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Oxytocin does not improve performance of patients with schizophrenia and healthy volunteers in a facial emotion matching task

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ABSTRACT

The neuropeptide oxytocin improves the performance in facial emotion recognition tests in healthy volunteers and in individuals with schizophrenia. Different paradigms are used in emotion recognition tasks, engaging different neurobiological bases. To date, the effects of oxytocin in facial emotion matching tasks have not been studied. The objective of this study was to evaluate the effects of intranasal oxytocin in a facial emotion matching task in patients with schizophrenia and healthy volunteers. Twenty patients and 20 healthy volunteers received 48 IU intranasal oxytocin and placebo in a double-blind, randomized, placebo-controlled, within subjects design. Fifty minutes after treatment, subjects completed a facial emotion matching task and three control tests. Oxytocin failed to improve facial affect processing, in contrast with previous results. Possible explanations are the fact that we used a facial emotion matching paradigm instead of emotion labeling tasks and a higher dose of oxytocin than the one used in most similar studies.

1. Introduction

The neuropeptide oxytocin plays an important role in the modulation of social behavior in mammals and it is particularly associated with affiliative behavior and pro-social effects. Studies in animals show that oxytocin promotes maternal and sexual behavior, regulates social memory and moderates stress responses and anxiety (Insel, 2010). In humans, oxytocin has been associated with facilitation of social contact in several ways, acting in parental and couple bonds, increasing trust and generosity in tasks simulating financial investments (Kosfeld et al., 2005; Baumgartner et al., 2008), and reducing anxiety in models of elicited social anxiety (de Oliveira et al., 2012). In facial emotion recognition tasks, oxytocin also acts as a pro-social agent by improving emotion recognition in healthy volunteers (Domes et al., 2007; Fischer-Shofty et al., 2010; Marsh et al., 2010), which may be a result of its capacity to increase gaze towards the eye region of human faces (Guastella et al., 2008).

The discovery of oxytocin's pro-social effects made this peptide of particular interest in neuropsychiatric disorders in which social dysfunction is an important characteristic, such as schizophrenia and autism. In this regard, it has been shown that oxytocin improves emotion recognition in individuals with autism spectrum disorders (Guastella et al., 2010), that higher plasma levels of oxytocin are associated with lower symptom severity in patients with schizophrenia (Goldman et al., 2008), and that the intranasal administration of the peptide for 2 weeks reduces psychotic symptoms (Feifel et al., 2010; Pedersen et al., 2011). In addition, two studies showed improvement in facial emotion recognition by patients with schizophrenia after a single dose of intranasal oxytocin (Goldman et al., 2011; Averbeck et al., 2011), a noteworthy result, since impaired facial emotion recognition is widely described in schizophrenia and is related to social dysfunction (Edwards et al., 2002). Facial emotion recognition studies use many different tasks; one of the main differences among them lies in the use of emotion labeling tests. In affect labeling studies, emotional faces are presented together with options of words describing emotions and subjects have to make a forced choice among them. Emotion matching tasks, however, consist of an exclusively non-verbal approach to the study of facial emotion processing, since subjects are asked to pair faces expressing similar emotions without labeling them. To date, oxytocin has not been tested in emotion matching tasks in patients with schizophrenia. The aim of this study, therefore, was to investigate the effects of oxytocin in patients with schizophrenia and healthy volunteers during a facial emotion matching task. Based on evidence from earlier studies using different paradigms to investigate facial affect processing, we hypothesized that intranasal

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oxytocin would improve performance in a facial emotion matching task compared to placebo in subjects with schizophrenia and healthy volunteers.

2. Methods

2.1. Subjects

Twenty male patients with schizophrenia and 20 male healthy volunteers with similar age (patients [mean ± S.D.]: 29.6 ± 6.83; controls [mean ± S.D.]: 29.7 ± 9.29) and years of education (patients [mean ± S.D.]: 11.55 ± 1.27; controls [mean ± S.D.]: 11.55 ± 1.70) were recruited for the study. All patients were in treatment in an outpatient clinic at the University Hospital of Ribeirão Preto Medical School – University of São Paulo. The healthy volunteers were recruited through advertisement at the university campus. All schizophrenia patients were in treatment with one or more antipsychotic medications (olanzapine [$n=8$], clozapine [$n=8$], aripiprazole [$n=3$], haloperidol [$n=1$], risperidone [$n=1$], pipotiazine [$n=1$], and chlorpromazine [$n=1$]). The mean dose of antipsychotics in chlorpromazine equivalents was 445 mg. Among the patients with schizophrenia, six were using antidepressants (clomipramine [$n=1$], fluoxetine [$n=3$], sertraline [$n=1$] and citalopram [$n=1$]). All participants went through an initial screening visit to determine their eligibility to participate. The diagnosis of schizophrenia was made with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM IV – SCID) (First et al., 1997), translated and validated to Brazilian Portuguese (Del Ben et al., 2001). The exclusion criteria for patients were substance abuse or dependence (other than nicotine), significant medical disorder, score of 2 or less in items relative to psychotic symptoms and disorganization (suspiciousness, hallucinations, unusual thought content and bizarre behavior) disorder of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962, adapted by Bech et al. (1986)). The following exclusion criteria were applied to healthy volunteers: history of DSM-IV Axis I psychiatric diagnosis (assessed with the SCID), significant medical disorder, and current use of medication. Participants were instructed to abstain from alcohol the day before the experiment and from eating, drinking (except water) and smoking for two hours before drug administration. All participants were male due to the risk of uterine contractions induced by oxytocin. The study was approved by the ethics committee of the Ribeirão Preto Medical School University Hospital, where the study was conducted (approval number: 1632/2009). A detailed description of the study was given to all participants, who signed an informed consent to participate before the experiment.

