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Associations Between Oxytocin Receptor Genotypes and Social Cognitive Performance in Individuals With Schizophrenia

Michael C. Davis[1,2], **William P. Horan**[1,2], **Erika L. Nurmi**[1], **Shemra Rizzo**[3], **Wendy Li**[1], **Catherine A. Sugar**[3,1], and **Michael F. Green**[1,2]

[1]UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA

[2]VA Desert Pacific Mental Illness Research, Education, and Clinical Center, Los Angeles, CA

[3]Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, CA

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.

Keywords

schizophrenia; social cognition; oxytocin; oxytocin receptor; single nucleotide polymorphism

Corresponding author: Michael F. Green, 11301 Wilshire Blvd. Bldg. 210A, Los Angeles, CA 90073, Phone: 310-268-3376, Fax: 310-268-4056, mgreen@ucla.edu.

Contributors

All authors contributed significantly and collaboratively to this work. Dr. Davis, Dr. Horan, Dr. Nurmi, and Dr. Green designed this study. Dr. Horan and Dr. Green developed the social cognitive assessment battery and interpreted the social cognitive data. Dr. Nurmi and Ms. Li performed genetic analyses and helped interpret genetic data. Dr. Rizzo and Dr. Sugar performed statistical analyses and provided support for data analysis. Dr. Davis wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

Potential Conflicts of Interest: None of the authors of this manuscript have conflicts of interest to disclose.

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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 (Montag et al., 2013b; Souza et al., 2010b; Watanabe et al., 2012), as well as with symptom severity and response to clozapine therapy (Montag et al., 2013b; Montag et al., 2012; Souza et al., 2010a). 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.

Experimental Methods

1.1 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 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 hour, 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.

1.2 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).

1.3 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.

1.4 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

1.5 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.

1.6 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).

2. Results

2.1 Social Cognitive Performance

Of the 7 genotyped SNPs, only one showed statistically significant ($p<.05$) differences among allele subgroups on the social cognitive measures (Table 3). Rs2268493 genotypes showed significant differences on the social cognition summary score, as well as the TASIT and PONS. The differences involving this SNP (using z-scores of individual social cognitive measures) are shown in Figure 1. Participants with the 'TT' genotype (n=50), the identified risk allele (Campbell et al., 2011; Damiano et al., 2014; Kawamura et al., 2010), performed more poorly across these measures than those in the combined 'CC + CT' group (n=23). The only other SNP that approached significance was rs1042778, which showed trend level associations with the TASIT ($p=.091$).

2.2 Psychiatric Symptoms

None of the SNPs we genotyped were significantly associated with BPRS positive symptoms or SANS scores (Table 4). There were trend level associations for the rs1042778 genotype with the SANS expression subscore ($p=.087$).

3. Discussion

These findings provide preliminary support for the involvement of genetic variants of the OXTR in social cognitive impairments in schizophrenia. Of the 7 SNPs examined, one of these, rs2268493, showed a significant association with social cognitive performance in this sample of schizophrenia individuals. Our finding that the "T" allele of this SNP was associated with poorer social cognition, particularly in the areas of mentalizing and social perception, is consistent with prior studies in other samples. The "T" allele of rs2268493 has been associated with risk for autism spectrum disorders (Campbell et al., 2011), depressive temperament (Kawamura et al., 2010), and decreased mesolimbic activation during reward anticipation (Damiano et al., 2014). This convergence of results bolsters support for further investigation of OXTR and related genetic polymorphisms in schizophrenia.

The genetic mechanism by which rs2268493 variants could affect social cognitive processes is not known, but it is possible that these variants alter OXTR expression. Rs2268493 is an intronic SNP and its locus appears to overlap 6 different regulatory motifs, as well as predict an enhancer chromatin state (HaploReg; (Ward and Kellis, 2012)). This indicates that variations in genotype may affect transcription factor binding and gene expression. Along these lines, differences in regional OXTR expression density have been found to affect the processing of social information and affiliative behaviors in animals (Ross and Young, 2009). Another explanation for these results could involve linkage disequilibrium. The rs2268493 locus is in disequilibrium $r^2 \geq 0.7$ with 6 other intronic OXTR SNPs (rs2268492, rs60902022, rs60345038, rs13316193, rs11131148, and rs11131149) with associated regulatory motifs and enhancing chromatin states (Ward and Kellis, 2012). This linkage among OXTR SNPs suggests that the effects we observe with rs2268493 could be caused by a related SNP.

The main limitation of this study is that the sample size is small. This limited our power to examine the effects of race or gender in our analyses. Futhermore, our statistical tests were not corrected for multiple comparisons so replication in larger samples will be essential. Our failure to replicate a prior association between rs2254298 and a social cognitive measure in schizophrenia (Montag et al., 2012) may be attributable to our use of performance-based rather than self-report outcome measures. Alternatively, this difference, as well as the absence of significant associations with clinical symptoms, may reflect limited statistical power associated with the modest sample size. Despite these limitations, this preliminary study supports further investigation of OXTR and related polymorphisms (e.g., oxytocin and vasopressin genes, vasopressin receptor genes) in schizophrenia and our results may be valuable for hypothesis generation and planning future studies.

