이학박사 학위논문

Modulatory effect of oxytocin on neural activity in response to fearful emotion in schizophrenia

조현병 환자의 공포 정서 지각에 대한 옥시토신의 뇌 활동 조절 효과

2014 년 2 월

서울대학교 대학원

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Modulatory effect of oxytocin on neural activity in response to fearful emotion in schizophrenia

by

Na Young Shin

A thesis submitted in partial fulfillment of the requirement for the Degree of Doctor of Science in Interdisciplinary Cognitive Science Program

In Seoul National University

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Approved by Thesis Committee:

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ABSTRACT

Introduction: Impaired facial emotion recognition is a core deficit in schizophrenia. Oxytocin has been shown to improve social perception in patients with schizophrenia; however, the effect of oxytocin on the neural activity underlying facial emotion recognition has not been investigated. This study was aimed to assess the effect of a single dose of intranasal oxytocin on brain activity in patients with schizophrenia using a facial emotion recognition paradigm.

Methods: Sixteen male patients with schizophrenia and 16 age-matched healthy male control subjects participated in a randomized, double blind, placebo-controlled crossover trial at Seoul National University Hospital. Delivery of a single dose of 40 IU intranasal oxytocin and the placebo were separated by 1 week. Drug conditions were compared by performing a region of interest (ROI) analysis of the bilateral amygdala and a whole-whole brain analysis of responses to the emotion recognition test.

Results: Oxytocin attenuated bilateral amygdala activity in response to fearful and neutral faces in the patients, whereas inhalation of

oxytocin significantly increased amygdala activity in response to happy faces in the control group, which was related to attachment style.

Conclusions: The present results indicate that intranasal oxytocin attenuated amygdala activity evoked by fearful and neutral faces in patients with schizophrenia, suggesting that inhalation of oxytocin may reduce social anxiety and the salience of perceived negative and ambiguous emotions. This study provides new evidence to support a therapeutic role for intranasal oxytocin in schizophrenia.

Keywords: Oxytocin, Schizophrenia, Intranasal, Emotion, fMRI

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LIST OF ABBREVIATIONS

ANOVA, analyses of variance

BOLD, blood oxygenation level-dependent

fMRI, functional magnetic resonance imaging

FWHM, full-width at half-maximum

HC, Healthy Controls

IRI, Interpersonal Reactivity Index.

ITC, inferior temporal cortex

K-WAIS, Korean version of Wechsler Adult Intelligence Scale-Revised

MNI, Montreal Neurological Institute

MTC, middle temporal cortex

PANAS, Positive and Negative Affect Schedule

PANSS, Positive and Negative Syndrome Scale

PSC, percent BOLD signal change

ROI, region of interest

RSQ, Relationship Style Questionnaires

SD, standard deviation

SPR, schizophrenia

SCID, Structured Clinical Interview for DSM-IV

SCID-NP, Non-Patient Edition of the Structured Clinical Interview for DSM-

SFC, superior frontal cortex

SPM 8, Statistical Parametric Mapping

SPSS, Statistical Package for the Social Sciences

TP, temporal pole

VAS, visual analog scale

WFU, Wake Forest University

INTRODUCTION

Oxytocin and social behaviors in human

Oxytocin is a hypothalamic neuropeptide that is synthesized in the paraventricular nuclei and supraoptic nuclei of the hypothalamus (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Early animal studies have implicated an important role of oxytocin on executing and maintaining social behaviors such as infant bonding, maternal attachment, stress response, and sexual behavior (Marazziti & DellOsso, 2008). Contrary to peripheral administration, intranasal application of oxytocin has been known to penetrate blood brain barrier. Born et al.(2002) reported that concentration of intranasally administered arginine vasopressin, a neuropeptide with similar properties to oxytocin, remains in the cerebrospinal fluid from 10 min up to 80 min after administration. Further, recent studies observed that salivary oxytocin level lasted 2 to 7 hours after nasal spray treatment (Huffmeijer et al., 2012b; Van IJzendoorn, Bhandari, van der Veen, Grewen, & Bakermans-Kranenburg, 2012). From these observations, the researches involving the oxytocin-related effects on social behaviors have been expanded to human subjects and to patients with psychiatric disorders such as autism and social anxiety disorder.

Since a pioneering study of Kosfeld et al.(2005) that reported positive effect of oxytocin on trust in others, substantial researches have demonstrated the beneficial effects of intranasal oxytocin on social behaviors as well as related brain activity. Most of the studies were a placebo controlled within-subject design, and began main experiments 30-50 min after single treatment of oxytocin or placebo (Bartz, Zaki, Bolger, & Ochsner, 2011). Previous studies showed that intranasal administration of oxytocin improved various social behaviors including social emotion recognition (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Domes et al., 2007a; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007b; Domes et al., 2009; Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010; Kirsch et al., 2005; Marsh, Yu, Pine, & Blair, 2010; Petrovic, Kalisch, Singer, & Dolan, 2008; Schulze et al., 2011), empathy (Bartz et al., 2010b; Hurlemann et al., 2010), social memory (Rimmele, Hediger, Heinrichs, & Klaver, 2009; Savaskan, Ehrhardt, Schulz, Walter, & Schächinger, 2008), trusting behavior (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Mikolajczak, Lane, Gross, de Timary, & Luminet, 2010; Theodoridou, Rowe, Penton-Voak, & Rogers, 2009), generosity (De Dreu et al., 2010; Zak, Stanton, & Ahmadi, 2007), and cooperation (De Dreu, 2012; Declerck, Boone, & Kiyonari, 2010) in healthy people (Table1). A few researchers have investigated

therapeutic potential of oxytocin for psychiatric patients who suffer from social dysfunction. The studies have witnessed alleviation of primary symptoms (Feifel et al., 2010; Guastella, Howard, Dadds, Mitchell, & Carson, 2009; Pedersen et al., 2011), improvement of social cognitive function (Fischer-Shofty et al., 2013; Labuschagne et al., 2010; Modabbernia et al., 2013; Pedersen et al., 2011), and pro-social behaviors (Anagnostou et al., 2012; Andari et al., 2010; Domes et al., in press; Guastella et al., 2010; Hollander et al., 2007) in patients with autism spectrum disorder, social anxiety disorder and schizophrenia.

Table 1. Summary of the effect of oxytocin on social cognition in healthy persons

First author	Year	Task	The effect of oxytocin
Kosfeld	2005	trust	↑
Theodoridou	2009	facial trustworthiness	↑
Mikolajczak	2010	trust	↑
Mikolajczak	2010	trust	↑
Domes	2007	theory of mind	↑
Alvares	2010	social rejection	null
Unkelbach	2008	social relations	↑
Bartz	2010	recollection of maternal care	↑
Heinrichs	2004	memory	↓
Zak	2007	generosity	↑
Savaskan	2008	face memory	↑

Rimmele	2009	face memory	↑
Guastella	2008	eye gaze to face	↑
De Dreu	2011	ethnocentrism	↑
Singer	2008	empathy	null
Bartz	2010	empathy	↑
Guastella	2008	emotional face memory	↑
Di Simplicio	2009	emotional face recognition	↑ (fear only)
Guastella	2009	emotional face recognition	null
Marsh	2010	emotional face recognition	↑ (happy only)
Schulze	2011	emotional face recognition	↑ (more in happy)
Evan	2011	emotional face recognition	↑
Shamay-Tsoory	2009	envy and schadedfruede	↑
Declerck	2010	cooperation	↑
Keri	2009	biological motion	↑
Buchheim	2009	attachment security	↑
De Dreu	2010	altruism	↑

↑ and ↓ indicate increased and decreased effects of oxytocin, respectively.

Impact of oxytocin on emotion recognition

The ability to recognize emotional states of other persons from social cues such as facial expression and bodily gestures is crucial for social interaction and communication in human. A number of studies have explored oxytocin-related changes in an ability to recognize other person's emotion (Bartz et al., 2011; Gupta, 1997) and in neural activity during recognizing emotion (Bethlehem, van Honk, Auyeung, & Baron-Cohen, 2013; Zink & Meyer-Lindenberg, 2012). At the behavioral level, oxytocin has been shown to increase the ability to identify fearful and happy facial expressions (Di Simplicio et al., 2009; Domes et al., 2007b; Fischer-Shofty et al.,

2010; Marsh et al., 2010; Schulze et al., 2011), although the results are inconsistent across studies. The first behavioral experiment conducted by Di Simplicio et al (2009) reported slowed reaction time to correctly discriminate fearful faces after oxytocin treatment, but no effect of hormone on other kinds of emotions. Similarly, in an Israeli sample, oxytocin improved recognition of fearful faces but not of other basic emotions (Fischer-Shofty et al., 2010). In contrast to the findings from these two studies, Marsh et al. (2010) observed that subjects who received oxytocin recognized happy facial expression more accurately than those who received placebo. Similarly, in a German study, the effect of oxytocin on emotion detection was larger in happy than angry emotion (Schulze et al., 2011) (Figure 1). However, another German study reported null effect of oxytocin across the different types of emotion. Methodological differences such as presentation time of target stimuli across the studies might be one of contributors to the divergent results (Graustella & Macleod, 2012).

