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Differential correlations between plasma oxytocin and social cognitive capacity and bias in schizophrenia

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ABSTRACT

Social cognitive impairment is related to poor social functioning in schizophrenia. This impairment includes both deficits in emotion perception and theory of mind (ToM), and cognitive biases including attributional bias and jumping to conclusions. Oxytocin (OXT) is a hormone that has been implicated in human social behavior, and that has also been associated with regulation of inflammation. In a cross-sectional study involving 60 patients with schizophrenia and 20 healthy controls, we examined associations between OXT and social cognitive capacity and bias. Secondary analyses examined associations between OXT and inflammation. We found significant correlations between OXT and social cognitive bias in the control group and in patients with delusions, but not in patients without delusions. Social cognitive capacity only correlated significantly with OXT in patients with delusions. A correlation between OXT and inflammation was observed only in patients without delusions. Findings suggest that OXT may be implicated in social cognition both in controls and in patients with delusions, but that this association may be blunted in patients without delusions. Inflammation appears to be related to OXT rather independently of social cognition. Future longitudinal and intervention studies with OXT are needed to clarify causality in the identified associations.

1. Introduction

Poor social functioning is a hallmark of schizophrenia, and research suggests that it may be due in part to social cognitive impairments (Couture et al., 2006; Fett et al., 2011). Social cognition in schizophrenia is a multidimensional construct (Mancuso et al., 2011) comprised of several different deficits and biases. Areas of deficit include emotion perception (the ability to identify others' emotional states) and theory of mind (ToM; the ability to infer others' mental states and intentions), while biases include self-referential bias (the tendency to infer others as looking at (Hooker and Park, 2005) and/or harboring intentions toward oneself (Combs et al., 2009)) and jumping to conclusions bias, among others (Penn et al., 2008). The extant literature suggests that social cognitive deficits are pervasive in schizophrenia whereas biases may be more pronounced in the subset of schizophrenia patients who have delusions (Martin and Penn, 2002; Bentall and Fernyhough, 2008). However, there is a need for improved understanding of the relationship between social cognitive deficit and bias in schizophrenia (Green et al., 2008).

Oxytocin (OXT) is a nonapetide hormone produced in the brain that has been implicated in social behavior (Churchland and Winkielman, 2012) and social cognitive functions including emotion perception, trust and social coping (Rosenfeld et al., 2010). Although most studies support OXT's prosocial effects (Macdonald and Macdonald, 2010), some studies have shown that OXT's effects may depend on social context, promoting affiliative behaviors like cooperation, generosity and trust towards in-group members while also motivating out-group derogation as evidenced by decreased adherence to fairness norms and low cooperation towards those perceived as not belonging to one's group (De Dreu et al., 2011; Radke and de Bruijn, 2012).

Because of its link to social functioning, OXT has gained increasing attention in schizophrenia research. Several studies measuring OXT or its binding protein in plasma and cerebrospinal fluid have shown increased baseline levels in schizophrenia (Linkowski et al., 1984; Beckmann et al., 1985; Legros et al., 1992) while others have shown levels that are decreased (Goldman et al., 2008; Keri et al., 2009) or commensurate with healthy controls (Glovinsky et al., 1994). OXT plasma levels are assumed to strongly correlate with its relevant brain levels (Churchland and Winkielman, 2012; Macdonald and Feifel, 2012) and a number of studies have reported correlations between peripheral levels of OXT and behavior in schizophrenia (reviewed in Meyer-Lindenberg et al., 2011). Preclinical data from animal models of schizophrenia have shown reversal of social cognitive deficits and antipsychotic-like effects in response to OXT administration (Lee et al., 2005; Caldwell et al., 2009). In patients with

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schizophrenia, several trials have reported improvements in social cognitive deficits and classical psychiatric symptoms after administration of intranasal OXT (Feifel et al., 2010; Pedersen et al., 2011; Averbeck et al., 2012). However, studies of endogenous OXT levels have been more equivocal, with one study reporting a negative correlation between CSF OXT and negative symptoms (Sasayama et al., 2012) and another reporting a negative correlation between blood plasma level of OXT and both positive and general symptoms, but only in women (Rubin et al., 2010). Similarly, this research group found links between blood plasma level of OXT and emotion perception in healthy controls and females with schizophrenia, but not in ill males (Rubin et al., 2011). Finally, despite evidence that OXT plays a role in mediating in-group/out-group bias in healthy individuals, there has been limited research on OXT and social cognitive bias in schizophrenia.

In addition to its role in social behavior, OXT has also been associated with regulation of inflammation. Preclinical studies have shown OXT to have anti-inflammatory properties that include deceleration of atherosclerotic inflammation (Ahmed and Elosaily, 2011; Szeto et al., 2013). In humans, OXT has been shown to have anti-inflammatory properties in cultured vascular cells (Szeto et al., 2008) and to decrease neuroendocrine and cytokine activation after administration of bacterial endotoxin (Clodi et al., 2008). Since increased inflammatory response has been consistently shown in patients with schizophrenia (Meyer et al., 2011; Miller et al., in press), we hypothesized inflammation could be implicated in the relationship between OXT and social cognition in schizophrenia.

