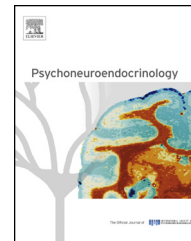




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# Oxytocin administration enhances controlled social cognition in patients with schizophrenia



J.D. Woolley<sup>a,b,\*</sup>, B. Chuang<sup>a</sup>, O. Lam<sup>a</sup>, W. Lai<sup>a</sup>,  
A. O'Donovan<sup>a,b</sup>, K.P. Rankin<sup>c,d</sup>, D.H. Mathalon<sup>a,b</sup>,  
S. Vinogradov<sup>a,b</sup>

<sup>a</sup> Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

<sup>b</sup> San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA, USA

<sup>c</sup> UCSF Memory and Aging Center, University of California San Francisco, San Francisco, CA, USA

<sup>d</sup> Department of Neurology, University of California San Francisco, San Francisco, CA, USA

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## KEYWORDS

Oxytocin;  
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## Summary

**Background:** Individuals with schizophrenia have functionally significant deficits in automatic and controlled social cognition, but no currently available pharmacologic treatments reduce these deficits. The neuropeptide oxytocin has multiple prosocial effects when administered intranasally in humans and there is growing interest in its therapeutic potential in schizophrenia. **Methods:** We administered 40 IU of oxytocin and saline placebo intranasally to 29 male subjects with schizophrenia and 31 age-matched, healthy controls in a randomized, double-blind, placebo-controlled, cross-over study. Social cognition was assessed with The Awareness of Social Inference Test (TASIT) and the Reading the Mind in the Eyes Test (RMET). We examined the effects of oxytocin administration on automatic social cognition (the ability to rapidly interpret and understand emotional cues from the voice, face, and body); controlled social cognition (the ability to comprehend indirectly expressed emotions, thoughts, and intentions through complex deliberations over longer time periods); and a control task (the ability to comprehend truthful dialog and perform general task procedures) in individuals with and without schizophrenia using mixed factorial analysis of variance models.

**Results:** Patients with schizophrenia showed significant impairments in automatic and controlled social cognition compared to healthy controls, and administration of oxytocin significantly improved their controlled, but not automatic, social cognition,  $F(1, 58) = 8.75$ ;  $p = 0.004$ . Conversely, oxytocin administration had limited effects on social cognition in healthy

\* Corresponding author at: 4150 Clement Street, 116C-1, San Francisco, CA 94121, USA. Tel.: +1 415 221 4810x4117.  
E-mail address: [Josh.Woolley@ucsf.edu](mailto:Josh.Woolley@ucsf.edu) (J.D. Woolley).

participants. Patients and controls performed equally well and there were no effects of oxytocin administration on the control task.

*Discussion:* Intact social cognitive abilities are associated with better functional outcomes in individuals with schizophrenia. Our data highlight the potentially complex effects of oxytocin on some but not all aspects of social cognition, and support the exploration of intranasal oxytocin as a potential adjunct treatment to improve controlled social cognition in schizophrenia.

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## 1. Introduction

Social cognition, the ability to understand the thoughts and intentions of others, is critical for effectively navigating the social world. In fact, a range of social cognitive and affective operations are required to understand other people's mental states and behavior (Olsson and Ochsner, 2008), and these operations tend to be distinct from non-social cognition (Fett et al., 2011). Patients with schizophrenia (SZ) have widespread social cognitive deficits that interfere with social relationships and impair occupational functioning (Fett et al., 2011). Moreover, social cognitive deficits are more strongly associated with quality of life and functional outcomes than "positive" symptoms (e.g., hallucinations) or non-social cognition in SZ (Fett et al., 2011; Mancuso et al., 2011). Unfortunately, current antipsychotic treatments are ineffective in remediating social cognitive deficits (Kucharska-Pietura and Mortimer, 2013).

Previous studies attempting to examine social cognition in patients have often been hampered by the use of complex, multifaceted tests measuring multiple aspects of social cognition simultaneously. Advances in cognitive affective neuroscience have made it clear that understanding patient behavior in this domain requires the use of constructs that break social cognition down into subcomponents that reflect distinct neurologic systems. A clear distinction has been established during the past decade breaking socioemotional processing down into automatic, "reflexive" versus controlled, "reflective" dimensions (Lieberman, 2007). The automatic system operates quickly and unconsciously, is sensitive to subliminal cues, depends primarily on sensory processing, learns slowly, and is associated with basic person perception and immediate social cue detection (Bar et al., 2006) as measured by such tests as the Reading the Mind in the Eyes Test (RMET) (Bora et al., 2009). On the other hand, the higher-level, reflective controlled processing system operates on socioemotional information slowly and requires reflective consciousness, is insensitive to subliminal cues, depends on linguistic semantic processing, learns quickly, and makes more complex inferences based on deliberations performed over longer time periods (Lieberman, 2007).