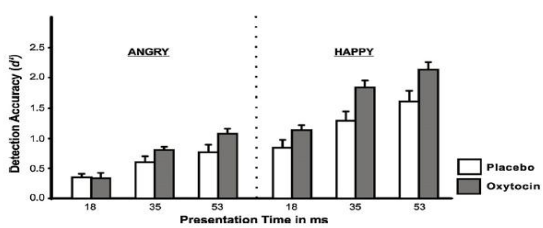

Figure 1. The more pronounced effect of oxytocin on happy faces than on angry faces. Adapted from the study of Schulz et al.(2011).

To detect neural mechanism underlying the beneficial effect of oxytocin on emotion recognition, several functional magnetic resonance imaging (fMRI) studies have been focused on the amygdala reactivity using the region of interest (ROI) approach. Amygdala has been known as a critical region for emotional processing (Adolphs, 2010; Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006). Evidence have shown that oxytocin is released and bound in this brain region (Huber, Veinante, & Stoop, 2005). The first fMRI study dealing with the effect of oxytocin on emotion recognition detected attenuated activation of left amygdala in response to fearful faces in male (Kirsch et al., 2005) (Figure 2). Another study using fearful conditioning design supported the findings of the prior study by showing reduced right amygdala activation during processing aversive conditioned faces (Petrovic et al., 2008). Domes et al.(2007a) employed happy as well as fearful faces for the fMRI experiment and presented the attenuated activation of left amygdala regardless of emotional valences. For this result, the authors suggested the effect of oxytocin toward decrease of uncertainty about emotional stimuli. However, the study from Gamer et al.(2010) reported increased activity in left amygdala in response to happy faces. Although it is unknown what causes these mixed findings, it might be arisen from different experiment paradigm across studies and from individual differences

in neural response for oxytocin.

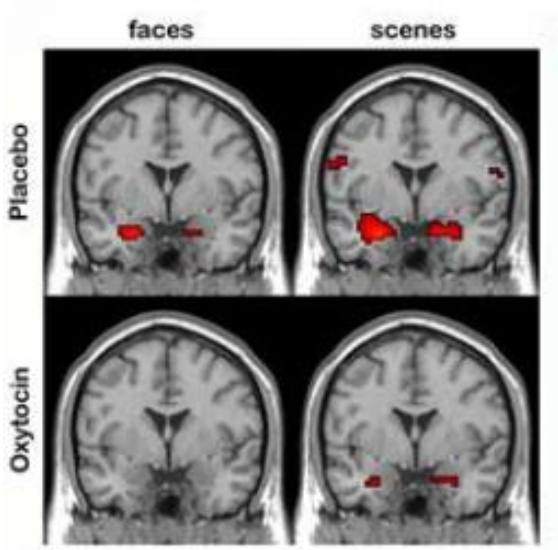

Figure 2. Attenuated amygdala activation for fearful facial expression in oxytocin condition compared with placebo condition. Adapted from the study Kirsch et al.(2005).

Emotional processing in schizophrenia

Schizophrenia is characterized by impairments in cognitive function, emotional processing, and social functioning. Patients with schizophrenia suffer from positive symptoms, such as hallucination and delusion, and negative symptoms, such as reduced emotional expression and anhedonia. Considering their symptoms, it is not surprising that patients with schizophrenia have deficit in recognizing facial expression. Converging evidence indicates that the identification of facial emotion, particularly fearful expressions, is impaired in schizophrenia (Morris, Weickert, & Loughland, 2009).

The emotion recognition deficit in schizophrenia is larger compared other psychiatric disorders including depression and bipolar disorder (Addington & Addington, 1998; Schneider, Gur, Gur, & Shtasel, 1995), and is more severe in male than in female (Scholten, Aleman, Montagne, & Kahn, 2005).

Decreased activity in the amygdala, which plays a critical role in emotional processing (Adolphs, 2010; Fitzgerald et al., 2006), is thought to underlie the deficit in emotion recognition in schizophrenia (Aleman & Kahn, 2005; Gur et al., 2002; Michalopoulou et al., 2008). Previous studies in patients with schizophrenia have found that amygdala activity evoked by a fearful face was diminished relative to that evoked by a neutral face. However, recent neuroimaging studies suggest that this is the result of increased activation in response to the neutral faces rather than a decreased response to fearful faces (Hall et al., 2008; Holt et al., 2006). These studies have focused on whether reduced amygdala activity is arisen from lower amygdala activation during the presentation of fearful faces or higher activation during the presentation of neutral faces. The study of Holt et al.(2006) reported excessive amygdala activation in responses to fearful and neutral faces in patients with schizophrenia. Hall et al.(2008) provided the confirming evidence showing augmented amygdala activation for neutral faces, with a similar magnitude of activation

for fearful faces in patients with schizophrenia by employing a baseline comparison condition (Figure 3). This suggests that increased social anxiety or social fear in patients with schizophrenia results in the tendency to perceive neutral faces as aversive (Morris et al., 2009).

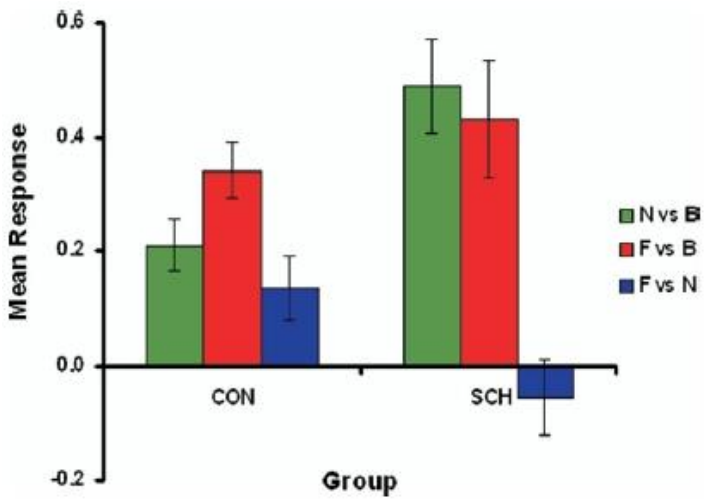

Figure 3. Increased amygdala activation in response to fearful and neutral faces in patients with schizophrenia. Adapted from the study of Hall et al.(2008).

Oxytocin and schizophrenia

Patients with schizophrenia have been reported to have low oxytocin levels, which are associated with an increase in psychotic symptoms and fewer prosocial behaviors (Keri, Kiss, & Kelemen, 2009; Rubin et al., 2010). Oxytocin restored socially aberrant behaviors in rats with schizophrenic symptoms (Caldwell, Stephens, & Young, 2008; Lee, Brady, Shapiro, Dorsa, & Koenig, 2005),

suggesting a link between oxytocin and symptoms or social behaviors in schizophrenia. Indeed, recent studies have shown that intranasal oxytocin treatment decreased psychotic symptoms (Feifel et al., 2010; Pedersen et al., 2011) and improved mentalizing ability (Pedersen et al., 2011), verbal memory (Feifel, MacDonald, Cobb, & Minassian, 2012), and olfactory identification (Lee et al., 2013) in patients with schizophrenia. These promising findings strongly suggest "formulation of oxytocin, oxytocin analogs or oxytocin mimetics approved for the treatment of neuropsychiatric disorders and among schizophrenia" as stated by Feifel (2011), who is a pioneered researcher commencing oxytocin study in schizophrenia.

Research that explores oxytocin-induced neural changes on social behaviors for psychiatric disorders has just started. A few studies investigated changes of neural activity for social perception after oxytocin administration in autism spectrum disorders and social anxiety disorder. In autism spectrum disorders, amygdala activity was diminished during viewing human faces relative to houses after a single-dose intranasal oxytocin treatment (Domes et al., in press). Data from the social anxiety disorder indicated attenuation of neural activities in brain regions including amygdala and medial frontal cortex in responses to fearful and sad faces (Labuschagne et al., 2010; Labuschagne et al., 2011). There

has yet been a study to investigate the effect of oxytocin on brain reactivity for schizophrenia. Rosenfeld et al.(2011), in his review paper about the issue on oxytocin and schizophrenia, proposed that fMRI studies using facial emotion recognition, trustfulness, or theory of mind would be helpful to elucidate the effect of oxytocin on social brain in schizophrenia.

Aim and Hypothesis

To date, the effect of oxytocin on the neural activity underlying facial emotion recognition in schizophrenia has not been investigated. The present study examined the effect of a single dose of intranasal oxytocin on amygdala activity in patients with schizophrenia using a facial emotion recognition paradigm. Based on previous findings, we hypothesized that inhaled oxytocin would attenuate amygdala activity evoked by viewing fearful faces in patients with schizophrenia and healthy controls. Additionally, we expected that intranasal oxytocin would reduce amygdala hyperactivity in response to neutral faces in patients with schizophrenia. Empathy and attachment style was measured to determine whether oxytocin-related behaviors affected the oxytocin-induced neural effect. I predicted that the effect of oxytocin on the amygdala activity underlying facial emotion recognition would be modulated by oxytocin-related behaviors.

