronisation (ERS), which is defined as a localised increase in oscillatory power[39], was predominant in the amygdala compared to other parts of the brain, especially during the perception of negative facial emotions (e.g., angry or fearful)[40,41]. This gamma ERS in the amygdala is a candidate for the neurological underpinning of brain responses to emotionally negative stimuli[40–45].

OT has critical implications for ASD[2–5,27,28,30], attenuates stress from negative stimuli[6,7,46,47], and is associated with modulation of the brain response in the amygdala[9–12,18]. Thus, we examined whether, even in healthy individuals, higher SQ or AQ scores and/or lower EQ scores (i.e., personality traits often found in ASD) would be significant predictors of an OT-induced reduction in the hostility detection ratio (i.e., the percentage of hostile responses among all responses) during the perception of others' angry and/or ambiguous facial expressions and in the OT-induced attenuation of gamma ERS in the amygdala. From the perspective of functional lateralisation in the amygdala, the involvement of both the left and the right amygdala in response to emotional faces has been reported using fMRI[48,49]; however, the reason why individual studies report greater lateralisation for one side or the other remains unclear. Then, in the present study, we analysed gamma ERS in the amygdala in each hemisphere. From the perspective of diversity in facial expression, as shown in Figure 1B, we employed ambiguous facial expression in addition to the conventional facial expressions (anger, happiness and neutral) because one recent study suggested that increased amygdala reactivity is associated with behavioural responses to ambiguous facial expression[48]. In this study, we defined ambiguous facial expression as follows: it is difficult to infer the emotions although some facial expressions are present.

Results

As shown in Figure 2, the experimental sessions were conducted in a single-blind, placebo-controlled, within-subject, crossover design, with an interval of at least two weeks. The order of the two conditions (OT or placebo) was counterbalanced across subjects by random selection. We excluded one subject from the neurophysiological analysis because of unrecoverable magnetic noise caused by a dental bridge. Thus, in the statistics for the physiological data, subjects consisted of 19 men (10 started with the OT condition, and 9 started with the placebo condition), whereas all subjects were included in the statistics for behavioural data (10 started with the OT condition, and 10 started with the placebo condition).

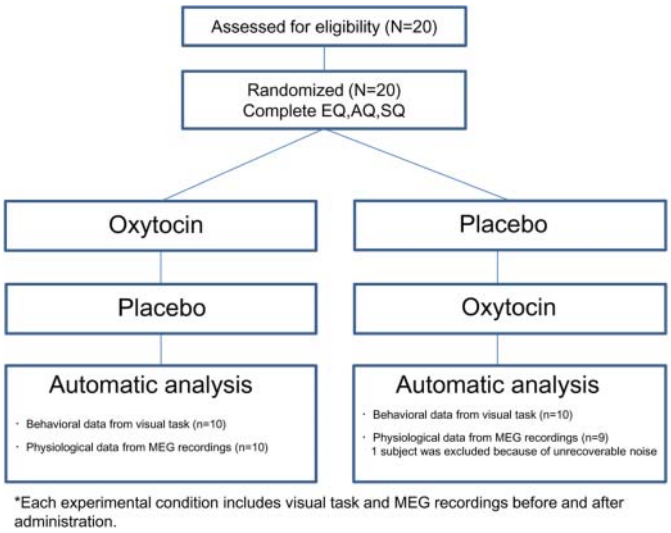

Figure 2 | Design of this study.

Correlation between oxytocin-induced behavioural changes and autistic traits (n = 20). In the present study, our main concern was to evaluate how prosocial effects are constrained by individuals' personality in each emotional condition. We performed multiple linear regressions to predict the placebo-subtracted changes after OT treatment in the hostility detection ratio or reaction time (i.e., dependent variables) using AQ, EQ, and SQ scores as predictors (i.e., three independent variables) for each emotional condition. Statistical significance was defined as $P<0.05$.

There were no significant correlations among independent variables (correlation coefficients = −0.190, −0.085, and 0.207 when comparing AQ and EQ, AQ and SQ, and EQ and SQ scores, respectively).

For the hostility detection ratio, the multiple regression model revealed that a high SQ score was a significant predictor of the placebo-subtracted changes in the hostility detection ratio for facial emotions after OT treatment only in the anger condition ($n=20$, $\beta=-0.334$, $P=0.032$), whereas AQ ($n=20$, $\beta=-0.368$, $P>0.05$) and EQ scores ($n=20$, $\beta=-0.306$, $P>0.05$) did not reach statistical significance (Table 1). In other emotional conditions (i.e., happiness, ambiguous, or neutral), no independent factors were significant predictors of the placebo-subtracted behavioural changes after OT treatment ($P>0.05$) (Table 1).