Automatic social cognitive functions such as recognizing emotional cues and sarcasm, and making rapid personalized evaluations rely on anatomically discrete and phylogenetically ancient regions of the brain such as the medio-temporal salience structures including the amygdala and latero-temporal audiovisual integration areas (Rankin et al., 2009), as well as ventromedial orbitofrontal regions and the subcortical reward regions associated with them (Shany-Ur et al., 2012). In contrast, the higher-level, controlled system integrates social information collected over time from multiple modalities involving complex associative deliberations. Tests

that measure these aspects of social cognition have traditionally involved making complicated, executively demanding deliberations about different perspectives in a social interaction and include higher-order theory of mind and *faux pas* tests, and moral reasoning deliberations (Chiong et al., 2013). In general, controlled social cognition requires more recently evolved higher-order cortical networks such as the dorsal executive-control networks and latero-anterior temporal structures, which mediate complex socioemotional semantics (Parker et al., 2005). Finally, this hierarchical separation of social cognition into separate neurologic systems has functional implications, as deficits in lower-level automatic and higher-level controlled social cognitive processing make independent contributions to functional outcomes in SZ (Mancuso et al., 2011; Sparks et al., 2010). Because of the neural and functional separation between automatic and controlled social cognitive processes, when investigating a pharmacological intervention to improve social cognition, it is important to test these processes separately.

The neuropeptide oxytocin (OT) has been implicated in bonding and sociality in mammals and when administered intranasally to humans has powerful prosocial effects (Macdonald and Macdonald, 2010). In patients with autism, a single dose of OT improves facial affect recognition (Guastella et al., 2010). There is also a burgeoning literature on the role of OT in SZ. In healthy subjects, peripheral OT levels increase after entrusting a secret to an experimenter. However, individuals with SZ do not show this increase and the severity of their negative symptoms predicts their OT response to the situation (Keri et al., 2009). Furthermore, in patients with SZ, plasma OT levels predict the ability to identify facial affect (Rubin et al., 2011), and cerebrospinal fluid (CSF) OT levels correlate with negative symptoms (Sasayama et al., 2012). Moreover, three recent clinical trials found that two (Pedersen et al., 2011), three (Feifel et al., 2010), and eight (Modabbernia et al., 2013) weeks of intranasal OT administration significantly decreased positive and negative symptoms, although one three-week clinical trial failed to find any effects of intranasal OT on positive or negative symptoms of schizophrenia (Lee et al., 2013). Together, this suggests that OT administration may be an effective treatment for schizophrenia.

In addition to these promising effects of OT on the clinical symptoms of schizophrenia, several studies have found that OT administration has positive effects on multiple aspects of social cognition in SZ, including automatic processes such as affect recognition (Averbeck et al., 2011; Goldman et al., 2011), and controlled processes such as theory of mind (Pedersen et al., 2011). With regard to controlled social cognition, one study found that OT administration improved recognition of multiple emotions expressed on the face

(Averbeck et al., 2011; Goldman et al., 2011) and another found that OT administration improves recognition of fearful but not happy facial expressions (Fischer-Shofty et al., 2013b). For controlled social cognition effects of OT administration in schizophrenia, one study found that two-weeks of OT administration improved some, but not all, components of a theory of mind false belief test (Pedersen et al., 2011) and another study found that OT administration improved patient's ability to recognize kin relationships although whether this is a controlled social cognitive process is unclear (Fischer-Shofty et al., 2013a). In addition, in a recent, small, single-dose, between-subject design study, OT administration was found to improve high-level but not low-level social cognition in patients with SZ (Davis et al., 2013). While early results are promising, sample sizes have been relatively small, no two studies have used the same measures of social cognition, and few studies have examined the effects of OT on both automatic and controlled social cognitive domains in patients and matched healthy individuals simultaneously, which would allow for the specificity of OT effects to be determined.

In order to elucidate the effects of OT on distinct aspects of social cognition in individuals with SZ, we performed a randomized, double-blind, placebo-controlled, cross-over investigation examining OT's effects on automatic and controlled social cognition in male patients with chronic SZ and age-matched healthy controls (HC). Given the heterogeneity of effects of oxytocin on social cognition in previous studies in schizophrenia, the neural and functional separation between automatic and controlled social cognitive processes, and the paucity of studies investigating the effects of OT administration on controlled-social cognition in schizophrenia or that include matched healthy controls, we examined the effects of OT administration on automatic and controlled social cognition in patients with SZ and HC.