METHODS

Participants

The study included 16 male patients with schizophrenia and 16 age-matched healthy male controls. The patients (age range, 18- 46 years) were recruited from the Seoul National University Hospital outpatient clinic and fulfilled the DSM-IV criteria for schizophrenia evaluated using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbson, & Williams, 1996). Patients were included if their symptoms had persisted for ≥1 year and their dose and type of psychotropic drugs had been stable for least for 4 weeks. All patients were taking psychotropic drugs at the time of experiments (antipsychotics, n=13; benzodiazepines, n=13; selective serotonin reuptake inhibitors, n=12; beta-blocker, n=3; psychostimulant, n=3; anticonvulsant, n=2; antiepileptics, n=1). Symptom severity was evaluated using the Positive and Negative Syndrome Scale (PANSS). Among the patients, 43.8% was paranoid type (n=7), 31.3% undifferentiated (n=5) and 25% residual (n=4). All patients had no comorbid Axis I disorders except 1 patient who had coexistent obsessive-compulsive disorder.

The age-matched healthy controls (age range, 18- 47 years) were recruited through internet advertisements and were screened

for Axis I disorders using the Non-Patient Edition of the Structured Clinical Interview for DSM-IV (SCID-NP).

All participants were right-handed with the exception of one patient who was ambidextrous and one control subject who was left-handed. The exclusion criteria were mental retardation, brain injury, neurological illness, alcohol or substance abuse, and acetic acid allergy.

Intelligence was estimated by four-subtest of Korean version of Wechsler Adult Intelligence Scale-Revised (K-WAIS) (vocabulary, picture arrangement, block design, and arithmetic) (Lee & Kim, 1995; Wechsler, 1981).

The present study was approved by the Institutional Review Board of Seoul National University Hospital, and written informed consent was obtained from each subject and from the parents when the subject was under 20 years of age.

Experimental paradigm

The study had a randomized, double-blind, placebo-controlled crossover design. Subjects underwent fMRI experiment on two occasions 1 week apart. The order of the drug administration was counterbalanced. Double-blind randomization for drug condition was conducted using a computerized program, and the order of drug condition was counterbalanced. Subjects were instructed to abstain

from alcohol, nicotine, caffeine, and physical exercise for 24 h prior to the experiment and to avoid food and to drink only water for 2 h prior to the experiment.

Upon arrival, subjects completed the following baseline self-reported questionnaires: the Relationship Style Questionnaire (RSQ) (Griffin & Bartholomew, 1994) and Interpersonal Reactivity Index (IRI) (Davis, 1983; Kang et al., 2009) to measure adult attachment style and empathy, respectively. Under the supervision of an experimenter, the subjects self-administered 10 puffs of oxytocin (40 IU) or placebo contained in a nasal spray (see the Supplement for drug preparation), switching nostrils at 30- 60-s intervals 45 min prior to the fMRI scan. Participants completed the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) and a visual analog scale (VAS) before administration of the drugs and after the fMRI session to assess the effect of oxytocin on mood (Figure 4).

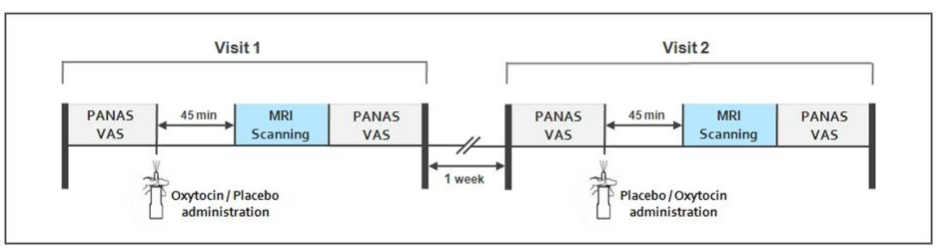

Figure 4. Experimental procedure. Subjects underwent the experiment on two occasions with either oxytocin or placebo 1 week apart. fMRI session was commenced 45 min after drug application and the mood scales were

performed before drug administration and after the MRI scanning.

The fMRI design was similar to that reported previously (Hall et al., 2008). In this block design, blocks of six faces showing fearful, happy, or neutral expressions were interspersed with baseline blocks (12 s) consisting of fixation cross hairs. The face stimuli from 3 Korean females and 3 Korean males were randomly presented for 3 s, followed by the fixation cross hairs (0.5 sec). Each run consisted of three fearful (22 s each), three happy (22 s each), and three neutral blocks (22 s each) and 10 baseline blocks (12 s each). Each emotional faces from six persons was presented once within a block and repeated across block. Subjects were instructed to identify the gender of the face by pressing a button. The face blocks began with the word "Gender?" written in Korean for 1 s. The order of the face blocks was pseudo-randomized (Figure 5). The experiment consisted of two runs. The face blocks were presented in different pseudo-random orders across the runs with a restriction that the same conditions did not occur in successive blocks. The same task was used in oxytocin and placebo conditions. In the day of the first visit, the participants underwent an anatomical scan for about 15 min after the fMRI session.

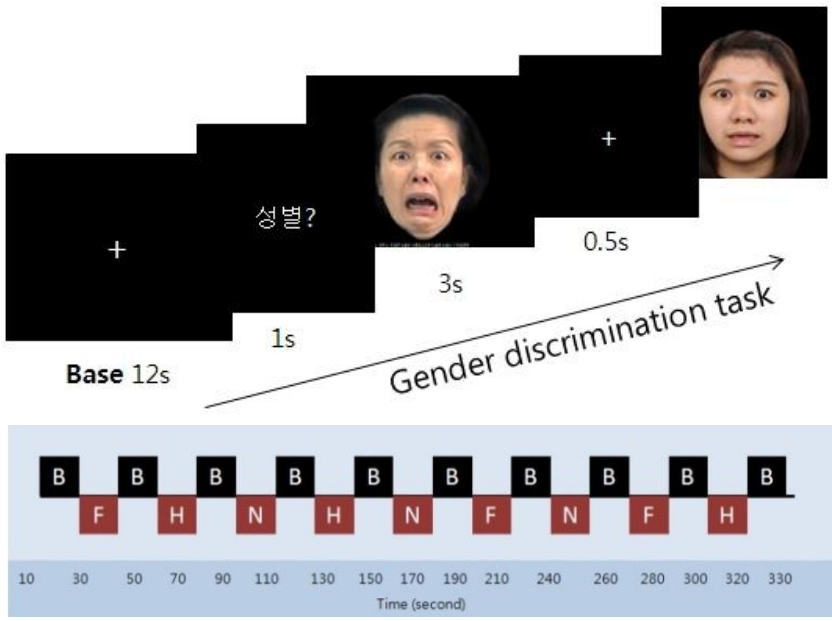

Figure 5. The fMRI task paradigm. Target faces were presented for 3 sec following the word "성별?" (1 sec) and were interleaved with cross-hair (0.5 sec). Subjects were asked to discriminate the gender of persons in the photo by clicking a button box. Each face block was presented for 22 sec and interleaved with a baseline block (12 sec).

Drug preparation

The oxytocin was prepared according to the protocol described in a previous study (Marsh et al., 2010). The oxytocin solution was prepared by the department of pharmacy in Seoul National University Hospital. The 50 mL of oxytocin (202 IU) was combined with 202.5 mL of a 0.9% saline solution. The pH was adjusted to 4.02 using 10x diluted acetic acid. The prepared solution was then distributed in sterilized vials (3ml) and was stored in the refrigerator. The experimenter transferred the oxytocin or saline solution placebo from the vial into a nasal spray device before the

experiment was started.

Face stimuli

Twelve Korean female and thirteen Korean male faces were selected from databases of Korean Facial Expressions of Emotion, ChaeLee Korean Facial Expression of Emotion (Zimmerman, Chelminski, & Posternak, 2004), and NimStim set (Tottenham et al., 2009), based on a preliminary assessment for valid facial expression. Each face depicted seven types of facial expression: happy, fearful, sad, angry, disgust, surprise, and neutral emotions. Forty university students (30 women, 10 men; mean age, 22.2 years) classified the facial expression presented in each photo into 7 basic emotions. The discrimination accuracy rate was the lowest in the fearful faces, which is consistent result with those reported in previous studies (Hall et al., 2008; Kohler et al., 2003). Thus, we selected 3 female and 3 male faces that showed the highest discrimination accuracy rates in fearful emotion (Figure 6). For the faces of six persons, the accuracy rates were all 100% in happy expression, ≥ 98% in neutral, and ≥68 in fearful. For the faces of six persons, the mean of accuracy rates were 99% in happy expression, 97% in neutral, and 79% in fearful.

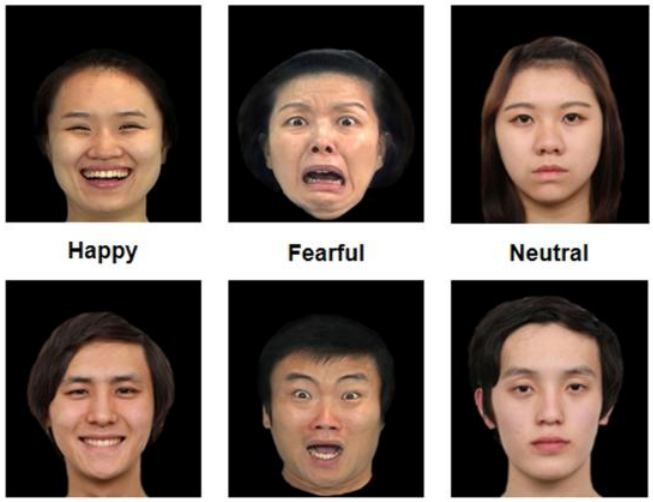

Figure 6. Examples of the face stimuli for the fMRI experiment.

