Journal of Psychiatric Research 112 (2019) 38–43

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Endogenous oxytocin levels are associated with impaired social cognition and neurocognition in schizophrenia

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ARTICLE INFO

Keywords:
Oxytocin
Cognition
Social cognition
Psychosis

ABSTRACT

Intranasal administration of the neuropeptide oxytocin (OT) has yielded inconsistent effects on social cognition and general cognition in individuals with schizophrenia (SZ). Few studies have examined whether endogenous peripheral OT levels are also associated with social and general cognition in SZ. The current study examined whether plasma OT levels are associated with performance on a higher-order social cognition measure (i.e., a task that requires inferential processes and knowledge not directly presented in social stimuli), as well as domains of general cognition. Participants included 30 individuals with SZ and 21 demographically matched healthy controls (CN). The MATRICS Consensus Cognitive Battery was administered to assess neuropsychological impairment in relation to 7 domains (processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition). Plasma OT levels were measured via radioimmunoassay. SZ had significantly lower endogenous OT levels and poorer MCCB performance on all 7 domains than CN. In CN and SZ, lower endogenous OT was associated with poorer social cognition. In SZ, lower endogenous OT was also associated with poorer processing speed and working memory. The significant association between OT and social cognition in both CN and SZ highlights the importance of endogenous OT levels as a biological predictor of social cognition, irrespective of clinical status. Significant associations between plasma OT and general neurocognition may reflect either an anxiolytic effect of plasma OT that results in better neurocognitive performance, or OT's action on dopamine and enhancement of dopamine tone that results in improved cognition.

1. Introduction

Individuals with schizophrenia (SZ) display impairments in multiple aspects of social cognition (Green and Leitman, 2008; Pinkham et al., 2003) that predict poor community-based functional outcomes (Couture et al., 2006; Horan et al., 2012; Mancuso et al., 2011). Unfortunately, attempts to treat impairments in social cognition have been only moderately effective (Horan et al., 2009; Penn et al., 2000, 2007), suggesting that new approaches are needed).

In recent years, oxytocin (OT) has received increased attention as a potential pharmacological treatment for social cognition deficits in SZ. OT is a neuropeptide that is endogenously produced in the hypothalamus and released into peripheral circulation and the central nervous system where it binds to receptors in brain areas integral for social cognition (Churchland and Winkielman, 2012). In psychiatrically healthy individuals, OT has been shown to enhance several domains of social cognition (e.g., facial emotion perception, empathy) (Guastella and MacLeod, 2012). There is also evidence for positive effects of OT on social cognition and symptoms in psychiatric disorders, including social anxiety disorder (Guastella et al., 2009), autism (Guastella and MacLeod, 2012; Keech et al., 2018), and depression (McQuaid et al., 2014). Intranasal administration of OT has produced inconsistent effects on social cognition in SZ (Bürkner et al., 2017). These apparent inconsistencies can be partially resolved when one evaluates the tasks used in prior social cognition studies based on whether they measure "higher-order" (i.e., tasks requiring inferential processes that incorporates knowledge not directly present in the stimuli) or lower-level (i.e., tasks requiring minimal inferential processes beyond what is directly presented in the stimulus) social cognition dimensions (see Mancuso et al., 2011 for the original distinction made between these

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https://doi.org/10.1016/j.jpsychires.2019.02.017
Received 14 June 2018; Received in revised form 15 February 2019; Accepted 21 February 2019

Table 1
Demographics, OT levels, and MCCB scores.