## 2. Methods

### 2.1. Subjects

Twenty-nine patients (average age 44.6 years) with a chronic psychotic disorder (22 with SZ and seven with schizoaffective disorder) and 31 age-matched HC (average age 42.5 years) were recruited from across the San Francisco Bay Area. All diagnoses were established with the Structured Clinical Interview for DSM-IV (SCID) administered by trained clinical interviewers. Patients were clinically stable and on a stable dose of psychiatric medications for at least one month and throughout the study. Patients on mood stabilizers were excluded in order to minimize patient heterogeneity and because of unclear relationships between mood stabilizers and the OT system (You et al., 2001). HC had no Axis I DSM-IV disorder within the last year based on their SCID. All participants were in good general health, had no neurological disorders or substance dependence within the last 6 months, and had a negative urine toxicology test at each visit. We recruited only male participants in order to minimize inter-subject variation as OT administration may have sexually dimorphic effects (Meyer-Lindenberg et al., 2011). Written informed consent was obtained from each participant, and

the Committee on Human Research at the University of California, San Francisco, approved study protocols.

### 2.2. Design and procedures

We used a randomized, double-blind, placebo-controlled, cross-over design, with the two testing days separated by at least one week. On each test day, 40 IU of OT (Novartis, Switzerland) or saline placebo (PCB) was self-administered via nasal spray by alternating insufflations every 15-s between each nostril over a 5-min timeframe (Feifel et al., 2010) until the entire 1 mL volume was administered. At least 5 sprays per nostril were administered which resulted in about 100  $\mu$ L per spray. This dose has been effective in improving social cognition in patients with SZ in previous studies (e.g., Feifel et al., 2010). Intranasal administration has been proposed to deliver OT to the brain via two possible mechanisms: (1) intra-neuronal uptake by the olfactory or trigeminal nerves; and (2) extra-neuronal passive diffusion into the CSF through perineural clefts in the nasal epithelium (Veening and Olivier, 2013). Vasopressin enters the CSF of humans within 10 min following intranasal administration, and levels continue to increase for at least 80 min (Born et al., 2002). Given the molecular similarity between OT and vasopressin, CSF OT levels are believed to remain high for several hours after intranasal administration in humans. Testing began 30 min after administration of OT because at this delay, healthy subjects have shown robust OT-induced behavioral and physiological responses in previous studies (Macdonald and Macdonald, 2010).

### 2.3. Measures

#### 2.3.1. Social cognition assessments

Participants were assessed with the "Reading the Mind in the Eyes Test" (RMET) and "The Awareness of Social Inference Test" (TASIT). Within these tasks, we used measures assessing functions related to person perception and rapid social cue detection to index "automatic" social cognition and measures requiring more intensive, complex processing involving integration of multiple distinct non-social and social cognitive functions to index "controlled" social cognition.

The RMET was chosen for the current study because: it measures the ability to label mental states based only on viewing subtle affective facial expressions; it has been widely used in healthy and patient populations including SZ (Bora et al., 2009); and OT administration has improved performance on this task in healthy (Domes et al., 2007) and autistic individuals (Guastella et al., 2010). Subjects select mental states depicted in 36 photographs of the eye region of faces from four options (Baron-Cohen, 2001). Although the mental states depicted in the task are semantically complex (e.g., "jealous"), the RMET does not require further integration of that state with other social cues or contextual information to identify the broader social implications of that mental state (e.g., who the person is jealous of and why) (Baron-Cohen, 2001). Thus, we categorized the RMET as an index of automatic social cognition. Scores range from 0 to 36 questions correct.

In TASIT, participants make social inferences after viewing video clips of actors engaging in social scenarios of various

types and complexity. TASIT was chosen because it has good test–retest reliability and discriminant validity (McDonald et al., 2006) in patients with neuropsychiatric illness, and it was designed to separately test multiple levels of social cognitive processing. Validated alternate forms of the stimuli were used on each test day and order was randomized between participants. TASIT is divided into three parts each testing a progressively more complex aspect of social cognition: Emotion Evaluation Test (EET), Social-Inference Minimal (SI-M), and Social Inference Enriched (SI-E). For detailed description and further discussion of the categorization of the various components of the TASIT see [Supplementary materials](#).

In the EET, actors depict an emotion in a dynamic realistic way using non-verbal cues (e.g., body language, facial expression, and tone of voice), while speaking from non-emotional, neutral, scripts. Participants choose the emotion displayed by the actor from a list of 6 potential emotions and neutral. This task was categorized as an index of automatic social cognition because it requires no further deliberation or integration about the actor's thoughts or intentions. Scores range from 0 to 14 questions correct.

The SI-M comprises vignettes that represent everyday conversational exchanges between two people. The participant must use non-verbal cues or paralinguistic information to correctly understand the otherwise ambiguous dialog. In sincere exchanges (SIN), speakers mean exactly what they say. The SIN items have been used as a control task in a previous study (Shany-Ur et al., 2012), and patients with SZ have demonstrated normal performance on the SIN items (Kern et al., 2009). Therefore, we used the SIN score as a control task to demonstrate that patients could understand and perform general task requirements. In simple sarcasm exchanges (SSR), the speaker means the opposite of what they say and uses paralinguistic cues to emphasize their actual meaning. Because the SSR requires immediate social cue detection (i.e., participants must intuit whether the actor is being sarcastic or sincere based on their body language, affect, and prosody but not on previously obtained information about the situation) to identify the speaker's meaning, we categorized it as an index of automatic social cognition. Scores range from 0 to 40 questions correct for SI-M.