For reaction time, no independent factors (i.e., AQ, EQ and SQ) were significant predictors of the placebo-subtracted changes in reaction time after OT treatment for any facial emotion ($P>0.05$).

Table 1 | Standardised regression coefficient β and t values for the multiple regression models with the placebo-subtracted behavioural changes for each facial emotion after OT treatment as the dependent variable. AQ, EQ, and SQ scores were utilised as the independent variables

		AQ	EQ	SQ	*n*	R^2
Happiness	β	−0.167	0.246	0.002	20	0.104
	t	−0.692	1.001	0.008		
Anger	β	−0.368	−0.306	−0.457	20	0.425 *
	t	−1.904	−1.553	−2.356 *		
Ambiguity	β	0.001	−0.029	−0.334	20	0.116
	t	0.003	−0.119	−1.388		
Neutrality	β	−0.245	0.069	−0.300	20	0.140
	t	−1.038	0.285	−1.264		

n: number of subjects, * $P<0.05$
OT, oxytocin; AQ, autism quotient; EQ, empathy quotient; SQ, systemising quotient.

Table 2 | Standardised regression coefficient β and t values for the multiple regression models with the placebo-subtracted gamma ERS changes in the right hemisphere for each facial emotion after OT treatment as the dependent variable. AQ, EQ, and SQ scores were utilised as the independent variables

Right amygdala		AQ	EQ	SQ	*n*	R^2
Happiness	β	0.058	−0.234	0.497	19	0.257
	t	0.257	−1.015	2.182		
Anger	β	−0.136	0.729	−0.550	19	0.706 **
	t	−0.956	5.032 **	−3.842 **		
Ambiguity	β	−0.161	−0.304	0.269	19	0.148
	t	−0.667	−1.234	1.103		
Neutrality	β	−0.052	0.091	0.406	19	0.196
	t	−0.219	0.378	1.714		

n: number of subjects, * $P<0.025$, ** $P<0.0025$
ERS, event-related synchronisation; OT, oxytocin; AQ, autism quotient; EQ, empathy quotient; SQ, systemising quotient.

Correlation between oxytocin-induced neurophysiological changes and autistic traits (n = 19). We performed multiple linear regressions to predict the placebo-subtracted changes after OT treatment in neurophysiological variables (i.e., dependent variables) using AQ, EQ, and SQ scores as predictors (i.e., three independent variables) for each emotional condition. Statistical significance was defined as 0.025 for neurophysiological variables (in the left and right region of interests (ROIs).

For the right amygdala, the multiple regression model revealed that lower EQ ($n=19$, $\beta=0.729$, $P<0.001$) and higher SQ ($n=19$, $\beta=-0.550$, $P=0.002$) scores were significant predictors of placebo-subtracted neurophysiological changes (i.e., decreased gamma ERS in the right amygdala) for facial emotion after OT treatment only in the anger condition, whereas the AQ score ($n=19$, $\beta=-0.136$, $P>0.025$) did not reach statistical significance (Table 2). In other emotional conditions (i.e., happiness, ambiguous, or neutral), no independent factors were significant predictors of placebo-subtracted neurophysiological changes after OT treatment ($P>0.025$) (Table 2).

For the left amygdala under all emotional conditions (i.e., happiness, anger, ambiguous, or neutral), no independent factors were significant predictors of the placebo-subtracted neurophysiological changes after OT treatment ($P>0.025$) (Table 3).

A two-way ANCOVA (emotion×drug) for behavioural changes after treatment (n=20). For behavioural changes (pre-treatment

Table 3 | Standardised regression coefficient β and t values for the multiple regression models with the placebo-subtracted gamma ERS changes in the left hemisphere for each facial emotion after OT treatment as the dependent variable. AQ, EQ, and SQ scores were utilised as the independent variables

Left amygdala		AQ	EQ	SQ	*n*	R^2
Happiness	β	−0.409	0.087	0.284	19	0.274
	t	−1.831	0.381	1.101		
Anger	β	−0.131	0.045	−0.417	19	0.178
	t	−0.553	0.187	−1.738		
Ambiguity	β	0.036	−0.090	−0.381	19	0.172
	t	0.150	−0.368	−1.583		
Neutrality	β	0.198	0.117	0.259	19	0.137
	t	0.811	0.715	1.056		

n: number of subjects. These results did not reach significance ($P>0.025$).
ERS, event-related synchronisation; OT, oxytocin; AQ, autism quotient; EQ, empathy quotient; SQ, systemising quotient.