	SZ (n = 30)	CN (n = 21)	Test statistic, p-value
Age	46.67 (8.86)	42.57 (9.29)	$F = 2.53$, $p = 0.12$
Participant Education	12.73 (2.18)	15.10 (1.89)	$F = 16.10$, $p < 0.001$
Parental Education	13.22 (2.34)	14.38 (2.45)	$F = 2.94$, $p = 0.09$
% Male	73.3%	61.9%	$\chi^2 = 0.75$, $p = 0.54$
Ethnicity			$\chi^2 = 3.39$, $p = 0.34$
Caucasian	76.7%	95.2%	
African American	16.7%	4.8%	
American Indian	3.3%	0%	
Mixed-Race	3.3%	0%	
OT (pgml)	9.93 (5.06)	16.64 (7.08)	$F = 15.63$, $p < 0.001$
MCCB Performance			
Processing speed	35.00 (10.97)	55.90 (8.99)	$F = 51.26$, $p < 0.001$
Attention/Vigilance	37.79 (13.35)	56.43 (6.08)	$F = 35.46$, $p < 0.001$
Working memory	38.86 (9.89)	55.62 (8.14)	$F = 40.37$, $p < 0.001$
Verbal learning	38.38 (10.77)	57.48 (9.65)	$F = 41.72$, $p < 0.001$
Visual learning	33.52 (14.37)	48.52 (11.10)	$F = 15.97$, $p < 0.001$
Reasoning/Problem solving	43.14 (10.69)	52.86 (9.84)	$F = 10.75$, $p < 0.01$
Social cognition	33.03 (12.56)	54.62 (10.04)	$F = 42.35$, $p < 0.001$

Note. Mean (SD); SZ = schizophrenia group; CN = control group; OT = endogenous oxytocin level; MCCB = MATRICS Consensus Cognitive Battery.

factors). As highlighted in the meta-analysis by Bürkner et al. (2017), there is evidence for a positive effect of OT on “higher-order" social cognition (Davis et al., 2013; Fischer-Shofty et al., 2013; Guastella et al., 2015; Woolley et al., 2017, 2014), but not “lower-level" social cognition in SZ (Brambilla et al., 2016; Davis et al., 2013; Gibson et al., 2014; Goldman et al., 2011; Guastella et al., 2015; Horta de Macedo et al., 2014; Shin et al., 2015; Woolley et al., 2014, 2017).

OT has inconsistently been associated with effects on several domains of general cognition in SZ. For example, Feifel et al. (2012) found significant improvement from OT on short-term verbal memory and long-term verbal memory, but not working memory. Michalopoulou et al. (2015) found no effect on processing speed, but did find an effect on the executive component of working memory. Cacciotti-Saija et al. (2015) and Guastella et al. (2015) evaluated other aspects of general cognition (e.g., immediate memory, language, attention, visuospatial construction, delayed memory) and found no benefits of OT. Beneficial effects of OT on general cognition have not been observed in the general population, for which OT has an impairing effect on memory (Bruins et al., 1992).

Few studies have examined whether individuals with SZ have abnormalities in endogenous OT levels and whether these levels are associated with performance on social cognition tasks. Studies evaluating endogenous OT levels in cerebrospinal fluid and plasma have produced inconsistent results, with some evidence for lower endogenous OT levels in polydipsic participants with SZ (Goldman et al., 2008, 2011), higher OT levels in people with SZ in other studies (Beckmann et al., 1985;Strauss et al., 2015a; 2015b, 2015c), and no group differences in the majority of studies (Rubin et al., 2014, 2013, 2011, 2010). Despite these inconsistencies in mean group differences, lower endogenous OT levels have fairly consistently been associated with greater symptom severity (positive and negative) (Rubin et al., 2010, 2011, 2015, 2017; Sasayama et al., 2012; Strauss et al., 2015a; Walss-Bass et al., 2013; however, see Rubin et al., 2013, 2014) and poorer performance on tasks measuring higher-order and lower-level social cognition (e.g., social cue perception, facial affect perception, identification of emotional body gestures, hedonic judgments) (Goldman et al., 2008; Rubin et al., 2011; Strauss et al., 2015a; 2015b, 2015c). Associations between peripheral OT and social cognition may be particularly strong among females with SZ (Rubin et al., 2011; Strauss et al., 2015c). It is unclear whether lower endogenous OT is also associated with poor general cognition in SZ. One study found that OT was associated with verbal memory and semantic fluency (Rubin et al., 2015), whereas another found OT associations with delayed memory and language (Rubin et al., 2017). Notably, these papers found associations with similar cognitive domains, but in different directions, which may be due to one study focusing on premenopausal women and the other on peri/post-menopausal women.