The SI-E comprises vignettes with enriched contextual information to help the viewer fully comprehend the speaker's state of mind, intentions, and emotional state. Half of the clips depict a "white lie", where the main speaker attempts to hide information from another character. The other eight clips depict complex sarcasm, where the main speaker emphasizes the truth through both paralinguistic and contextual cues. Each video includes additional visual or verbal contextual information (a physical object or a dialog), equally distributed, that helps viewers determine the speaker's and listener's actual beliefs or opinions. At the end of each clip, participants answer four yes–no questions regarding the speaker's true belief ("think"), intention ("do"), what the speaker intended the listener to comprehend from their speech ("say"), and the speaker's emotional state ("feel").

Interpreting these insincere statements, whether the speaker is telling a white lie or being sarcastic, requires deciphering the speaker's intention, a complex process relying on integration of semantic and syntactic comprehension,

contextual and paralinguistic information processing, pragmatic knowledge, visual perspective taking, emotion reading, and theory of mind (ToM). Thus, the various subscales of SI-E require complex processing to decode speakers' thoughts and intentions based on extended social transactions and were therefore used as measures of higher-level, controlled social cognition (Shany-Ur et al., 2012). Scores range from 0 to 64 questions correct for SI-E.

### 2.3.2. Calculation of automatic and controlled social cognition composite scores

Based on our and others' work (Mancuso et al., 2011; McDonald et al., 2006; Shany-Ur et al., 2012; Sparks et al., 2010), we analyzed the following components: (1) *automatic social cognition* – measuring the ability to read emotional cues in voices, faces, and body language (composed of RMET; EET; and SSR scores); (2) *controlled social cognition* – measuring comprehension of indirectly expressed emotions, thoughts, intentions, and based on complex integration of social contextual information in dialog and interpersonal behavior (composed of SI-E "think visual"; "think verbal"; "do"; and "feel" items, reflecting a composite score previously used in cognitively impaired patients (Shany-Ur et al., 2012)); and (3) *control task* – composed of SIN scores. Cronbach's Alpha showed inter-task convergence was 0.69 for automatic social cognition and 0.77 for controlled social cognition, suggesting that the organization of the tasks into these subcomponents was meaningful.

### 2.3.3. Symptom severity

We administered the Positive And Negative Symptom Scale (PANSS) to a subset ( $N = 19$ ) of patients. This is a symptom scale that assesses the positive and negative symptoms of SZ (Kay et al., 1987). A limited number of patients were administered the PANSS because this measure was not implemented until later in the study.

### 2.3.4. Medications

In order to quantify patient's antipsychotic and anticholinergic burden, we calculated cogentin and chlorpromazine (CPZ) equivalents for patients using a standardized conversion table (Andreassen et al., 2010). This was done to both better describe our patient population and to explore whether medication dosages interacted with OT effects.

## 2.4. Data analysis

Differences between groups in demographic factors were examined using independent sample *t*-tests for continuous variables and chi-square tests for categorical variables. In order to investigate our primary hypothesis that OT would have differential effects on controlled versus automatic cognition in SZ and HC, we performed a mixed factorial ANOVA with two within-subject factors: *drug* (OT and PCB) and *task* (automatic and controlled social cognition); and one between-subject factor: *group* (SZ and HC). For this primary analysis,  $p$  was set at  $<0.05$ . To examine the nature of the overall Drug  $\times$  Task  $\times$  Group interaction, we conducted tests of Drug  $\times$  Group interactions separately within each task (automatic, controlled). Next, this was followed-up with an examination of the Drug effect within each Group (SZ, HC). Finally, in secondary analyses, we conducted repeated measures



ANOVAs with Drug (OT, PCB) as within subjects factor across each subscale item to examine the effects of OT on these subscales separately in patients with SZ and HC. Given the number of comparisons per group in these secondary analyses ( $k = 8$ ), we used a Benjamini and Yekutieli (B–Y) correction for family-wise error (Narum, 2006) to control for multiple comparisons (adjusted  $\alpha = 0.0184$ ). For exploratory analysis of possible moderators of OT's effects on social cognition and exploratory analyses for additional subscales, see [Supplementary material](#). SPSS version 21.0 (IBM Inc.) was used for all analyses.

