Schizophrenia Research 159 (2014) 353–357

Contents lists available at ScienceDirect

Schizophrenia Research

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

Associations between oxytocin receptor genotypes and social cognitive performance in individuals with schizophrenia

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ARTICLE INFO

Article history:
Received 7 June 2014
Received in revised form 26 August 2014
Accepted 2 September 2014
Available online 20 September 2014

Keywords:
Schizophrenia
Social cognition
Oxytocin
Oxytocin receptor
Single nucleotide polymorphism

ABSTRACT

Individuals with schizophrenia often show substantial deficits in social cognitive abilities, which are strongly associated with social functioning. To advance our understanding of the genetic variation that is associated with social cognitive deficits in schizophrenia, we genotyped 74 schizophrenia outpatients who completed social cognitive performance measures assessing mentalizing, social perception, and emotional intelligence, as well as clinical symptoms. We assessed seven single nucleotide polymorphisms (SNPs) of the oxytocin receptor (OXTR) previously found to show replicable associations with socio-emotional processes. For one of the seven SNPs, rs2268493, the 'T' allele was significantly associated with poorer performance on a composite social cognition index, as well as specific tests of mentalizing and social perception. None of the SNPs were associated with clinical symptoms. Though the sample size is small, these findings provide initial support for the involvement of genetic variants of the OXTR in social cognitive impairments in schizophrenia.

Published by Elsevier B.V.

1. Introduction

Individuals with schizophrenia often show marked deficits in social cognitive abilities, and these deficits are predictive of poor functioning (Fett et al., 2011; Horan et al., 2012). However, the mechanisms underlying impaired social cognition and its variability across patients are largely unknown. One possible contributor is the oxytocin system, which plays an important role in social cognition and behaviors in humans and other animals (Meyer-Lindenberg et al., 2011). This system is of particular interest in schizophrenia, given several recent studies suggesting potential use of intranasal oxytocin as a therapeutic agent (MacDonald and Feifel, 2012).

Many genetic studies have investigated the role of the oxytocin system in social processes, primarily in healthy individuals, and most have focused on genetic variation of the oxytocin receptor (OXTR) (Ebstein et al., 2012). The two most widely studied single nucleotide polymorphisms (SNPs) of the OXTR are rs53576 and rs2254298. These SNPs have frequently shown associations with empathy and various pro-social behaviors, though not all studies have supported such links (Bakermans-Kranenburg and van Ijzendoorn, 2014). Other OXTR SNPs have also shown replicable associations with similar pro-social behaviors (Kumsta and Heinrichs, 2013).

In schizophrenia research, several OXTR SNPs have shown initial associations with the schizophrenia diagnosis in case–control studies (Souza et al., 2010b; Watanabe et al., 2012; Montag et al., 2013b), as well as with symptom severity and response to clozapine therapy (Souza et al., 2010a; Montag et al., 2012, 2013b). Very little is known about the relationship of OXTR in schizophrenia and social cognition. Only one previous report examined this connection and used a self-report measure of empathy. That study found schizophrenia patients with an 'A' allele of rs2254298 scored higher on one subscale (i.e., Empathic Concern) than those with the 'GG' genotype (Montag et al., 2012).

Given the potential importance of genetic variation in the OXTR and the limited knowledge of its role in schizophrenia, we genotyped seven OXTR SNPs in schizophrenia patients who had been characterized on social cognitive performance measures. The seven SNPs were chosen based on their replicated associations with socio-emotional processing variables in prior studies. Considering the relatively small sample size, we view these findings as hypothesis-generating for future larger studies.

2. Experimental methods

2.1. Participants

Participants were a subset of a larger study on social cognitive determinants of outcome (Green et al., 2012) and consisted of 74 schizophrenia outpatients (Table 1) recruited from the VA Greater Los Angeles

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http://dx.doi.org/10.1016/j.schres.2014.09.006
0920-9964/Published by Elsevier B.V.

Table 1
Sample characteristics (N = 74).

Characteristic		Value
Gender:	Male	72%
	Female	28%
Age:	Mean years (SD)	46.1 (10.5)
Education:	Mean years (SD)	12.7 (1.7)
Race:	White	61%
	Black	39%
Symptoms:	BPRS positive symptom score (SD)	2.2 (.9)
	SANS expression score (SD)	1.0 (1.1)
	SANS experience score (SD)	2.6 (1.1)
Social cognitive performance:	TASIT III total (SD)	45.7 (7.6)
	PONS total (SD)	78.9 (7.7)
	MSCEIT total (SD)	81.4 (13.4)

Healthcare System (VAGLAHS) and the surrounding community. Selection criteria included age 18–60, black or white race, no active substance use disorder within the prior 6 months, no neurological disorders, IQ > 70 based on medical record review, no prior loss of consciousness >1 h, fluency in English, and capacity to give informed consent. Current use of an antipsychotic medication was not an inclusion criterion; however, 80% of the participants in the same were taking an atypical antipsychotic; 7% were taking a typical antipsychotic; 7% were taking both atypical and typical antipsychotics; and 6% were not taking an antipsychotic. The study was approved by the VAGLAHS Institutional Review Board.