Oxytocin dosage

A dose of intranasal oxytocin (40IU) was determined according to results of the pilot study that was designed to investigate an efficient dose of oxytocin nasal spray for face emotion recognition in healthy Korean males. Subjects were assigned in 32 IU (n= 19; mean age [SD] = 22.8 [3.2]) or 40 IU (n=18; mean age [SD] = 23.1 [2.3]) drug condition, and performed the emotion discrimination task 45 min after drug administration.

The emotion recognition test was used to test the effect of oxytocin. Six types of facial emotion were morphed into four intensities of 25, 50, 75, and 100%. All subjects performed the tasks 45 min after drug administration. Subjects in 40 IU condition carried out the tasks before drug treatment as well. As shown in Figure 7, Oxytocin-induced enhancement was found only in 40 IU

condition in response to happy faces (t_{17} = 3.22, p = 0.005), but not in 32 IU condition for any types of facial expression. Thus, we decided to administer 40 IU oxytocin or placebo for the fMRI experiment.

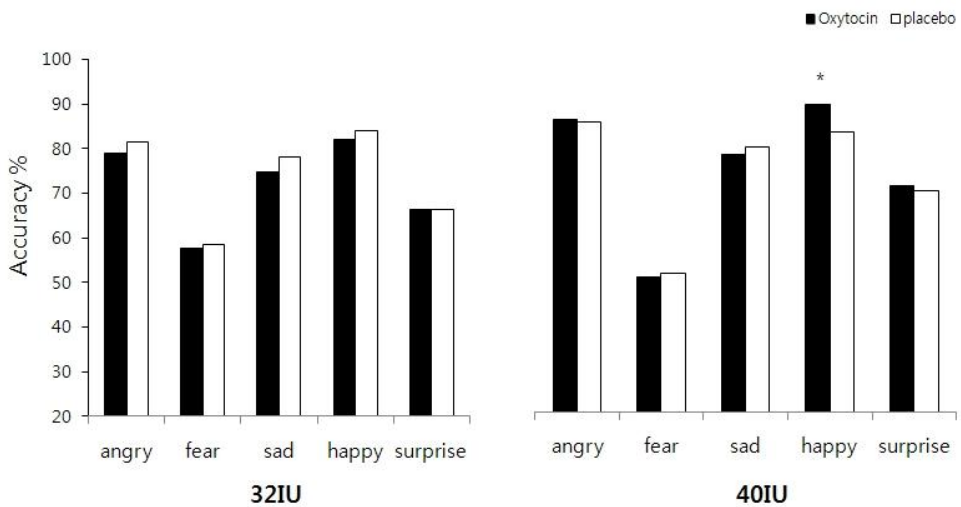

Figure 7. The performances of the emotion recognition test in 32 IU and 40 IU conditions. * Significant difference for paired t-test; p < 0.005 (two-tailed).

Behavioral questionnaires

The Korean versions of the Relationship Style Questionnaires (RSQ) (Griffin & Bartholomew, 1994) was administered to assess attachment stymeasures attachment style. The RSQ is a self-rated 5-point Likert scale that consists of 18 items and involves four attachment subscales: secure, preoccupied, dismissing, and fearful. Each item represents the feeling about close personal relationship.

Interpersonal Reactivity Index (IRI) is administered to assess

empathy (Davis, 1983; Kang et al., 2009). This is a self-administered 5-point Likert scale that measures multi-components of empathy: empathic concerns, perspective taking, fantasy, and personal distress (28 items).

Image acquisition

The blood oxygenation level-dependent (BOLD) signal was acquired using a 3T Siemens Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) using T2-weighted gradient echo planar imaging (repetition time [TR] = 2000 ms; echo time [TE] = 30 ms; field of view [FOV] = 220 mm; flip angle = 90° ; 4-mm thickness; 27 axial slices; matrix = 64 x 64). T1 anatomical volume reference images were also acquired (TR = 1670 ms; TE = 1.89 ms; FOV = 250 mm; flip angle = 9° ; 1-mm thickness; 208 slices; matrix = 256 x 256). Foam pads were used to reduce head motion. Data from one control subject were excluded from the analysis due to excessive head motion larger than 3mm during scanning. Data from the previous and present studies demonstrated maximal amygdala activation during the first session (Breiter et al., 1996; Hall et al., 2008), and, thus, the primary analysis was based on the first run. To examine the potential effect of oxytocin on amygdala habituation, an additional analysis was performed for the second run.

Image preprocessing and analysis

Images were processed and analyzed using Statistical Parametric Mapping (SPM 8) software (http://www.fil.ion.ucl.ac.uk/spm/ software /spm8/). The first three images were discarded to avoid unstable magnetic artifacts. The remaining images were spatially realigned to the first image for head-motion correction. The mean realigned functional image was normalized to the EPI template in the Montreal Neurological Institute (MNI) space and was resampled into 3-mm^3 voxels. Data were smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel. Contrast images were obtained for each emotion against baseline in each subject and entered in the second-level random-effects model for within- and between-group analysis.

In line with the hypothesis, ROI analysis was performed on the left and right amygdala regions defined as all voxels in the anatomically defined region according to the Wake Forest University (WFU) PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas). The mean percent BOLD signal change (PSC) was extracted from the ROIs based on activation for each face condition (fearful, happy, and neutral) and the baseline using the MarsBaR toolbox (http://marsbar.sourceforge.net/) (Orme-Johnson, Schneider, Son, Nidich, & Cho, 2006). The mean PCS for the fearful, happy, or neutral face contrasts versus baseline were calculated. The effect of

oxytocin on amygdala activation was tested using repeated measures analyses of variance (ANOVA) with drug (oxytocin, placebo), emotional valence (fearful, happy, neutral), and hemisphere (left, right) as within-subjects factors and group (patients, controls) as the between-subjects factor. The analyses were performed using the IBM Statistical Package for the Social Sciences version 18 (SPSS, http://www.spss.com/statistics). Post-hoc *t*-tests were performed on significant interactions to examine the effect of drug within each group ($p < 0.05$, two tailed).

In addition to the hypothesis-driven analysis, we performed a whole-brain voxel-wise analysis to assess whole-brain activity. I performed a general linear model ANOVA with drug as the within-subject factor and group as the between-subjects factor for each first-level contrast (fearful, happy, or neutral faces > baseline) to examine the (1) main effect of drug and (2) drug x group interaction. The threshold for significance was set at $p < 0.001$ (uncorrected) with a cluster extent of $k = 10$. For brain regions showing significant activity in the whole-brain analysis, ROIs were extracted from spheres with a radius of 5 mm around the peak voxel, and the mean PSC in each ROI region was calculated. Subsequent paired *t*-tests were performed in each group to test the effect of drug within the group.

Correlation analysis

Pearson correlation analysis was performed to examine relations of brain activity with clinical symptoms and psychological scales within each group. For correlation analysis, the contrasts of oxytocin > placebo for each first-level contrasts were computed to measure neural changes after oxytocin treatment compared to placebo. The threshold of significant *p* value was adjusted for multiple correlations by dividing significance level of 0.05 with the number of variables that entered in correlation analysis.

Statistical analysis for demographical and behavioral data

Independent *t*-test was performed to compare age, education level, and IQ between the two groups. A repeated measures ANOVA was used for the VAS and PANAS with 2 (positive and negative affects) or 6 mood variables (alertness, calmness, happiness, sadness, anxiety, and anger) and drug (oxytocin, placebo) as within-subject factors and with the group as between-subject factor to examine change in mood after drug administration.

RESULTS

Behavioral outcomes

There was no significant differences in age (t_{30} = 0.25, p = 0.80) and education level (t_{30} = 0.57, p = 0.57) between patients and control subjects, but a significant difference in IQ (t_{26} = 2.15, P = 0.04) (Table 2).

Table 2. Demographic and clinical characteristics in whole participants

	HC (N = 15)	SPR (N = 16)	Statistics t	df	p
Age (year)	31.3 ± 7.6	32.0 ± 7.8	0.25	30	0.83
Education years	14.4 ± 2.1	14.8 ± 1.5	0.57	30	0.57
Intelligence	113.1 ± 8.7	104.4 ± 13.4	2.15	26	0.04
Duration of illness (year)		8.7 ± 4.9			
Onset years		22.8 ± 5.8			
PANSS					
positive symptoms		12.1± 3.1			
negative symptoms		16.5 ± 5.8			
general symptoms		30.6 ± 8.2			

Data are presented as mean ± SD; HC, Healthy Controls; SPR, schizophrenia; PANSS, Positive and Negative Syndrome Scale.

I found no significant main effect of drug or group and no drug × group interaction in performance to discriminate gender of

emotional faces presented during fMRI scanning (Figure 8).