### 3. Results

#### 3.1. Sample characteristics

Demographic and clinical information for participants with SZ and HC is presented in [Table 1](#). SZ and HC groups were similar in mean age and ethnicity. Although SZ were significantly less educated than HC, education was not correlated with performance on either automatic or controlled social cognition ( $p$ 's > 0.29).

#### 3.2. The effects of oxytocin on automatic and controlled social cognition in individuals with and without schizophrenia

In our primary analysis, we found a significant Drug  $\times$  Task  $\times$  Group interaction,  $F(1, 58) = 8.75$ ,  $p = 0.004$ , Cohen's  $d = 0.78$  ([Fig. 1](#)). We also found a main effect for Group ( $F(1, 58) = 45.85$ ,  $p < 0.001$ ) reflecting the fact that patients with SZ showed worse performance overall compared to HC's on our tests of social cognition, but no significant main effect for Drug ( $F(1, 58) = 2.94$ ,  $p = 0.09$ ). To follow up on these

results, we then examined the effects of OT on automatic and controlled social cognition in separate models.

#### 3.2.1. Oxytocin effects on automatic and controlled social cognition

**3.2.1.1. Automatic social cognition.** For low-level, automatic social cognition, we found no significant Drug  $\times$  Group interactions for the composite score or for any of the five subscales ([Table 2](#)). Thus, OT does not impact automatic social cognition and does not have a differential effect for SZ and HC.

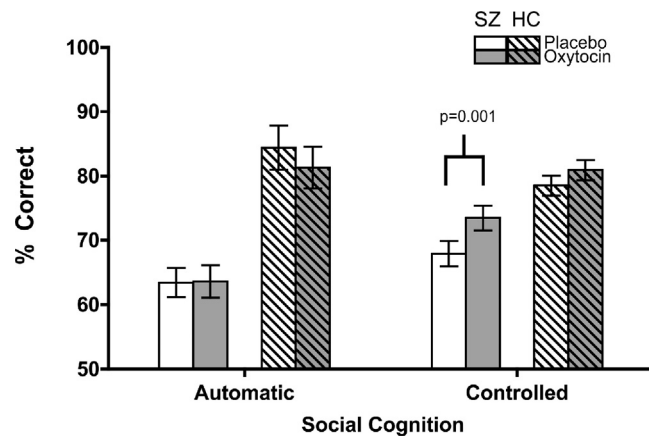
**3.2.1.2. Controlled social cognition.** For high-level, controlled social cognition, we found a significant Drug  $\times$  Group interaction ( $F(1, 58) = 8.55$ ,  $p = 0.005$ ) for the composite score. Thus, OT appears to have differential effects on controlled social cognition in SZ and HC. In follow-up analysis, we indeed found a significant Drug effect for SZ, ( $F(1, 28) = 12.39$ ,  $p = 0.001$ ), but not for HC, reflecting the fact that OT administration selectively improved performance on controlled social cognition in patients with SZ. In our secondary analyses, we found that OT significantly improved performance for SI-E "think" verbal,  $F(1, 28) = 7.16$ ,  $p = 0.01$  and "say",  $F(1, 28) = 7.64$ ,  $p = 0.01$  subscales in patients with SZ. In contrast, OT administration was only associated with a trend toward worse performance on the SI-E "feel" scale,  $F(1, 30) = 4.85$ ,  $p = 0.04$  and had no significant effect on any other subscale in HCs. This overall pattern of results remained the same when we adjusted for order of drug administration in our main analytic models.

#### 3.3. Control task

Groups did not significantly differ in performance on the control task ( $F(1, 59) = 0.04$ ,  $p = 0.85$ ) indicating that patients were capable of understanding literal, truthful remarks and were able to manage the various non-specific

**Table 1** Demographics and clinical information.

	Schizophrenia patients ( $N = 29$ )		Healthy controls ( $N = 31$ )		$p$ -Value
	Mean/ $N$	SD/%	Mean/ $N$	SD/%	
<b>Demographics</b>					
Age (years)	44.6	10.7	42.5	14.1	0.53
Range	23–61	–	20–64	–	–
Education Level	13.7	2.1	15.2	1.9	0.008
Race					0.24
Caucasian	8	27.6%	16	51.6%	
African American	7	24.1%	6	19.4%	
Latino/Hispanic	3	10.3%	4	12.9%	
Asian American	10	34.5%	5	16.1%	
Other	1	3.4%	0	0.0%	
<b>Clinical symptoms (<math>N = 19</math>)</b>					
Positive	16	4.1	–	–	–
Negative	15.9	5.2	–	–	–
General	31.4	9.5	–	–	–
<b>Medications equivalents</b>					
Cogentin	0.3	0.5	–	–	–
Chlorpromazine	312	319	–	–	–
Antidepressants	5	–	–	–	–



**Figure 1** Oxytocin and social cognition composite scores. *Notes:* SZ = schizophrenia patients, HC = healthy controls. Social cognition scores are in mean % correct for both composite scores (automatic, controlled) with standard error bars. SZ are significantly impaired on both automatic and controlled social cognition on both OT and PCB as compared to HC ( $F(1, 58) = 45.85, p < 0.001$ ). OT selectively improves controlled social cognition in patients with SZ (Drug  $\times$  Group  $\times$  Task interaction  $p = 0.004$ ).

requirements of TASIT such as following the dialog, remembering instructions, etc. We found no significant Drug  $\times$  Group interaction ( $F(1, 58) = 0.72, p = 0.40$ ) indicating that OT did not affect either group’s ability to understand literal, truthful remarks.