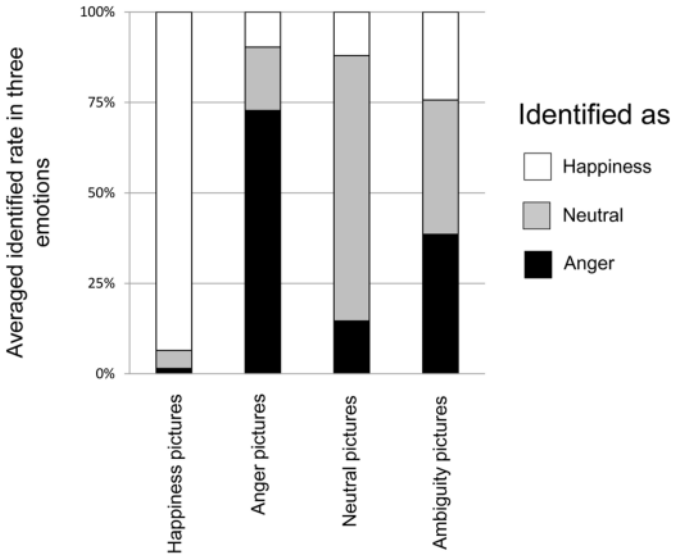

Figure 3 | Validation of the facial emotional pictures in other subjects (n=15).

values were subtracted from post-treatment values) in the hostility detection ratio or reaction time, a two-way ANCOVA was performed (emotion×drug) using the AQ, EQ and SQ scores as covariates. All factors were within subjects for emotion effect (happiness vs. anger vs. ambiguity vs. neutral) and drug effect (OT vs. placebo). Statistical significance was defined as $P<0.05$.

For behavioural changes in the hostility detection ratio after treatment, there were no significant emotion effects (df=3, F=1.04, $P>0.05$) or drug effects (df=1, F=1.28, $P>0.05$), and there were no significant interactions between these two factors (df=3, F=1.00, $P>0.05$). There were no significant interactions between these two factors and covariates ($P>0.05$).

For behavioural changes in reaction time after treatment, there were no significant emotion effects (df=3, F=1.69, $P>0.05$) or drug effects (df=1, F=0.03, $P>0.05$), and there were no significant interactions between these two factors (df=3, F=0.37, $P>0.05$). Among these factors and covariates, only one significant interaction was found between an emotion effect and the AQ score (df=3, F=4.79, $P=0.017$).

A three-way ANCOVA (emotion×hemisphere×drug) for changes in gamma ERS (n=19). For changes in neurophysiological variables after treatment (i.e., gamma ERS in the amygdala), a three-way ANCOVA was performed (emotion×hemisphere×drug) using the AQ, EQ and SQ scores as covariates. All factors were within subjects for an emotion effect (happiness vs. anger vs. ambiguity vs. neutral), hemisphere effect (left vs. right), and drug effect (OT vs. placebo). Statistical significance was defined as $P<0.05$. A three-way ANCOVA revealed no significant emotion effect (df=3, F=1.39, $P>0.05$), hemisphere effect (df=1, F=0.81, $P>0.05$), or drug effect (df=1, F=0.02, $P>0.05$). There were no significant interactions among factors, i.e., emotion × hemisphere (df=3, F=1.40, $P>0.05$), hemisphere ×drug (df=1, F=0.21, $P>0.05$), emotion × drug (df=3, F=0.55, $P>0.05$), or emotion×hemisphere ×drug (df=3, F=1.23, $P>0.05$). Among these factors and covariates, only one significant interaction was found between emotion, drug and SQ score (df=3, F=4.81, $P=0.018$).