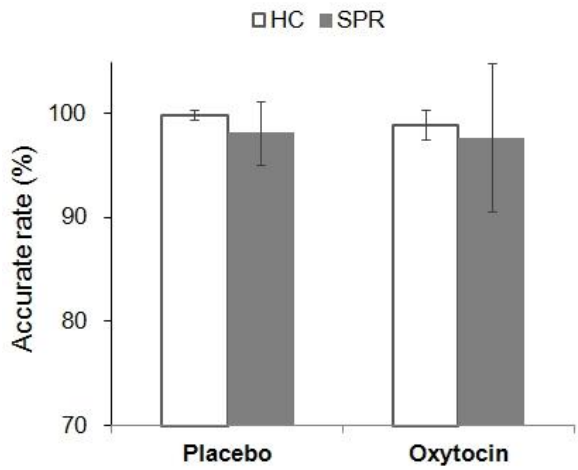

Figure 8. Behavioral performances in gender discrimination task done during the fMRI scanning. No significant drug-related effect was found. Error bars indicate standard deviation.

For mood change scores (post- minus pre-treatment) measured by the VAS and PANAS, a significant main effect of emotional valence was observed in the PANAS ($F_{1,29}$ = 5.90, p = 0.022), denoting overall reduction of negative mood following drug administration (Figure 9). Any other significant main or interaction effect was not found in the mood scales.

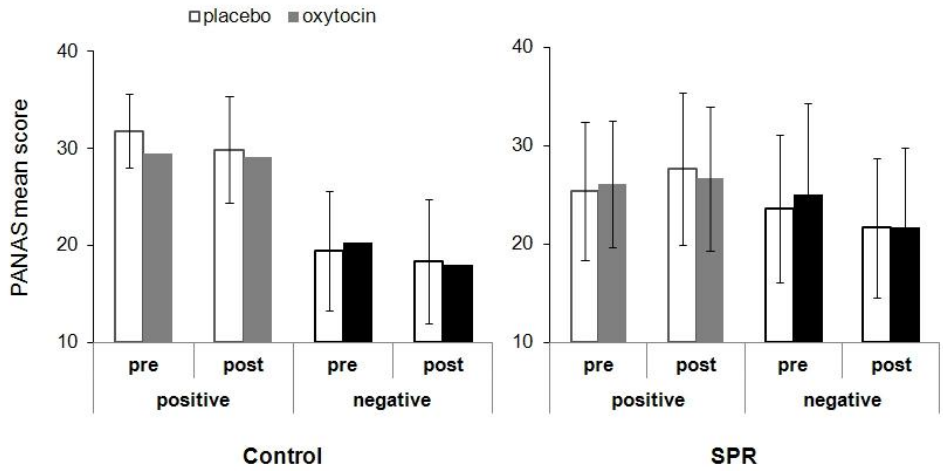

Figure 9. Positive and negative mood changes measured by the PANAS before and after drug administration in the control and patient groups. Error bars indicate standard deviation.

The analysis of attachment style revealed that secure attachment scores were significantly lower (t_{29} = 3.00, p = 0.006) and fearful attachment scores were significantly higher (t_{29} = −2.09, p = 0.045) in patients with schizophrenia compared with control subjects. Regarding empathy, patients had significantly lower scores for fantasy (t_{29} = 2.07, p = 0.048) and perspective taking (t_{29} = 2.04, p = 0.050) and higher scores for personal distress (t_{29} = −3.95, p < 0.001) than did control subjects (Table 3).

Table 3. Comparisons in attachment and empathy between the groups

	HC (N = 15)	SPR (N = 16)	Statistics *t*	*df*	*p*
RSQ					
secure	18.9 ± 2.3	15.6 ± 3.4	3.00	29	< 0.01
preoccupied	10.8 ± 1.6	11.9 ± 2.8	−1.31	29	0.20
dismissing	13.9 ± 2.4	14.3 ± 2.6	−0.42	29	0.68
fearful	8.7 ± 2.9	11.0 ± 3.2	−2.09	29	< 0.05
IRI					
empathic concern	25.5 ± 2.4	24.2 ± 3.6	1.28	27	0.21
perspective taking	26.0 ± 4.1	22.6 ± 5.0	2.04	29	0.05
fantasy	23.3 ± 2.7	20.4 ± 4.7	2.07	29	<0.05
personal distress	17.1 ± 3.5	22.4 ± 4.0	−3.95	29	<0.01

Data are presented as mean ± SD; HC, Healthy Controls; SPR, schizophrenia; RSQ, Relationship Style Questionnaires; IRI, Interpersonal Reactivity Index.

ROI analyses

To compare amygdala activity for fearful and neutral faces under placebo condition between the groups, we performed independent *t*−test. It was found a marginally significant hyperactivity for neutral faces in right amygdala in patients, compared to control subjects (t_{29} = −1.74, p = 0.092, Cohen' s d = 0.63). No significant group difference was found in amygdala activities on response to fearful faces under placebo condition (Figure 10).

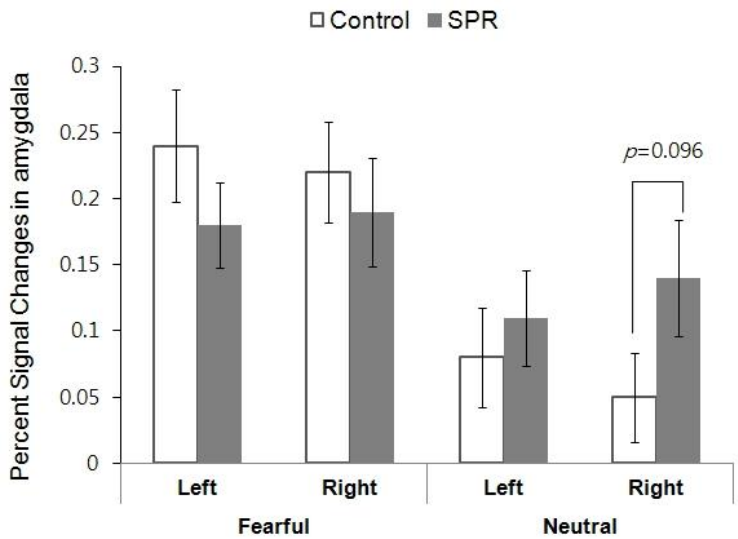

Figure 10. Group comparison between the control and patient groups for amygdala activities following placebo administration. Error bars indicate standard error of mean.

Descriptive data of PSC for each emotion in each group was presented in Table 4 and Figure 11. A 2 (drug) x 3 (emotional valence) x 2 (hemisphere) x 2 (group) ANOVA yielded a significant main effect of emotional valence ($F_{2,58}$ = 4.98, p = 0.010), denoting less reactivity to neutral relative to emotional faces. No main effect of drug, group, or hemisphere in amygdala activities was found (Table 5). However, the drug × group interaction was significant ($F_{1,29}$ = 7.61, p = 0.010), indicating differential effects of oxytocin in the patient and control groups. Post-hoc analysis was based on the contrasts of oxytocin > placebo to compute oxytocin-induced signal change, averaged PSCs across emotional valences extracted from bilateral amygdala. Independent t-test revealed significant

group differences (t_{29} = 2.76 p = 0.010), indicating that the patient group showed attenuated activation after oxytocin treatment, whereas the control group exhibited increased activation (Figure 12). In order to further explore the effect of oxytocin on specific emotion, additional paired t-test was performed within each group. The analysis revealed that oxytocin attenuated bilateral amygdala activity in response to the fearful faces (left amygdala: t_{15} = −2.53, p = 0.023; right amygdala: t_{15} = −2.28, p = 0.037; Figure 13a) and right amygdala activity in response to neutral faces (t_{15} = −1.78, p = 0.096) in the schizophrenia group. In the control group, oxytocin increased bilateral amygdala activity in response to the happy faces only (left amygdala: t_{14} = 2.45, p = 0.028; right amygdala: t_{14} = 2.61, p = 0.02; Figure 13b)

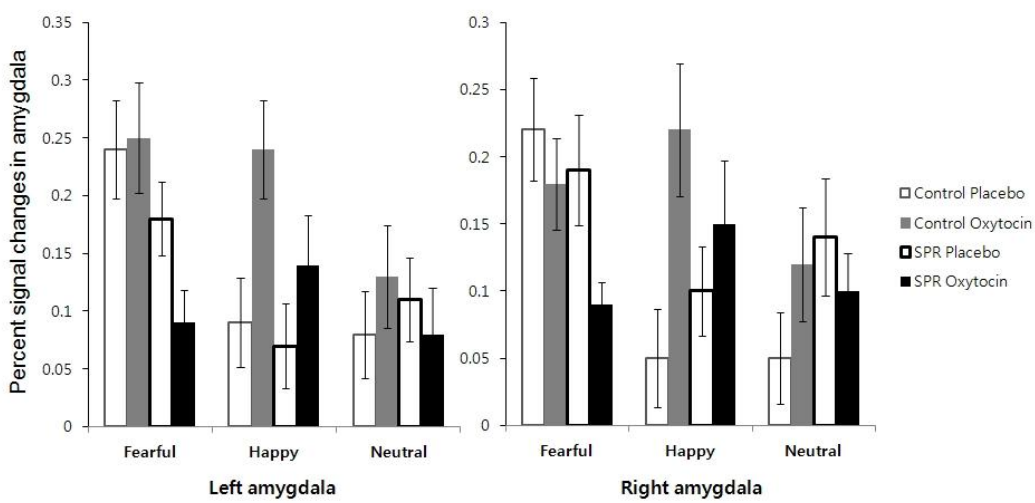

Figure 11. Percent signal changes extracted from left and right amygdala ROIs in response to fearful, happy, and neutral faces in each group during

placebo and oxytocin sessions. Error bars indicate standard error of mean.