### 3.4. Manipulation checks

Our blinding procedure was adequate with groups not differing from chance in their guess of when they received OT (SZ: 65.2%,  $p = 0.26$ ;  $\chi = 4.62$ , HC: 37.0%,  $p = 0.28$ ;  $\chi = 3.38$ ).

**Table 2** Social cognition measures.

Tasks	Schizophrenia patients				Healthy controls				p-Value (Drug $\times$ Group)
	Placebo	Oxytocin	p-Value (drug)	Cohen’s d	Placebo	Oxytocin	p-Value (drug)	Cohen’s d	
	Mean(SD)	Mean(SD)			Mean(SD)	Mean(SD)			
Automatic social cognition	3.4(12.3)	63.6(13.7)	0.90	0.03	78.5(8.5)	80.9(8.7)	0.18	0.35	0.42
RMET total	64.7(12.5)	64.5(15.4)	0.92	0.03	72.9(10.1)	74.2(10.0)	0.42	0.21	
TASIT EET	63.8(17.5)	63.5(16.0)	0.93	0.02	78.1(10.3)	78.6(10.3)	0.84	0.05	
TASIT SI-M simple sarcasm	61.7(19.9)	62.9(21.6)	0.80	0.07	84.4(16.6)	90.0(13.9)	0.19	0.34	
Controlled social cognition	67.9(10.6)	73.5(10.2)	0.001*	0.93	84.9(9.9)	83.5(8.9)	0.43	0.20	0.005*
TASIT SI-E “think” items visual cues	71.1(19.2)	78.0(21.8)	0.14	0.40	88.7(11.8)	86.3(10.4)	0.47	0.19	
TASIT SI-E “think” items verbal cues	66.4(23.6)	75.9(11.5)	0.01*	0.85	85.5(13.3)	87.1(13.1)	0.56	0.15	
TASIT SI-E “do” items	67.7(13.5)	70.7(13.9)	0.33	0.26	82.1(15.5)	84.1(13.1)	0.56	0.15	
TASIT SI-E “feel” items	67.2(11.8)	72.8(12.4)	0.06	0.51	85.5(11.9)	79.6(13.4)	0.04	0.56	
TASIT SI-E “say” items	64.2(12.4)	71.6(12.0)	0.01*	0.73	79.6(13.4)	80.6(14.0)	0.74	0.09	
Control task	83.3(15.5)	85.0(15.1)	0.65	0.12	84.4(19.1)	81.3(18.0)	0.47	0.19	0.40

*Notes:* (B–Y adjusted  $\alpha$ ). Means refer to percent correct values. Drug  $\times$  Group  $\times$  Task interaction  $p = 0.004$  with effect size Cohen’s  $d = 0.78$ . \*  $p \leq 0.0184$ ,

Interestingly, patients with SZ did correctly guess which day they received OT more often than HC but this difference was not significant ( $\chi = 3.746$ ,  $p = 0.053$ ). The order of drug administration was not significantly different between groups ( $\chi = 0.545$ ,  $p = 0.46$ ) or from chance ( $\chi = 2.41$ ,  $p = 0.12$ ). We also conducted an Order  $\times$  Drug  $\times$  Task  $\times$  Group analysis and found that there was no significant interaction ( $F(1, 56) = 0.001$ ,  $p = 0.98$ ), indicating that order did not moderate our main finding. For the RMET, which used the same stimuli on both tests days, there were no order effects ( $p$ 's  $> 0.3$ ). No participant experienced any negative side effects.

## 4. Discussion

Our data indicate that a single dose of intranasal OT significantly improved higher-level, controlled, but not lower-level, automatic, social cognition in male individuals with SZ, but not in HC. Specifically, OT administration improved patients' performance on multiple sub-components of controlled social cognition, including the ability to represent others' verbalized opinions and to understand deceitful and sarcastic counterfactual verbal communication, but did not improve patients' rapid, automatic, social cognitive abilities, defined as the ability to read emotional states from the face, behavior, and tone of voice. Furthermore, OT had no effect on the performance of HC on any of these tasks, except for trends toward improving performance on the more challenging items of a test of recognition of mental states from faces, and worsening their performance on one sub-component of controlled social cognition. Overall, the findings for patients with SZ are clinically promising because emerging research indicates that high-level, controlled social cognitive abilities as measured by the same tasks used in the current study (i.e., SI-E) are associated with better quality of life and real-world social functioning (Horan et al., 2012; Mancuso et al., 2011), lower personal distress, and higher levels of engagement in recreational activities (Sparks et al., 2010) in patients with SZ. Our data highlight the potentially complex effects of OT on different aspects of social cognition, and support the exploration of intranasal OT as a potential adjunct treatment to improve controlled social cognition in SZ.