Validation of the facial emotional pictures. To validate the facial emotional pictures used in our visual task, a group of another healthy volunteers (n = 15) was asked to evaluate whether the facial emotions indicated happiness, neutrality, or anger according to the emotion expressed by the photographic subject. As shown in

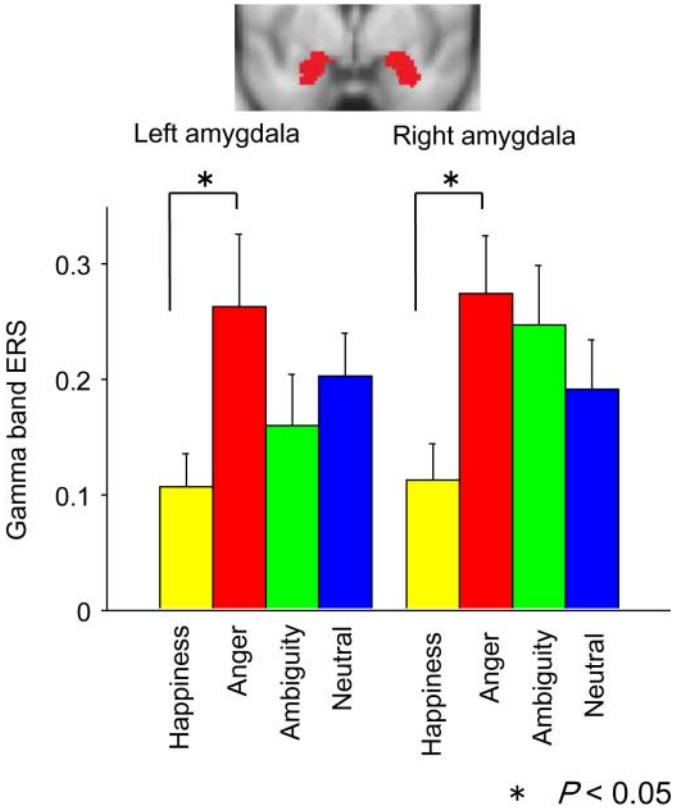

Figure 4 | A, ROI analyses for gamma ERS before placebo administration. A two-way ANOVA revealed a significant emotion effect (df=3, F=2.938, $P=0.041$) but no significant hemispheric effect (df=1, F=0.814, $P>0.05$). There was no significant interaction between these two factors (df=3, F=0.922, $P>0.05$). Post-hoc analyses showed that the gamma ERS in the amygdala was larger for the anger condition than for the happiness condition ($P = 0.005$). Error bars indicate 1 standard error.

Figure 3, all 37 pictures categorised as showing "happy", "angry", and "neutral" facial emotion were identified correctly by an average of more than 70% of all healthy volunteers. On the other hand, 37 pictures categorised as "ambiguous" were not recognised as happy, angry, or neutral by an average of more than 40% of the healthy volunteers.

A two-way ANOVA (emotion×hemisphere) for gamma ERS in the amygdala (n=19). To confirm the neurophysiological (i.e., gamma ERS) responses in the amygdala during the perception of various facial emotions, a two-way ANOVA was performed without any covariates (i.e., AQ, EQ and SQ scores) for the conditions before placebo administration. Two factors were analysed within subjects for the emotion effect (happiness vs. anger vs. ambiguity vs. neutral) and the hemispheric effect (left vs. right). Statistical significance was defined as $P<0.05$. A two-way ANOVA revealed a significant emotion effect (df=3, F=2.938, $P=0.041$) but not a significant hemispheric effect (df=1, F=0.814, $P>0.05$) (Figure 4). There was no significant interaction between these two factors (df=3, F=0.922, $P>0.05$). Post-hoc analyses (Bonferroni/Dunn procedure) showed that gamma ERS in the amygdala was larger for the anger condition than the happiness condition ($P=0.005$). These results indicate that gamma ERS in the amygdala during face perception depends on the emotional condition (i.e., gamma ERS is higher in the anger condition) regardless of the hemisphere (Figure 4).

Discussion

We examined how the effects of OT on human behaviour and underlying brain activity are constrained by the features of emotional

situations and/or individual characteristics. As we hypothesised, higher SQ scores and lower EQ scores were significant predictors of OT-induced attenuation of gamma band ERS in the right amygdala during angry facial perception (Figure 5B). In addition, a higher SQ score was a significant predictor of the OT-induced decrease in the hostility detection ratio during angry facial cognition (Figure 5A). Unexpectedly, during ambiguous facial cognition, no individual factors (i.e., EQ, AQ and SQ) were significant predictors of the behavioural changes after OT treatment both in behavioural and physiological results. These findings suggested that, in case of individuals with higher SQ and obvious negative emotional cognition, the OT tends to suppress brain activities in the right amygdala and decrease the emotional discomfort that can be associated with hostility detection.

