Schizophrenia Research 162 (2015) 47–51

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia

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ARTICLE INFO

Article history:
Received 2 October 2014
Received in revised form 19 January 2015
Accepted 21 January 2015
Available online 9 February 2015

Keywords:
Oxytocin
Social cognition
Psychosis
Interpersonal

ABSTRACT

Lower endogenous levels of the neuropeptide oxytocin may be an important biological predictor of social cognition impairments in schizophrenia (SZ). Prior studies have demonstrated that lower-level social cognitive processes (e.g., facial affect perception) are significantly associated with reduced plasma oxytocin levels in SZ; however, it is unclear whether higher-level social cognition, which requires inferential processes and knowledge not directly presented in the stimulus, is associated with endogenous oxytocin. The current study explored the association between endogenous oxytocin levels and lower- and higher-level social cognition in 40 individuals diagnosed with SZ and 22 demographically matched healthy controls (CN). All participants received the Social Cue Recognition Test (SCRT), which presents participants with videotaped interpersonal vignettes and subsequent true/false questions related to concrete or abstract aspects of social interactions in the vignettes. Results indicated that SZ had significantly higher plasma oxytocin concentrations than CN. SZ and CN did not differ on SCRT hits, but SZ had more false positives and lower sensitivity scores than CN. Higher plasma oxytocin levels were associated with better sensitivity scores for abstract items in CN and fewer false positives for concrete items in individuals with SZ. Findings indicate that endogenous oxytocin levels predict accurate encoding of lower-level socially relevant information in SZ.

1. Introduction

Although social cognition has been defined in several ways, it typically refers to the ability to perform mental processes that underlie social interactions, including interpreting, perceiving, and generating appropriate responses to the behaviors, dispositions, and intentions of others (Green et al., 2008). Individuals with schizophrenia (SZ) display impairments in multiple aspects of social cognition, and these deficits predict community-based social and vocational outcome (Horan et al., 2012; Couture et al., 2006). Impairments in social cognition have been found to load onto two distinct factors: lower-level and higher-level processes (Sergi et al., 2007). Lower-level social cognition involves evaluating and accurately encoding objective, socially relevant information from an immediately available stimulus (e.g., facial affect perception). Higher-level social cognition requires inferential processing and the ability to use knowledge not directly presented in a stimulus to make judgments about the thoughts, emotions, and intentions of others (e.g., theory of mind).

In mammals, there is evidence that the neuropeptide oxytocin plays a critical role in various aspects of social cognition and social interaction (Dantzer et al., 1990; Dickinson and Keverne, 1988; Dluzen et al., 1998; Wacker and Ludwig, 2012). Relatively few studies have examined whether endogenous oxytocin levels are abnormal in people with SZ. Those studies that have been conducted have yielded inconsistent results, with the majority indicating no group differences (Rubin et al., 2010, 2011, 2013, 2014) and some reporting lower (Goldman et al., 2008, 2011) or higher endogenous oxytocin concentrations in people with SZ compared to controls (Beckmann et al., 1985). Inconsistencies in endogenous oxytocin levels among studies may reflect differences in evaluating peripheral vs. cerebrospinal fluid levels, sample-related differences in demographics (e.g., sex, age, race), the proportion of participants taking different antipsychotics, differences in disease chronicity, and the proportion of participants displaying neuroendocrine dysfunction (e.g., polydipsia). Despite these inconsistencies regarding group-level differences among studies, lower endogenous oxytocin has consistently been associated with impairments in social cognition, especially lower-level processes such as facial affect perception (Goldman et al., 2008; Rubin et al., 2011). Lower endogenous oxytocin also predicts poor social functioning and greater severity of positive and negative symptoms (Goldman et al., 2008; Keri et al., 2009; Rubin et al., 2010, 2011; Walss-Bass et al., 2013; Strauss et al., 2015).

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http://dx.doi.org/10.1016/j.schres.2015.01.034
0920-9964/

Intranasal administration of oxytocin has generally shown beneficial effects on social cognition, with many studies showing effects on lower-level social cognitive processes and several on higher-order social cognition (Feifel et al., 2010; Pedersen et al., 2011; Averbeck et al., 2012; Davis et al., 2013, 2014; Fischer-Shofty et al., 2013a,b; Gibson et al., 2014; Woolley et al., 2014); however, not all studies have reported significant improvements on social cognition (Lee et al., 2013; Horta de Macedo et al., 2014). Furthermore, one study comparing differential effects of oxytocin on higher- and lower-level social cognition demonstrated improvements specific to higher-order processes (Woolley et al., 2014). Thus, oxytocin may be critically linked to impairments in social cognition and social functioning in people with SZ; however, additional work is needed to determine whether lower- or higher-level social cognition is most highly associated with oxytocin.

In the current study, we extended the literature on social cognition and oxytocin by administering a well-validated measure, the Social Cue Recognition Test (SCRT: Corrigan and Green, 1993), which requires participants to watch brief video-taped vignettes of social interactions and then respond to a series of questions pertaining to concrete or abstract aspects of the interaction. Importantly, the SCRT's use of concrete items allowed us to replicate prior associations between lower-level social cognition and endogenous oxytocin (Goldman et al., 2008; Rubin et al., 2011), and extend prior findings by also examining higher-level social cognition (abstract items). The SCRT is ideal for evaluating differential associations between oxytocin and lower- and higher-level social cognition because it evaluates these processes within a single paradigm that uses identical stimulus presentation and response formats across conditions. In line with prior studies, we hypothesized that people with SZ would have lower plasma oxytocin levels than healthy controls (CN) (Goldman et al., 2008, 2011), and that lower endogenous oxytocin would be associated with poorer SCRT performance for both concrete and abstract items.