2.2. Facial emotion and control tasks

The facial emotion-matching task featured five basic emotions (happiness, sadness, fear, anger and disgust) and neutral faces with photographs from the series of Ekman and Friesen (1978). Half of the target faces were male and half were female. During the task, three pictures of faces were presented on a computer screen and subjects were asked to choose between the two faces at the bottom, the one that expressed the same emotion as the target face presented at the top of the screen. The faces could be neutral or display emotions at different intensities, expressing 25%, 50%, 75% and 100% of the emotion. Each emotional intensity was used in 25% of the stimuli in order to make the task not too easy or too difficult.

There were three control tasks that followed the same design, but instead of emotional faces subjects had to match face identities, colors and shapes. In the identity-matching task, three pictures of faces were presented on the screen, one at the top and two at the bottom. The subjects had to choose the face at the bottom with the same identity as the face on the top of the screen. In the matching of shapes, three geometric figures were presented and the task was to choose the shape at the bottom with the same geometric format (e.g. triangle) as the figure at the top. Finally, in the color-matching color task the same geometric figures were presented, but participants were instructed to select the figure with the same color as the target stimulus.

There were a total of 100 stimuli in the emotion- and identity-matching tasks and 20 stimuli in the shape- and color-matching tasks. Among the 100 facial stimuli, 20 displayed neutral faces and 16 displayed each of the five emotions studied. The same stimuli were used in the two sessions, in different orders of presentation.

2.3. Procedures

All participants received 48 IU intranasal oxytocin (Synthocinon® – Novartis) and placebo (Synthocinon® vehicle – Novartis) through six puffs per nostril in two sessions, within a time interval of 15 days between sessions. The dose was defined based on the study by Feifel et al. (2010), who reported improvements in the psychopathology scores of schizophrenia patients after oxytocin treatment. Subjects were randomly assigned to the sequence of oxytocin and placebo sessions. Both subjects and researchers were blind to the treatment condition during the entire procedure.

Fifty minutes after the administration of the drug, subjects performed the emotion matching and control tests (identities, colors and shapes). For the assessment of psychiatric symptoms in patients with schizophrenia during the experimental session, two psychopathology scales were applied: the Negative Scale of Positive and Negative Syndrome Scale (PANSS-negative) (Kay et al., 1987) and the BPRS. A trained psychiatrist filled the scales immediately before the drug administration and 40 and 90 min later.

2.4. Statistical analyses

The effect of treatment was examined using a multifactorial, four-way analysis of variance (ANOVA) with independent groups (patients, controls) and repeated measures for emotions (neutral, disgust, fear, happiness, sadness, anger), drug (oxytocin, placebo), and session order (first, second). Bonferroni's post-hoc was used when significant differences were found.

Similar analyses were used to assess the effects of those same factors on the control tasks and BPRS and PANSS scores. The results of the identity-matching task were analyzed using a four-way, repeated measures ANOVA with task (identity matching, emotion matching), group (patients, controls), drug (oxytocin, placebo), and session order (first, second) as factors. The analysis of the color- and shape-matching tasks was made in the same way, changing the task factor (color, shape).

For the BPRS and PANSS scores, group (patients, controls) was not included as a factor as the scales were only completed for patients. Demographic variables (age and years of education) were analyzed with a *t*-test. We used version 17 of the Statistical Package for the Social Sciences (SPSS) for all the statistical analyses and adopted a significance level of $p < 0.05$.

3. Results

3.1. Socio-demographic data

There were no significant differences between the groups of patients and healthy volunteers in terms of age ($t_{38} = -0{,}39$; $p=0.969$) and years of education, ($t_{38}=0$; $p=1$). All patients were on stable doses of antipsychotics and no side effects were reported (Tables 1 and 2).

3.2. Performance in the facial emotion-matching task and control tasks

For the emotion-matching task, we found a main effect of diagnosis ($F_{1,36}=5.76$; $p=0.022$) showing that patients with schizophrenia performed worse than healthy volunteers. There was also a main effect of emotion ($F_{5,180}=57.54$; $p<0.001$) due to a difference in how accurately emotions were matched. Both groups were more accurate when neutral faces were used as target stimuli ($p<0.001$) and made more mistakes when matching faces expressed sadness and anger ($p<0.001$).

We found no significant main effects of drug ($F_{1,36}=0.685$; $p=0.413$) or session order ($F_{1,3.72}=0.71$; $p=0.792$) and no significant effects of emotion × drug ($F_{5,180}=1.376$; $p=0.235$), emotion × group ($F_{5,180}=0.559$; $p=0.73$), emotion × session ($F_{5,180}=0.22$; $p=0.95$), and emotion × group × drug ($F_{5,180}=1.05$; $p=0.39$) interactions.

Table 1
Descriptive data for patients with schizophrenia and healthy controls.

Variable	Patients Mean (S.D.)		Healthy volunteers Mean (S.D.)
Age	29.60 (6.83)		29.7 (9.29)
Years of education	11.55 (1.70)		11.55 (1.27)
Years of illness	8.90 (7.74)		
Number of hospitalizations	1.90 (2.34)		
	Oxytocin[a]	Placebo[a]	
BPRS	6.92 (6.58)	7.72 (7.07)	
PANSS negative	22.75 (5.29)	23.45 (6.26)	

S.D.: standard deviation.

[a] Mean basal values for oxytocin and placebo sessions.