Table 4. Within- and between-group comparisons of percent BOLD signal changes for amygdala ROIs on response to emotional faces

	Control (N=15)		Paired t-test		SPR (N=16)		Paired t-test	
	Placebo	Oxytocin	*t(14)*	*p*	Placebo	Oxytocin	*t(15)*	*p*
Left								
Fearful	0.24 (0.17)	0.25 (0.19)	0.21	0.839	0.18 (0.13)	0.09 (0.11)	−2.53	0.023**
Happy	0.09 (0.15)	0.24 (0.14)	2.45	0.028**	0.07 (0.15)	0.14 (0.17)	1.43	0.173
Neutral	0.08 (0.15)	0.13 (0.17)	0.98	0.343	0.11 (0.14)	0.08 (0.16)	−0.87	0.398
Right								
Fearful	0.22 (0.15)	0.18 (0.13)	−0.63	0.538	0.19 (0.16)	0.09 (0.07)	−2.28	0.037**
Happy	0.05 (.014)	0.22 (0.19)	2.61	0.020**	0.10 (0.13)	0.15 (0.19)	1.18	0.256
Neutral	0.05 (0.13)	0.12 (0.16)	1.67	0.118	0.14 (0.17)	0.10 (0.11)	−1.78	0.096*

Data represents mean (SD). ** $p < 0.05$, two-tailed; * $p < 0.05$, one-tailed

Table 5. Results from repeated measures ANOVA entered drug (oxytocin, placebo), emotion (fearful, happy, neutral), hemisphere (left, right) as within-subjects factors and group (control and patient) between-subject factor

	F	*df*	*p*
Drug	1.47	1, 29	0.235
Emotion	4.98	1, 28	0.010**
Hemisphere	0.45	1, 29	0.506
Group	1.84	1, 29	0.180
Emotion x Group	1.76	2, 28	0.181
Hemisphere x Group	4.58	1, 29	0.041*
Drug x Group	7.61	1, 29	0.010**
Drug x Emotion	6.64	2, 28	0.03*
Drug x Emotion x Group	0.04	2, 28	0.965

** p<0.01 (two-tailed)

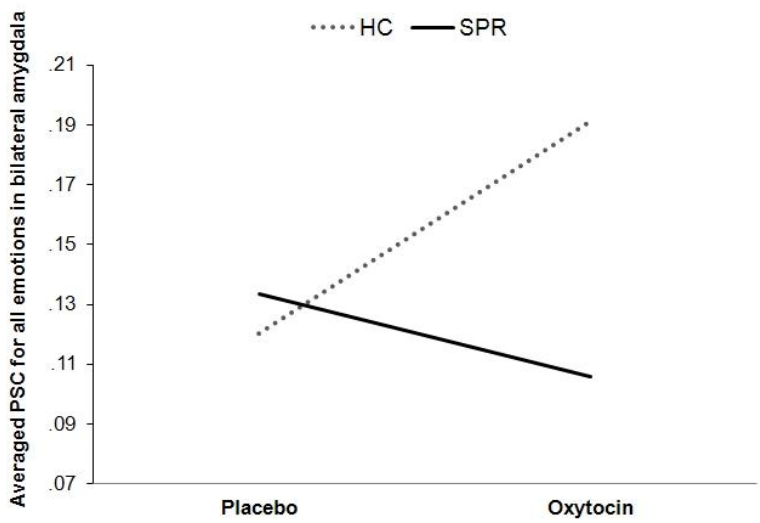

Figure 12. Interaction between drug and group for averaged percent signal changes across emotional valences extracted from bilateral amygdala

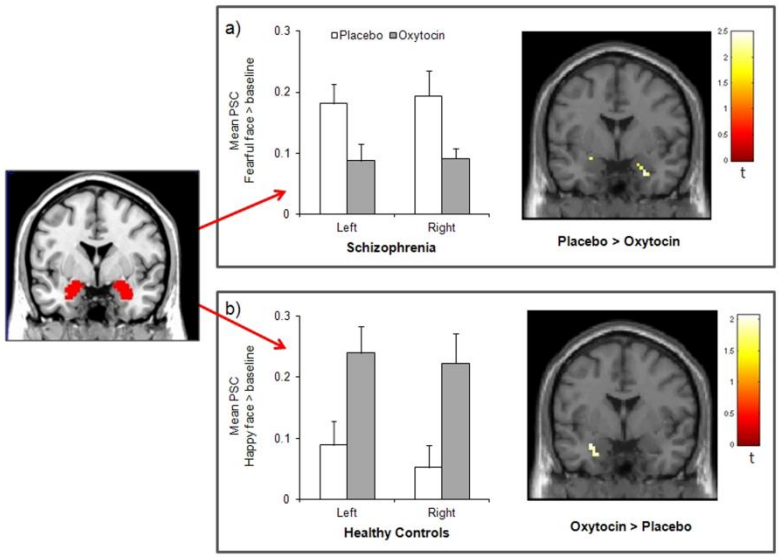

Figure 13. The effects of oxytocin on bilateral amygdala activity. a) oxytocin-induced decrease of activation in response to fearful faces in schizophrenia. b) oxytocin-induced increase of activation in response to happy faces in healthy controls. Threshold for t-maps was $p < 0.05$ (uncorrected) for illustration purposes. Error bars indicate standard error of mean.

I also found a significant drug x emotional valence interaction ($F_{2,58} = 6.64$, $p = 0.003$). For the post-hoc analysis, the contrasts of oxytocin > placebo were computed in a total sample, and were compared for different emotional valences (fearful vs. happy, fearful vs. neutral, happy vs. neutral), using paired t-test. When applying a Bonferroni-correction ($p = 0.017$), the comparisons between fearful and happy faces were significant ($t_{30} = -3.72$ $p = 0.001$), indicating attenuated activation in response to the fearful faces and increased activation in response to the happy faces (Figure 14).

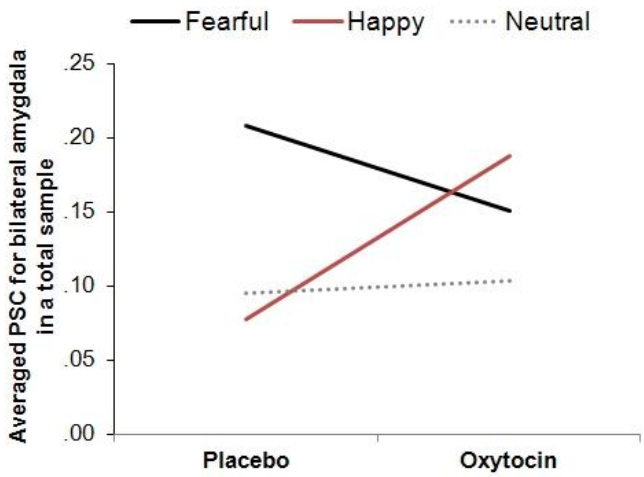

Figure 14. Interaction between drug and emotional valences for averaged percent signal changes extracted from bilateral amygdala in a total sample

There was a significant hemisphere x group interaction ($F_{1,29}$ = 4.58, p = 0.041). The post-hoc independent t-test showed significantly more activation in left amygdala in control than in patient groups (t_{29} = 2.10 p = 0.049), but no significant difference in right amygdala activation between the groups (t_{29} = 0.42 p = 0.676) (Figure 15). Any other interaction involving drug was not significant.

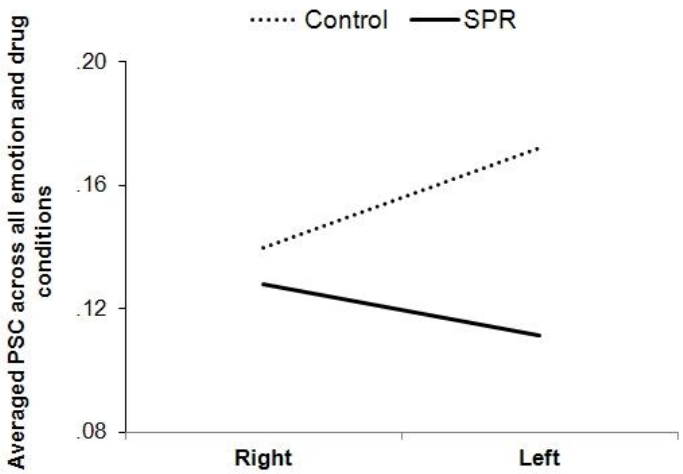

Figure 15. Interaction between group and hemisphere. Averaged percent signal changes across all emotional valences and drug conditions were computed for left and right amygdala in controls and patients

Whole-brain analysis

No significant main effect of drug was found for fearful faces. However, a significant drug × group interaction was found in left inferior temporal cortex (ITC, x, y, z; −39, −40, −8) and right middle temporal cortex (MTC, x, y, z; 57, 5, −26; Table 6 and Figure 16a) for fearful faces. A significant interaction for amygdala activation was detected when a lower threshold was applied (p < 0.005, uncorrected). Subsequent within-group paired t-tests for ROIs in the left ITC and right MTC showed decreased activation in both regions in patients with schizophrenia (left ITC: t_{15} = −2.20, p = 0.044; right MTC: t_{15} = −4.22, p = 0.001), whereas activity was increased in control subjects (left ITC: t_{14} = 3.38, p = 0.005; right

MTC: t_{14} = 1.77, p = 0.099).