2. Method

2.1. Participants

Participants included 40 individuals meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) criteria for schizophrenia (n = 35) or schizoaffective disorder (n = 5) (SZ) and 22 healthy controls (CN).

Individuals with SZ were recruited from the outpatient research program at the Maryland Psychiatric Research Center (MPRC) and evaluated during periods of clinical stability. Consensus diagnosis was established via a best-estimate approach based on review of medical records, and multiple interviews, and subsequently confirmed using the Structured Clinical Interview for DSM-IV (SCID: First et al., 1997). All participants with SZ were prescribed antipsychotic medications at the time of testing, including either alone (clozapine, n = 13; haloperidol, n = 5; ziprasidone, n = 3; aripiprazole, n = 2; fluphenazine, n = 2; olanzapine, n = 2; risperidone, n = 2; chlorpromazine, n = 1; quetiapine, n = 1; thioridazine, n = 1) or in combination with another antipsychotic (clozapine and risperidone, n = 5; clozapine and haloperidol, n = 1; clozapine and quetiapine, n = 1; haloperidol, aripiprazole, and clonazepam, n = 1). All participants with SZ were assessed after a minimum period of 4 weeks of stable treatment.

CN participants were recruited through random-digit dialing and word of mouth among enrolled participants. All controls underwent a screening interview, including the SCID-I and SCID-II (Pfohl et al., 1997), and did not meet lifetime criteria for a psychotic disorder or any current Axis I disorder. Controls had no family history of SZ and did not meet the DSM-IV criteria for substance use disorders. Lack of recent substance use was confirmed by urine toxicology at the time of testing. Participants were also screened for lifetime neurological disorders and were free from significant neurological conditions. As pregnancy can affect oxytocin levels, female participants completed a screen; no participants were pregnant.

SZ and CN groups did not significantly differ in age, parental education, sex, or ethnicity; SZ had lower personal education than CN (see Table 1).

2.2. Procedures

Participants completed a standard clinical interview that was performed by a clinical psychologist (GPS) trained to MPRC reliability standards (reliability > 0.80). After this interview, participants with SZ were rated on the Brief Negative Symptom Scale (Kirkpatrick et al., 2011; Strauss et al., 2012a,b), Brief Psychiatric Rating Scale (Overall and Gorham, 1962), and Level of Function Scale (Hawk et al., 1975).

Plasma oxytocin levels were determined by radioimmunoassay in extracted samples using a magnetic bead kit from Phoenix Pharmaceuticals, Inc. Samples were assayed in duplicate; the average of these samples was taken as the final oxytocin concentration. Assay sensitivity was 5 pg/ml, with minimal cross reactivity with vasopressin. The coefficient of variation averaged 5–8% across the assay.

2.3. Measures

The Social Cue Recognition Test (SCRT: Corrigan and Green, 1993) was administered to evaluate social cognition. The SCRT includes 8 brief (2–3 min) videotaped interpersonal vignettes. Four of the videos involve interpersonal interactions that are characterized by high emotional expressivity (e.g., a verbal argument); the other 4 are characterized by low emotional expressivity (e.g., a casual conversation). After watching each video, the scenario is recapped with the participant and they are asked to complete a series of true/false questions related to concrete or abstract aspects of the vignette. Concrete cues assess lower-level social cognition and evaluate accurate encoding of objective, socially relevant information (e.g., Mark and Sally were looking over a book together). Abstract cues assess higher-level social cognition and require inferential processing including the ability to use knowledge not directly presented in the stimulus to make judgments about the thoughts, emotions, and intentions of others (e.g., Carl felt hurt because Mark and Sally would not talk to him).

Several scores are calculated for the SCRT. Hits (i.e., correct true responses) and false positives (FP) (incorrect true responses) are calculated across two conditions: abstract and concrete cues. As done in prior

Table 1
Participant demographic and clinical characteristics.

	SZ (n = 40)	CN (n = 22)	Test-statistic, p-value
Age	43.73 (11.85)	43.14 (9.44)	$F = 0.05$, $p = 0.81$
Participant education	12.95 (2.08)	15.05 (1.86)	$F = 15.47$, $p < 0.001$
Parental education	13.46 (2.45)	14.18 (2.42)	$F = 1.03$, $p = 0.32$
% male	70.7%	68.2%	$\chi^2 = 0.04$, $p = 0.83$
Ethnicity			$\chi^2 = 1.12$, $p = 0.77$
% Caucasian	90.2%	95.5%	
% African-American	4.9%	4.5%	
% Native-American	2.4%	0%	
% bi-racial	2.4%	0%	
Plasma oxytocin (pg/ml)	24.46 (7.54)	19.66 (5.86)	$F = 6.69$, $p < 0.02$
Symptoms			
BNSS total	26.08 (16.97)	–	–
BPRS total	38.97 (9.09)	–	–
BPRS positive	2.41 (1.13)	–	–
BPRS negative	2.25 (1.12)	–	–
BPRS disorganized	1.51 (0.45)	–	–
Functional outcome			
LOF total	18.32 (7.01)	–	–
LOF social	4.55 (2.57)	–	–
LOF work	1.79 (2.60)	–	–

Note. BNSS = Brief negative Symptom Scale; BPRS = Brief Psychiatric Rating Scale; LOF = Level of Function Scale.