In the present study we sought to identify relevant associations between OXT and both social cognitive capacity and bias. A secondary aim was to examine the potential role of inflammation in these processes.

2. Materials and methods

2.1. Subjects

Sixty patients with DSM-IV-TR diagnoses of schizophrenia or schizoaffective disorder (American Psychiatric Association, 2000) were enrolled. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Twenty demographically matched healthy controls were recruited from the same community and screened with the SCID screening interview to rule out history of mental illness and family history of psychotic disorders. Subjects were excluded if they had prior history of significant neurological disorder, head trauma, mental retardation or recent substance use. The study was approved by the University of Texas Health Science Center at San Antonio Institutional Review Board and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Procedures

We conducted an observational, cross-sectional study in which all participants first provided a blood sample for assay of OXT and inflammatory markers and then completed social cognitive and neurocognitive tests and symptom rating interviews.

2.2.1. Blood measurements

Fasting blood was drawn by venipuncture from each subject. Blood samples were immediately processed by centrifugation at 3400 rpm for 10 min and plasma was separated into aliquots and stored at −80 °C until biological measurements were performed. One hundred microliters of plasma was used for measurement of OXT levels using the Oxytocin ELISA kit from Enzo Life Sciences (cat# ADI-900-153) and following manufacturer's instructions. This assay was selected because of its high sensitivity (<12 pg/ml) and because it does not detect vasopressin, providing confidence in the results. It has been previously validated and utilized extensively in studies detecting oxytocin from human samples (Dai et al., 2012; Sasayama et al., 2012). Samples were run in duplicate, un-extracted, diluted 1:1 in dilutent provided by the kit. Fifty microliters of plasma was used for detection of levels of 39 inflammatory markers using bead-based flow immunoassays from Millipore in a Luminex 100 system. These multiplex microbead assays measure protein levels with sensitivity and range comparable to standard sandwich ELISA. A subset of nine inflammatory markers (interleukin-1β [IL-1β], IL-1 receptor antagonist [IL-1RA], IL-2, soluble IL-2 receptor [sIL-2R], IL-6, IL-8, IL-10, tumor necrosis factor-α [TNF-α] and interferon-γ [IFN-γ]) was chosen for principal component analysis (PCA) based on previous studies evidencing their implication in inflammatory processes in schizophrenia (Potvin et al., 2008; Meyer et al., 2011).

2.2.2. Social cognition assessment

Social cognition was assessed with the Waiting Room Task (WRT) (Roberts et al., under review), which is designed to assess both social cognitive capacity and self-referential bias in schizophrenia. Participants view 26 brief videos simulating the experience of facing an unknown person in a waiting room. Across videos, the target person varies the direction of gaze (at or away from the camera), duration of gaze, and facial expression. For each video, the subject makes dichotomous judgments of gaze direction (whether the person looks directly at the subject or not) and ToM (whether or not it seemed that the person had a thought about the subject). Accuracy of gaze responses is determined objectively. Accuracy of ToM responses is determined based on normative consensus from previous norming samples (Roberts et al., under review), following conventions of similar measures (Mayer et al., 2003). Scoring of WRT responses enables the dissociation of capacity and self-referential bias parameters by measuring accuracy (percent correct answers; higher indicates better performance) and false alarm rates (percent endorsement of self-referentiality on non-self-referential items; higher indicates worse performance), yielding the following four variables:

1) Gaze accuracy: correctly identified direct gazes;
2) ToM accuracy: correctly identified self-referential thought;
3) Gaze bias: incorrectly identified away gazes as direct; and
4) ToM bias: incorrectly identified non self-referential thought as self-referential.

2.2.3. Neurocognitive assessments

Regarding neurocognition, verbal memory was assessed with the Hopkins Verbal Learning Test (HVLT)—Revised (Shapiro et al., 1999) and verbal fluency was assessed using Phonemic (letter) and Category (animals and occupations) tests (Joyce et al., 1996). HVLT scores were computed as the total number of correct answers after three sequential trials. For verbal fluency tests, we considered the total number of valid answers in each of the three tasks (letter, animal and occupations) separately. Executive function was evaluated with the Trail Making Test Parts A and B (Reitan, 1992), for which a total score was recorded as the seconds required to complete both parts.

2.2.4. Psychiatric assessments

In patients, symptom severity was evaluated using the Brief Psychiatric Rating Scale (BPRS)—extended version (Lukoff et al., 1986) and the Negative Symptom Assessment—16-item version (NSA-16) (Axelrod et al., 1993). For both scales, total scores were computed as the sum of individual items scores. Because self-relevant biases in schizophrenia have been found primarily among patients with delusions (Fine et al., 2007), Item 11 of the BPRS ("Unusual Thought Content") was used to classify patients as having delusions (scores 2 to 7) or not (score 1).

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