As shown in the results of a two-way ANCOVA (emotion × drug) for the behavioural data, we did not find any significant main effect of drug (i.e., OT or placebo) or drug-related interactions. Thus, we found no significant prosocial effect of OT, whereas two previous behavioural studies indicated that it had prosocial effects in facial cognition[6,16]. These differences may be due to dissimilarities between the participants within the different samples. For example, one previous study recruited subjects from universities[16], whereas we recruited subjects from the general population. Most of the subjects in the present study were workers in non-technical fields which is different from mathematically intensive fields (mathematics, engineering, computer science, and physical sciences) in which populations could have deviated traits (e.g., high systemising and/or low empathising traits)[36]. Furthermore, our results were consistent with the recent suggestion that the effect of OT is not prosocial in everyone[26].

Recent fMRI studies in male subjects demonstrated the suppressive effects of OT on the amygdala response to negative facial emotions[10,11,18], whereas our MEG study, as a whole, did not demonstrate a significant effect of OT in the amygdala. These differences could be explained by different methodologies (i.e., fMRI vs. MEG). There are essential differences in the time scale and meaning to which these two imaging modalities are applied. MEG records neuronal activity directly; thus, in the present study, we could record real-time neural activity with 200-ms time windows starting 100 ms after stimulus onset, whereas fMRI measures the brain haemodynamic response that occur a few seconds after the start of the stimulus and is an indirect measurement of neuronal activity[50]. In addition, these differences may also be due to dissimilarities between participants of the different samples, as mentioned above. In terms of the diversified effect of OT administration on amygdala and the individuals' characteristics, one suggestive study demonstrated that female subjects showed enhanced haemodynamic response in the amygdala during the perception of negative emotional face after OT administration[9]. This result is at odds with the previously reported suppressive effects on amygdala found in men[10,11,18]. This diversified effect of OT on amygdala in previous studies may be explained by the opposing empathising and systemising trends observed between men and women (i.e., men tend to show high systemising and/or low empathising traits compared with women)[36].

Significantly higher SQ and lower EQ scores have been reported in ASD subjects with normal intelligence[32]. In addition, recent studies reported that several symptoms of ASD can be ameliorated by OT administration[5,30]. These facts are consistent with the hypothesis that healthy individual with high SQ and low EQ (i.e., ASD traits) may also be beneficial responders to OT administration (i.e., that OT will suppress the amygdala).

To confirm the neurophysiological (i.e., gamma ERS) responses in the amygdala during the perception of various facial emotions, a two-way ANOVA was performed without any covariates (i.e., AQ, EQ and SQ scores) before placebo administration. In the present study, we confirmed the emotion-dependent gamma band (30–50 Hz) ERS in the amygdala, which was predominant during the perception of negative facial emotion (e.g., anger) (Figure 4) and largely replicated the results of previous MEG studies[40,41]. A number of neurophysiological studies have suggested that gamma band synchronisation plays a crucial role in integrating distributed neural processes into highly ordered cognitive functions[51–54]. With regard to emotional processing, gamma band oscillation has been associated with negative emotional face processing within the amygdala[40–42]. Therefore, we hypothesised that the observed higher gamma ERS in the present study indicated the brain emotional responses to the negative facial emotions.

There were some limitations in the present study. First, the sample of 20 participants was rather small and consisted only of male subjects. It will be important to replicate the findings in a larger sample that includes both sexes with a greater age range. Second, the phenomenon that decreases of the hostility detection ratio after OT