### 4.1. Social cognitive deficits in schizophrenia

Individuals with SZ in our sample were impaired on both automatic and controlled social cognition. In SZ, deficits in controlled social cognition, such as those measured by the SI-E, are separable and partially distinct from non-social cognitive deficits and are generally stable across the course of the illness (Green et al., 2012). Indeed, patients with recent-onset psychosis, unaffected family members, and individuals at ultra-high risk for developing psychosis (Bora and Pantelis, 2013), all have significant deficits in ToM, an important aspect of controlled social cognition, suggesting these deficits may be an endophenotype for SZ. Consistent with our findings, patients with prodromal, recent-onset, and chronic SZ are impaired at recognizing sarcasm (Kern et al., 2009) and white lies in the SI-E compared to age-matched controls (Green et al., 2012). Furthermore, deficits on these tasks

correlate with positive and negative symptoms (Green et al., 2012), show good 12-month test–retest reliability, and strongly predict occupational and social functioning (Fett et al., 2011) 12 months after assessment (Horan et al., 2012). Given our finding that OT administration improves performance on these tasks and the strong relationship between SI-E performance and functional outcomes, chronic OT administration may help to improve controlled social cognition and real-world social behavior of patients with SZ.

### 4.2. Potential mechanisms of oxytocin's effects

The specific neurocognitive mechanisms of OT's salutary effects in SZ are unknown. Non-mutually exclusive possibilities include the following. First, OT may improve patients' working memory for social stimuli (e.g., improving the ability to track the intentions of multiple actors simultaneously). In support of this hypothesis, OT receptor knockout mice show deficits in recognizing familiar mice that are reversed by OT infusion (Hammock and Young, 2006). Second, OT may increase patients' interest in social interactions to the point where they are more likely to remain cognitively engaged, even when complex social processing is required (i.e., increased social salience). Indeed, OT administration to humans has been found to modulate activity in reward-related brain regions (Strathearn et al., 2009). Third, OT may improve other non-social cognition that in turn supports patients' social cognitive abilities. As evidence, previous research indicates that OT administration to patients with SZ improves verbal memory (Feifel et al., 2012) and that OT administration to healthy individuals improves memory for negative social stimuli (Weigand et al., 2013). Consistent with this, our findings suggest that OT improved performance on social tasks requiring semantic processing and episodic memory (i.e., SI-E), but not on tasks that did not require such abilities (e.g., SSR and EET). Further research is necessary to elucidate the relative contributions of these separate mechanisms toward improving controlled social cognition in patients with SZ.

### 4.3. No effects of oxytocin on automatic social cognition in patients

It is not clear why OT administration had effects on controlled, but not automatic, social cognition in patients, particularly because previous studies have found positive effects of OT administration on various aspects of social cognition, including automatic processes such as affect recognition (Averbeck et al., 2011; Fischer-Shofty et al., 2013b; Goldman et al., 2011), in patients with SZ (Pedersen et al., 2011). However, consistent with our findings, a recent, small, single-dose study, found that OT administration to patients with SZ improved a composite score of high-level social cognition including the sarcasm items from the SI-E but not a composite score of low-level social cognition including the white lies items of the SI-E (Davis et al., 2013). These discrepant results may be explained by previous studies including both male and female patients, using different dosages of OT, and not excluding patients on mood stabilizers. Furthermore, several prior studies did not make the distinction between automatic and controlled social

cognition, which may be an important distinction based on the work of [Davis et al. \(2013\)](#) and the present findings.

It is also not clear why OT administration had limited effects in the healthy comparison participants. The lack of effect was not due to ceiling effects in either automatic or controlled social cognition tasks. The current study did replicate the finding that OT administration improves healthy individual's performance on the hard items of the RMET (see [Supplementary material](#)) ([Domes et al., 2007](#)), which is an important positive control as it demonstrates that our healthy participants showed a meaningful response to OT administration, consistent with the extant literature. One factor that may explain the lack of effect on other aspects of social cognition is dosage; we used 40 IU, while most prior studies in healthy individuals use lower doses of 20 or 24 IU. At high concentrations, OT can bind to vasopressin receptors ([Manning et al., 2012](#)). Thus, the higher concentrations of OT used in the current study may have activated both OT and vasopressin receptors, which could result in competing effects. In contrast, while patients with SZ do not have low levels of endogenous OT as a group, OT levels do correlate with social cognition and negative symptoms with the most impaired individuals having the lowest OT concentrations ([Rubin et al., 2011](#); [Sasayama et al., 2012](#)). Therefore, the higher dose used in the current study may have specifically helped patients with low levels of OT.