2.2. SNP selection

We selected seven OXTR SNPs based on a literature review, genotyping SNPs with previous positive findings related to social cognitive or emotional processes in any type of sample, and at least one replication by an independent research group. All seven SNPs had a minor allele frequency >0.10 (see Table 2).

2.3. Genotyping

Blood samples (30–40 mL) were obtained from participants to extract DNA. DNA extraction was performed with the QIAamp Blood Maxi Kit according to the manufacturer's protocol (Qiagen, Hilden, Germany). SNPs were genotyped using Life Technologies' TaqMan SNP Genotyping Assays and TaqMan probes for 7 selected SNPs according to the manufacturer's protocol (Life Technologies Corp., Carlsbad, CA). All SNPs were in Hardy–Weinberg equilibrium and repeat genotyping of a subset (~10%) of the samples produced complete concordance.

2.4. Social cognition assessments

The social cognitive battery included measures of social perception, mentalizing, and emotion intelligence and is described more fully in Green et al. (2012). Social perception was assessed using the Half-Profile of Nonverbal Sensitivity (PONS; (Rosenthal et al., 1979)) with administration modified to reduce demands on reading comprehension and attention (Green et al., 2012). The dependent measure was the number of correct items out of 110. Mentalizing was assessed using The Awareness of Social Inference Test — Part III (TASIT; (McDonald et al., 2003)), with the number of correct items out of 64 as the dependent measure. Emotional intelligence (the ability to identify, use, understand, and manage emotions) was assessed using the Mayer–Salovey–Caruso Emotional Intelligence 2.0 (MSCEIT; (Mayer et al., 2003)), with the total score (standardized score based on community norms) used as the dependent measure. A composite social cognition summary score was calculated based on the mean of the z-scores of the individual measures.

2.5. Clinical symptom assessments

Psychiatric symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) 24-item version (Ventura et al., 1993) and the Scale for the Assessment of Negative Symptoms (SANS; (Andreasen, 1984)). We report the BPRS positive symptom score (mean of unusual thought content, hallucinations, and conceptual disorganization items) and the expression (mean of affective blunting and alogia) and experience (mean of avolition and anhedonia) subscores for the SANS.

2.6. Statistical analysis

Statistical tests were performed with SPSS Statistics version 20 (IBM). Genotype associations with social cognitive and symptom measures were evaluated using a series of ANOVA's with allele subgroups for each SNP entered as independent variables. Race and gender were initially included as covariates but were removed from all the reported models because no significant main or interaction effects involving race or gender were found. In situations in which there were ≤3 subjects in an allele group, we collapsed across categories by combining the low-frequency homozygotic individuals with the heterozygotic subjects. This occurred for 3 SNPs: rs2268493, rs2254298, and rs2686302. Effect sizes were calculated using Cohen's *f*, which is based on explained variance. It generalizes Cohen's *d* to a multigroup ANOVA. Cohen's *f* is equivalent to *d*/2 in SNPs that were collapsed to two levels (Cohen, 1988).

Table 2
List of analyzed OXTR SNPs.

SNP identification	Minor allele frequency[a]	Position	References
rs1042778	0.365	3′ UTR	Israel et al. (2009); Campbell et al. (2011); Feldman et al. (2012); Malik et al. (2012)
rs7632287	0.238	3′	Campbell et al. (2011); Walum et al. (2012)
rs237887	0.429	IVS	Israel et al. (2009); Wu et al. (2012); Skuse et al. (2013); Tabak et al. (2013)
rs2268493	0.227	IVS	Kawamura et al. (2010); Campbell et al. (2011); Damiano et al. (2014)
rs2254298	0.214	IVS	Wu et al. (2005); Jacob et al. (2007); Lerer et al. (2007); Costa et al. (2009); Kawamura et al. (2010); Liu et al. (2010); Thompson et al. (2011); Feldman et al. (2012); Wu et al. (2012); Montag et al. (2013a)
rs53576	0.413	IVS	Wu et al. (2005); Bakermans-Kranenburg and van IJzendoorn (2008); Costa et al. (2009); Lucht et al. (2009); Rodrigues et al. (2009); Kim et al. (2010); Park et al. (2010); Tost et al. (2010); Chen et al. (2011); Kogan et al. (2011); Saphire-Bernstein et al. (2011); Tops et al. (2011); Marsh et al. (2012); Sturge-Apple et al. (2012); Chang et al. (2014); Hostinar et al. (2014); Moons et al. (2014); Smith et al. (2014)
rs4686302	0.147	Ala ➔ Thr	Wu et al. (2012); Chang et al. (2014)

In the third column, *Position* refers to the location of the SNP in the *OXTR* gene. UTR = untranslated region. IVS = intervening sequence (i.e., an intron). Ala ➔ Thr = mutation in the coding sequence causing threonine to be incorporated in the protein instead of alanine.
[a] Obtained from 1000 Genome dataset (1000 Genomes Project Consortium, 2012).