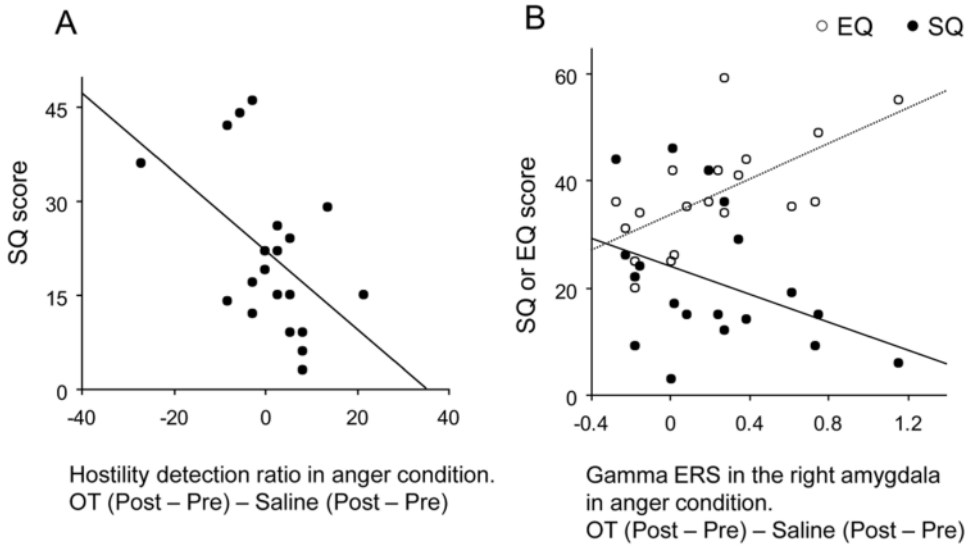

Figure 5 | A, Scatter plot of the hostility detection ratio in the anger condition (placebo-subtracted per cent change after OT treatment) and the SQ score ($r=-0.489$). B, Scatter plot of the gamma ERS in the right amygdala in the anger condition (placebo-subtracted per cent change after OT treatment) and the EQ (○) or SQ (•) score ($r=0.637$, -0.387, respectively). Solid line; regression line for SQ, broken line; regression line for EQ, SQ; systemising quotient, EQ; empathy quotient.

administration could be explained by either "deterioration of cognitive performance" or by "prosocial effect". Further study with fine evaluation of OT effect on facial cognition is necessary to distinguish between these explanations. Third, relative to previously published studies in males without ASD, our participants had relatively lower SQ and AQ scores (e.g., 114 healthy males in previous study[32] showed a mean scores (±SD) of 30.3 ± 11.5 on the SQ and 38.8 ± 12.4 on the EQ; 76 healthy males in a previous study[31] showed a mean scores (±SD) of 17.8 ± 6.8 on the AQ). We cannot exclude the possibility that these differences in the characteristics of participant have an impact on our results. Fourth, because substance administration was executed in a single-blind manner (i.e., the experimenter knew the composition of the groups but the participants did not), this strategy does not allow us to firmly exclude the possibility that the experimenter involuntarily influenced the findings. This possibility is unlikely because (a) the verbal contact with the experimenter was limited (all instructions during the task were given by the computer), and (b) instructions were fully standardised.

This is the first study indicating how empathising and systemising traits modulate the effects of OT in the amygdala during the perception of social stimuli and how the neural effects of OT parallel its nuanced prosocial behavioural effects. We characterised the emotion- (i.e., anger) and individual- (i.e., low EQ and/or high SQ score) dependent nature of the prosocial effects of OT, which may enable refined theorising on the social effects of OT in humans. Viewing the effects of OT in this way sheds new light on existing and emerging experimental data and has crucial implications for more individualised use of OT as a therapeutic agent for ASD and/or other psychiatric disorders.

Methods

Participants. Twenty right-handed adult men participated in the experiment. The participants had a mean age of 31.4 years (20–46). The mean scores (±SD) of the AQ[31], EQ[33] and SQ[32] were 13.9±4.7, 37.3±9.8 and 21.6±12.7, respectively. All subjects were native Japanese and had no previous or existing psychiatric, neurological, or medical illnesses. Subjects were screened with a structured clinical interview for DSM-IV (SCID-I/NP)[55] to exclude a personal history of psychiatric illness. Subjects were not on any medication at least 6 weeks prior to testing and reported a normal sleep/wake cycle. Written informed consent was obtained prior to enrolment in the study. The Ethics Committee of Kanazawa University Hospital approved the methods and procedures, all of which were performed in accordance with the Declaration of Helsinki.

Experimental design. The experimental sessions were conducted in a single-blind, placebo-controlled, within-subject, crossover design, with an interval of at least two weeks. The order of the two conditions (OT or placebo) was counterbalanced across subjects by random selection. Thereafter, participants completed the AQ[31], EQ[33], and SQ[32]. Participants were randomly assigned to receive either a single intranasal dose of either 24 IU OT (Syntocinon; Novartis, Basel, Switzerland) or the placebo control during the first experiment. Following published pharmacokinetics[56], 45 minutes after substance administration, we investigated the effects of OT on the social interpretation of emotional faces and amygdala activity using an automatic computer visual task.