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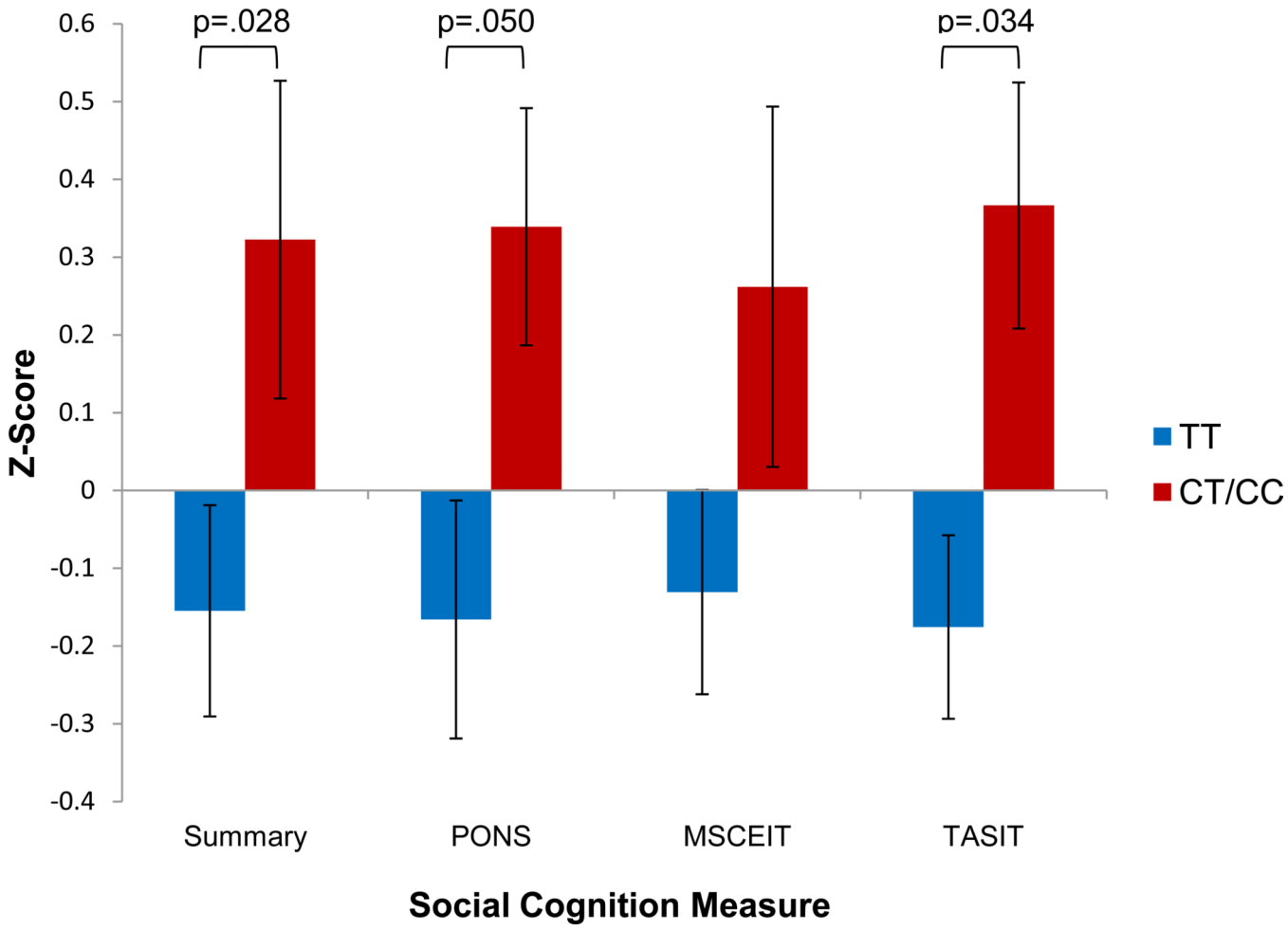

Figure 1.

Performance on Individual and Summary Social Cognitive Measures by rs2268493 Genotype: Summary represents the mean of z-scores from the three social cognitive measures. Error bars indicate standard errors of the mean.

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 symptoms 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)

Table 2

List of Analyzed OXTR SNPs

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

* obtained from 1000Genome dataset (Consortium, 2012)

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.

Table 3

Genotypic Differences in Social Cognitive Performance (expressed as effect size Cohen's *f*, p value)

Measure	rs1042778	rs7632287	rs237887	rs2268493[1]	rs2254298[2]	rs53576	rs4686302[3]
Summary	.25, .108	.07, .843	.11, .647	.25, .031	.04, .710	.11, .672	.08, .519
TASIT III	.26, .091	.01, .993	.16, .388	.25, .034	.11, .371	.12, .584	.14, .225
PONS	.21, .208	.08, .788	.09, .758	.23, .050	.01, .953	.05, .926	.02, .883
MSCEIT	.21, .218	.13, .543	.05, .907	.17, .148	.05, .674	.14, .518	.09, .463

[1] Compared TT vs. CC/CT combined

[2] Compared GG vs. AA/AG combined

[3] Compared CC vs. TT/TC combined

Table 4

Genotypic Differences in Psychiatric Symptoms (expressed as effect size Cohen's *f*, p value)

Measure	rs1042778	rs7632287	rs237887	rs2268493[1]	rs2254298[2]	rs53576	rs4686302[3]
BPRS positive symptoms	.18, .291	.18, .302	.21, .212	.03, .833	.15, .198	.22, .161	.13, .273
SANS expression	.26, .087	.06, .885	.17, .333	.06, .604	.19, .109	.13, .529	.07, .577
SANS experience	.09, .749	.16, .395	.12, .623	.16, .181	.02, .874	.15, .438	.03, .776

[1] Compared TT vs. CC/CT combined

[2] Compared GG vs. AA/AG combined

[3] Compared CC vs. TT/TC combined

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