OT also modulates GABAergic, glutamatergic, and dopaminergic function ([Rosenfeld et al., 2011](#)). Thus, OT administration may have specific therapeutic effects through these systems in patients with SZ who have altered functioning of these systems due to their illness and its treatment, but not in healthy subjects who presumably have normal functioning of these systems. For example, antipsychotic dosage negatively correlates with social cognition in SZ ([Kucharska-Pietura and Mortimer, 2013](#)); if OT administration remediates antipsychotic-induced deficits in social cognition, OT effects would only be seen in patients with SZ. Additionally, the impact of OT on social cognition shows variation in healthy individuals depending on attachment style, personality traits, and baseline social skills ([Bartz et al., 2011](#)). For example, individuals with worse baseline social skills improve the most on empathic accuracy after OT administration ([Bartz et al., 2011](#)). In our sample, greater attachment avoidance was associated with higher OT-induced improvements in automatic social cognition in patients with SZ (see [Supplementary materials](#)). Finally, unaccounted for heterogeneity of SZ may explain some of the discrepant results as a previous study found that intranasal OT reversed facial affect discrimination deficits in SZ patients with, but not those without, polydipsia ([Goldman et al., 2011](#)). Future studies determining dose–response relationships and trait and state moderators of OT's effects in both clinical and non-clinical populations are now needed.

#### 4.4. Limitations

The current study has several limitations. First, our findings are only applicable to males and may not generalize to females. Second, we did not collect information that would better characterize the patients (e.g., number of years ill, hospitalizations, IQ, or whether patients with schizoaffective

disorder had the bipolar or depressed subtype). This limits our analysis and our ability to compare our findings to other studies. Third, only a single dose of OT was administered. Given that the short-term effects of some psychotropic agents can be very different from their chronic effects (e.g., short-term anxiogenesis from selective serotonin reuptake inhibitors versus their long-term anxiolytic effects ([Kent et al., 1998](#))), the implications of our findings must be interpreted with caution. Fourth, the sample size of the current study is modest, limiting the conclusiveness and generalizability of our findings. While we were adequately powered to detect medium effect-sizes, our ability to detect small effect sizes was limited. Fifth, the effects of OT on mood were not assessed and OT-induced changes in mood could conceivably account for some of the current findings. However, numerous previous studies failed to find significant effects of a single dose of OT on mood states in healthy individuals or patients with SZ ([Macdonald and Macdonald, 2010](#)). Finally, we did not measure relationship status, which has been shown to influence the OT system ([Grewen, 2005](#)), non-social cognition, or IQ. While several previous reviews and meta-analyses suggest that cognitive deficits and IQ cannot entirely explain the social cognitive impairment in SZ ([Harrington et al., 2005](#)), other meta-analyses have found that IQ, particularly in remitted patients with SZ such as those included in the current study, correlates with social cognitive abilities ([Bora et al., 2009](#)). Indeed, some authors have proposed that working memory deficits or IQ ([Bora et al., 2009](#)) could completely explain the social cognitive deficits of SZ. However, TASIT performance has been found to be impaired in remitted patients with SZ after controlling for IQ ([Sparks et al., 2010](#)). As the current study was designed with the goal of determining if OT could improve social cognitive abilities, it was underpowered to further test potential cognitive mediators of these effects. Thus we remain agnostic as to whether the social deficits or OT effects we observed could be entirely explained by cognitive factors. Future studies should examine if OT-induced improvements in higher-level, controlled social cognition are mediated by improvements in aspects of non-social cognition such as working memory.

## 5. Conclusions

We found that a single-dose of intranasal OT selectively improved multiple aspects of controlled social cognition, but not automatic social cognition, in patients with SZ. In contrast, OT had limited effects on social cognition in HC. Controlled social cognitive abilities strongly predict functional outcomes in individuals with SZ, and thus far have only been improved by often resource-intensive psychosocial rehabilitation programs ([Eack et al., 2007](#)). Our findings suggest that these complex functions may also be amenable to pharmacologic intervention with intranasal OT, and further indicate that future clinical trials of OT should assess controlled social cognition in addition to traditional clinical outcomes. Finally, our data raise a number of interesting questions for future research on the neurocognitive systems that support automatic versus controlled social cognitive functions in SZ and their malleability in response to a single dose of an endogenous neuropeptide.



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## Conflict of interest

Dan Mathalon is a consultant to Bristol Myers Squibb Inc. Sophia Vinogradov is a consultant to Brain Plasticity Institute. The remaining authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psychneuen.2014.04.024>.

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