Visual task procedures. Prior to this study, facial images of 37 Japanese volunteers (17 male and 20 female) with four different facial expressions (angry, happy, neutral, ambiguous; see Figure 1) were taken under controlled conditions with a digital camera (DMC-TZ7; Panasonic Osaka, Japan). All faces showed direct gaze and were presented on a black background. Details of the validation of these facial emotional pictures are presented in the supplemental information.

Subjects lay supine on a bed, facing a tilted white screen measuring 24×16 cm that was fixed above the bed in a dark magnetically shielded room (Daido Steel, Nagoya, Japan) in which the MEG apparatus was set. Using a video projector (PG-B10S; Sharp, Osaka, Japan) with a refresh rate of 60 Hz, a computer placed outside the magnetically shielded room projected a picture through a small window of the wall of the shielded room onto the screen above the head position of the bed. The distance from the subject's nasion to the centre of the screen was approximately 30 cm. Therefore, the visual angle of the picture projected on the screen was approximately 42°×34°. Visual tasks were generated using SuperLab 4.0 software (Cedrus Corporation, P.O. Box 6309, San Pedro, CA 90734 - USA). A total of 148 pictures were presented in random order. After the onset of each facial picture, the participants were instructed to judge whether they sensed hostility in each face by pressing a button on a two-button device. The presentation of each face was replaced by a central fixation cross just after each judgment (i.e., button press action). The interstimulus interval (i.e., during the presentation of the central fixation cross) was randomised between 1000 and 2000 ms. All participants were unfamiliar with the faces used in this task.

MEG recordings. Magnetic fields were measured in a whole-head-type system for adults at the Laboratory of Yokogawa Electric Corporation in Japan. This system (MEGvision PQA160C; Yokogawa Electric Corporation, Yokogawa, Japan) consisted of 160 channels. Sensors were configured as first-order coaxial gradiometers with a baseline of 50 mm; each coil of the gradiometers measured 15.5 mm in diameter. Magnetic fields were sampled at 1000 Hz per channel (band pass 0.16–200 Hz). Using a Signa Excite HD 1.5-T system (GE Yokogawa), all subjects underwent T1-weighted magnetic resonance imaging (MRI) study with spherical lipid markers placed at the 5 MEG fiduciary points to enable us to superpose the MEG coordinate system on the MRI data. The MRI consisted of 166 1.2-mm sequential slices, with a resolution of 512×512 points in a field of view of 261×261 mm. After reconstructing the three-dimensional MRI, the best-fit sphere was determined for each participant's head.

MEG data analysis for the gamma band ERS in the amygdala. On the basis of previous studies[40,41,45], the magnetic field data of each subject and each emotional face condition were refined into one frequency band of interest, i.e., gamma band oscillation (30–50 Hz). The current density for each voxel was then calculated by adaptive spatial filtering using a single spherical volume conductor-model based on the individual MR images. Power changes in the current density between the active and baseline periods for each voxel were calculated with 5-mm grid spacing. The baseline period was defined as the time between 200 and 0 ms before stimulus onset, and the active periods of interest were defined as 200-ms windows starting 100 ms after stimulus onset[40–42,45]. Adaptive spatial filtering is a spatial filtering approach to source reconstruction that can estimate neuromagnetic activities with high spatial resolution by forming a linear combination of sensors that can suppress the signals from environmental noise or other brain areas without attenuating the power from the target voxel. The approach is optimised for time frequency source reconstructions from MEG/EEG data[57,58]. Details of the adaptive spatial filtering in this study are presented in the supplemental information. The functional images were normalised relative to template brain images created by the Montreal Neurological Institute (MNI) template (in SPM8; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Region-of-interest (ROI) analysis was performed for amygdala gamma band ERS. Data extraction for ROI analyses was performed using MarsBaR provided with a sophisticated template for ROIs on SPM-normalised images [MARSeille Boîte À Région d'Intérêt[59]]. The details of this ROI procedure have been reported previously[60].

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Author contributions

Author Tetsu Hirosawa and Mitsuru Kikuchi designed the study and wrote the protocol. Author Haruhiro Higashida, Yuko Yoshimura, Toshio Munesue, Tsunehisa Tsubokawa, Yasuhiro Haruta, Hideo Nakatani, Takanori Hashimoto and Yoshio Minabe managed the literature searches and analyses. Authors Eiichi Okumura, Sanae Ueno and Kiyomi Shitamichi undertook the statistical analysis, and author Tetsu Hirosawa wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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