For happy faces, we found a significant main effect of drug in the right superior frontal cortex (SFC), right temporal pole (TP), and left MTC (Table 6 and Figure 16b). Post hoc paired t-tests revealed that oxytocin significantly increased right TP (t_{30} = 3.88, p = 0.001) and left MTC (t_{30} = 3.25, p = 0.003) activity, whereas activity in the right SFC was decreased (t_{30} = −2.04, p = 0.050). The drug × group interaction for happy faces was not significant.

For neutral faces, no significant main or drug-related interaction effect was found.

Table 6. Whole-brain voxel-wise ANOVA for main effect of drug and drug-related interaction for emotional faces

		Coordinates			cluster k	F
		x	y	z		
Fearful > baseline						
Drug x Group						
Inferior temporal cortex	L	−39	−40	−8	11	21.24
Middle temporal cortex	R	57	5	−26	17	17.52
Happy > Baseline						
Drug						
Superior frontal cortex	R	21	29	43	13	19.41
Middle temporal cortex	L	45	5	−29	13	18.25
Left temporal cortex	R	−51	−25	−11	16	17.33

Abbreviations: L, left; R, right. All results were at $p < 0.001$ uncorrected with a cluster extent of k ≥ 10.

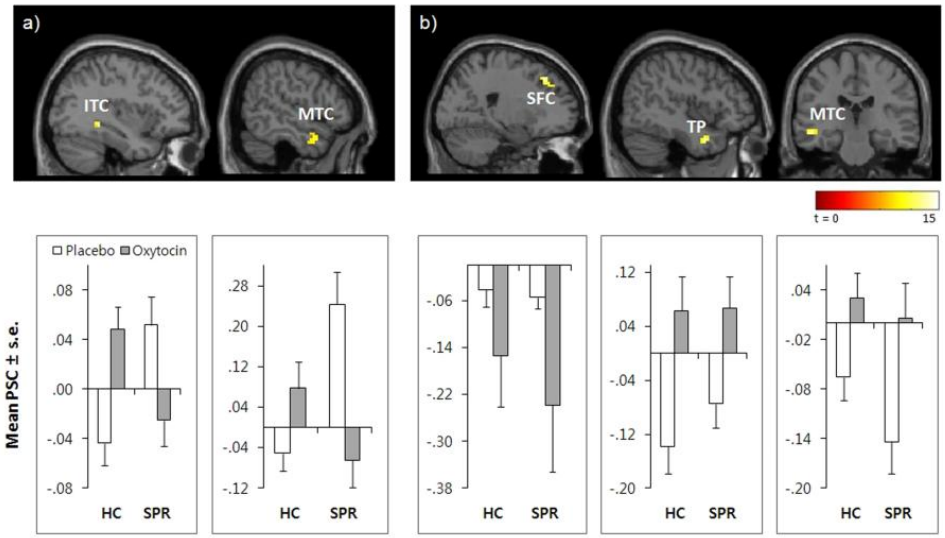

Figure 16. Statistical parametric map of whole brain analysis ($p < 0.001$ uncorrected). a) An interaction effect of drug x group in response to fearful faces. b) A main effect of drug in response to happy faces. Coordinates are reported in the Montreal Neurological Institute Space.

Correlations between amygdala activity and behavioral outcomes following oxytocin treatment

The Pearson correlation analysis revealed a significant negative correlation between the oxytocin$_{(happy-baseline)}$ > placebo$_{(happy-baseline)}$ contrast in the right amygdala and the RSQ preoccupied attachment score in control subjects ($r = -0.733$, $p = 0.002$; Figure 17). I did not find a significant correlation between oxytocin-related effects and symptom severity in the patients.

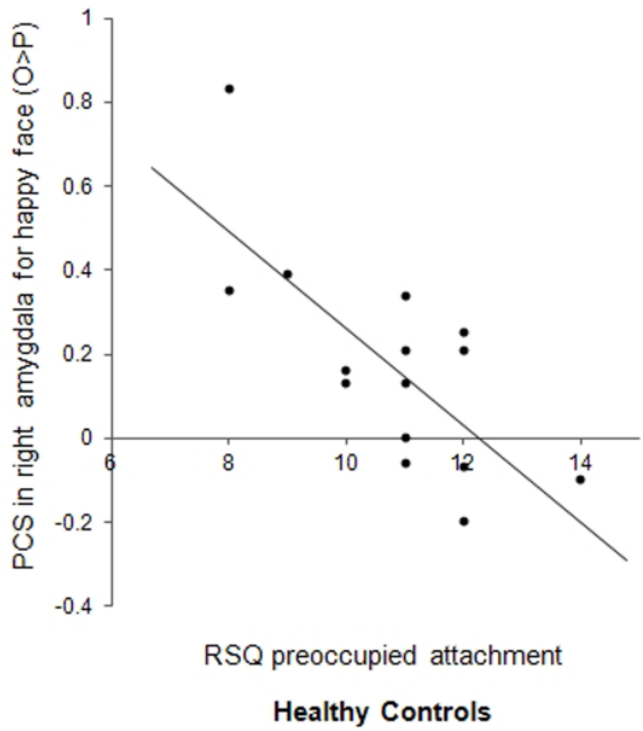

Figure 17. Significant correlations of oxytocin-induced effect in right amygdala with attachment style in healthy controls. O>P, the contrast for oxytocin - placebo

The effect of oxytocin on amygdala habituation

Data from one patient were excluded from the analysis due to head motion larger than 3 mm during the second run scanning. To examine an effect of oxytocin on amygdala habituation, a repeated measures ANOVA was conducted by entering run (run 1, run 2), drug (oxytocin, placebo), emotional valence (fearful, happy, neutral) and hemisphere (left, right) as within-subjects factors, and group as between subjects factor. The analysis showed a significant main

effect of run ($F_{1,28}$ = 11.26, p = 0.002), denoting overall less activation in run 2 compared to run 1. Any interactions between run and drug were not significant. I found a significant drug x group interaction ($F_{1,28}$ = 14.86, p = 0.001), a marginally significant main effect of drug ($F_{1,28}$ = 3.10, p = 0.089), and a marginally significant interactions of drug x emotion ($F_{1,28}$ = 2.63, p = 0.091) and hemisphere x group ($F_{1,28}$ = 3.58, p = 0.069). Any other main or interaction effects were not significant.

When the analysis was performed only for the second session, all main and interaction effects were insignificant except interaction between drug and group ($F_{1,28}$ = 6.15, p = 0.019).

DISCUSSION

To my knowledge, the present study is the first to investigate the effect of intranasal oxytocin on brain activity related to facial emotion recognition in patients with schizophrenia. In the present data, oxytocin inhalation exerted differential effects on amygdala activity across the groups and emotional valences. Intranasal oxytocin decreased bilateral amygdala activity in response to fearful faces and induced a slight reduction of right amygdala activity in response to neutral faces in patients with schizophrenia. These effects were not shown in healthy control subjects. For controls, intranasal administration of oxytocin increased bilateral amygdala activity in response to happy faces, an effect not seen in patients with schizophrenia. Data from this study suggests that oxytocin has a modulatory effect on amygdala activation for negative and ambiguous emotions in patients with schizophrenia, whereas oxytocin mediates the amygdala response to positive emotion in healthy Korean individuals.

The effect of oxytocin on amygdala activation in patients with schizophrenia

The inability to recognize facial emotion is a core deficit in schizophrenia. Previous neuroimaging studies have shown that

patients with schizophrenia demonstrated amygdala hyperactivity in response to fearful and/or neutral faces (Hall et al., 2008; Holt et al., 2006). In this study, it was found that right amygdala activity for neutral faces was slightly higher in patients with schizophrenia than in healthy controls, while activation level in response to fearful faces in the patient group did not differ from the control group. These results are similar with a prior study using a similar fMRI task (Hall et al., 2008). The current result indicated that amygdala activation for neutral emotion may be slightly increased even under placebo treatment in patients with schizophrenia.

The present study indicated differential effects of oxytocin on schizophrenia patients and mentally healthy subjects, and on emotional valences. A close investigation revealed that oxytocin attenuated amygdala activity in patients with schizophrenia as they viewed fearful and neutral faces, whereas neuropeptide increased amygdala activation in healthy subjects as they viewed happy faces. Previous studies have suggested that effects of intranasal oxytocin on emotion recognition may be differential in different groups of subjects (Domes et al. 2007, 2009(Bartz et al., 2010a) and across emotional valences within a specific amygdala subregion (Gamer et al., 2010). Additionally, evidence has implicated that individual or contextual differences may influence the effects of oxytocin on social cognitive function (Bartz et al., 2011).

Recent evidence has shown beneficial effects of intranasal oxytocin on various social behaviors in patients with schizophrenia. Intranasal oxytocin improves emotion recognition (Fischer-Shofty et al., 2010), social perception (Fischer-Shofty et al., 2013) and mentalizing ability (Pedersen et al., 2011), in those with schizophrenia. No studies have investigated the neural response to oxytocin in patients with schizophrenia. In the current study, oxytocin induced attenuation of amygdala responses in patients with schizophrenia, and this effect was specific to negative and ambiguous emotion. The present result is consistent with findings from a recent behavioral study showing oxytocin-related beneficial effect on fearful expression but not on happy faces in patients with schizophrenia (Fischer-Shofty et al., 2010). Researchers have proposed that reduction of social anxiety and silence following oxytocin administration are likely to underlie amygdala attenuation for fear (Bartz et al., 2010a). In the line with this, one of plausible explanation for the present results could be that inhaled oxytocin may reduce social anxiety and sensitivity to negative and ambiguous social information in patients with schizophrenia. Intranasal oxytocin might selectively response to social emotion that can be interpreted negatively in the schizophrenic group. Given a limited effect of current antipsychotic medications on the impaired ability to perceive facial emotion in patients with schizophrenia (Herbener, Hill, Marvin,

& Sweeney, 2005; Penn et al., 2009), oxytocin nasal spray may be beneficial to alter dysfunctional emotional processing in those with this deficit.

The effect of oxytocin on amygdala activation in healthy controls

Previous studies of emotion-related changes by oxytocin in amygdala activity have reported conflicting results in healthy individuals. I found that oxytocin administration increased bilateral amygdala activity in response to happy, but not fearful, faces in healthy controls. Several studies have reported an oxytocin-induced reduction in amygdala activity in response to fearful emotion in male subjects, and a single study observed an oxytocin-induced increase in amygdala activity in response to fearful emotion in female participants (Domes et al., 2009). Furthermore, one previous study observed an increase (Caldwell et al., 2008) and another found a decrease (Domes et al., 2007a) in amygdala activity in response to happy emotion. These disparate findings may be attributable to an influence of context or to individual differences on the relationship between oxytocin and social cognition, as proposed by Bartz et al.(2011). The effect of oxytocin has been reported to be restricted to individuals with specific traits (Bartz et al., 2010b; Singer et al., 2008) and moderated by task-related properties such

as difficulties (Bartz et al., 2010b; Domes et al., 2007b). Indeed, the oxytocin-induced increase in amygdala activity in response to happy faces in the healthy controls in the present study was strongly associated with attachment style. This finding agrees with previous observations involving the influence of parental-love withdrawal (Huffmeijer, Alink, Tops, Bakermans-Kranenburg, & van IJzendoorn, 2012a) and anxious attachment (Bartz et al., 2010a) on the oxytocin effect. Further, the influence of cultural factors on the results cannot be ruled out. Distinct differences in the recognition of facial expressions (Matsumoto, 1992) and the role of oxytocin receptor genes in emotional processing (Kim et al., 2011) have been reported in Asian and Western subjects. Future studies are needed to clarify the impact of cultural differences on the oxytocin nasal spray-induced effect on social cognition.

Whole brain analysis results

The whole-brain analysis revealed that in patients, oxytocin decreased activity in the ITC and MTC areas in response to fearful faces, whereas ITC and MCT activity was increased in the control subjects. Moreover, oxytocin increased TP and MTC activity in response to happy faces in both patients and control subjects. Previous studies have found oxytocin-related effects in the temporal areas involved in emotion recognition in male (Domes et

al., 2007a; Petrovic et al., 2008) and female (Domes et al., 2009) subjects. The current results and those of previous studies support evidence indicating that these brain areas are involved in face processing (Tsao & Livingstone, 2008).

Other results related to amygdala responses

In this study, patients with schizophrenia exhibited lower activation in left amygdala than control subjects. Hypoactivation in left amygdala for emotional faces has been found in a prior study using a similar task (Hall et al., 2008) and in young offsprings at risk for schizophrenia (Keshavan et al., 2002). Amygdala asymmetry in patients with schizophrenia has been supported by some evidence showing specific increase of dopamine concentration in left amygdala in patients with schizophrenia (Reynolds, 1983).

Consistently with previous observations (Breiter et al., 1996; Hall et al., 2008; Salgado-Pineda, Fakra, Delaveau, Hariri, & Blin, 2010), amygdala response to emotional faces was habituated over time regardless of the groups in the present study. While the differential effects across emotional valences following oxytocin administration were habituated over time, the differential effects of oxytocin across the groups were apparent even in the second run. This suggests that difference in response to oxytocin in amygdala region between patients and control subjects may be robust enough

to resist habituation.

Limitation of the study

This study has some limitations. First, the whole-brain analysis revealed a relatively weak effect of oxytocin on amygdala activity, possibly because of insufficient power to detect an effect in a two-way ANOVA with small sample size. Second, recognition accuracy for some of the fearful face stimuli was low, which may not have evoked as strong a neural response as easily identified ones. Third, we enrolled only male participants to exclude an interaction between exogenous (nasal spray) and endogenous oxytocin. Further studies are needed to assess the effect of oxytocin on emotion recognition in female patients with schizophrenia. Firth, oxytocin dose was determined on a basis of the findings from the pilot study in healthy Korean males. An effective dose of oxytocin on emotion recognition might be different in psychiatric states. Finally, all patients were taking psychotropic drugs at the time of the experiment; thus, we cannot exclude an interaction between the psychotropic drugs and intranasal oxytocin.

Conclusions

This study showed that oxytocin reduced amygdala activity in response to fearful and neutral faces in patients with schizophrenia,

whereas oxytocin increased amygdala activity in response to happy faces in healthy control subjects. The present data, together with previous findings showing a beneficial effect of intranasal oxytocin for psychiatric disorders such as autism and social anxiety, provide new evidence supporting the therapeutic potential of oxytocin for patients with schizophrenia. The slight changes in amygdala activity observed in the whole-brain analysis following administration of oxytocin treatment suggest that a single-dose of oxytocin may cause a subtle change in brain activity of stabilized schizophrenia patients who have taken psychotropic medications. However, even a small change in brain activity can alter the behavioral outcomes. Future studies are needed to investigate the effect of daily administration of intranasal oxytocin on neural activity and to compare the effectiveness of different doses in patients with schizophrenia.

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국문초록

연구배경: 조현병 환자들이 정서를 지각할 때 보이는 뇌활성화 패턴은 정상인과는 다른 것으로 알려져 있다. 가장 최근의 증거들은 조현병 환자들이 공포스런 얼굴이나 무표정한 얼굴을 지각할 때 편도체 영역이 과활성화 되는 것으로 보고하였다. 아울러 최근에 발표된 연구들에 따르면 비강내로 처치한 옥시토신이 건강한 남성과 조현병 환자 모두에 대해 정서 지각에 긍정적인 효과를 보이는 것으로 나타났다. 지금까지 조현병 환자들을 대상으로 정서지각에 있어 옥시토신이 뇌기능에 미치는 영향을 탐색한 연구는 없었다. 본 연구는 조현병 환자들과 정상 대조군을 대상으로 옥시토신이나 위약을 비강내로 처치한 후 정서를 지각하는 동안 뇌활성화 패턴이 어떻게 변하는지를 비교 분석하고자 한다.

연구방법: 16명의 조현병 남성 환자들과 환자와 연령을 맞춘 16명의 정상대조군 남성에게 1주일 간격으로 40IU의 옥시토신과 위약을 한차례 투여한 후 공포스런 얼굴과 행복한 얼굴, 무표정한 얼굴을 지각하는 동안 뇌 활성화 패턴을 자기공명 영상 기법을 활용해 조사하였다.

연구결과: 조현병 환자들은 공포스런 얼굴과 무표정한 얼굴을 볼 때 옥시토신 조건에서 양쪽 편도체 영역의 활성화 정도가 감소되는 것으로 나타났다. 정상인의 경우, 행복한 얼굴을 볼 때 옥시토신 조건에서 편도체 영역의 활성화 정도가 유의미하게 증가하는 것으로 나타났다.

정상인에 대한 옥시토신의 이러한 효과는 애착 스타일과 유의미한 상관을 보였다.

결론: 본 연구는 비강내로 처치하는 옥시토신이 조현병 환자들의 편도체의 과활성화 수준을 감소시켜 줄 수 있음을 시사한다. 옥시토신은 부정적인 정서나 애매한 정서가 주는 불안감과 현저함을 감소시키는 역할을 하는 것으로 보인다. 본 연구 결과는 조현병 환자들에게 있어서 옥시토신이 갖는 치료적 가능성을 시사하는 새로운 증거로 볼 수 있다.

주요어: 옥시토신, 조현병, 비강내 처치, 정서, 기능적 자기공명영상

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