Understanding the association between endogenous OT levels and performance on tests of social and general cognition has important implications for clinical trials administering exogenous OT, as it may lead to better understanding of issues related to dosing and individual differences in responsiveness to OT administration (Bradley and Woolley, 2017). The current study examined whether plasma OT levels differentially associated with performance on measures of general neurocognitive functioning and a measure of higher-level social cognition in SZ and CN groups. It was hypothesized that: 1) SZ and CN groups would not differ in plasma OT levels; 2) lower endogenous OT would be associated with poorer performance on measures of social cognition and general cognition in participants with SZ and CN.

2. Methods

2.1. Participants

Participants included 30 individuals meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for schizophrenia or schizoaffective disorder and 21 healthy controls. Participants with schizophrenia (SZ) were recruited from the outpatient research program at the Maryland Psychiatric Research Center and evaluated during periods of clinical stability. Consensus diagnosis was established via a best-estimate approach based on psychiatric history and multiple interviews and subsequently confirmed using the Structured Clinical Interview for DSM-IV (SCID: First et al., 2002). All participants in the SZ group were clinically stable, as indicated by no change in antipsychotic type or dosage for a period of four weeks or longer.

Control (CN) participants were recruited through random-digit dialing and word of mouth among enrolled participants. All CN underwent a structured diagnostic interview, including the SCID-I and SCID-II (Pfohl et al., 1997) and did not meet criteria for any current Axis I or II disorder or lifetime criteria for a psychotic disorder. CN also had no family history of psychosis.

No participants met criteria for substance dependence in the last 6 months and all denied lifetime history of neurological disorders associated with cognitive impairment (e.g. Traumatic Brain Injury, Epilepsy). Lack of substance use in the week prior to the study was

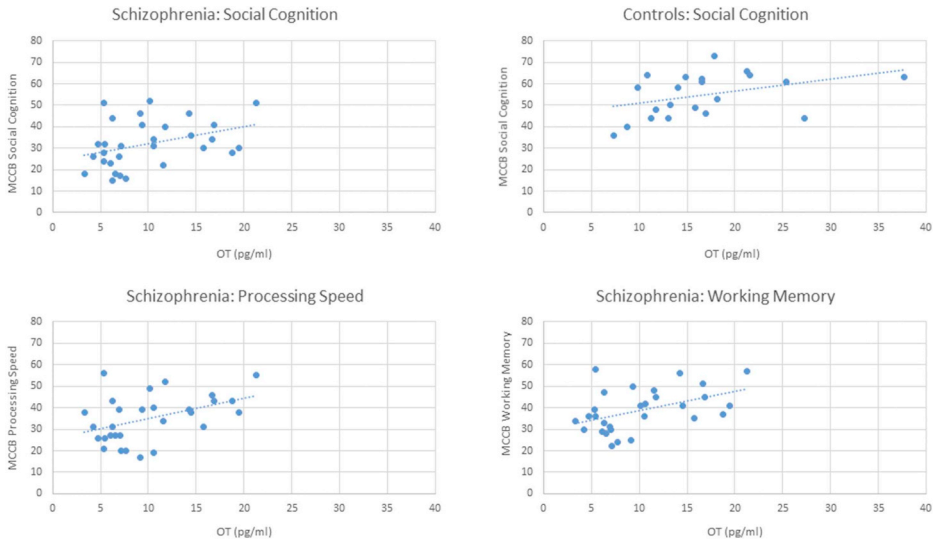

Fig. 1. Scatterplot of correlations in SZ and CN groups.

confirmed by urine toxicology. Female participants completed a pregnancy screen, as this can affect OT levels; no participants were pregnant.

Individuals with SZ and CN did not significantly differ in age, parental education, sex, or ethnicity. People with SZ had lower personal education than controls (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 were rated on the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011; Strauss et al., 2012a; 2012b), Brief Psychiatric Rating Scale (BPRS: Overall and Gorham, 1962), and Level of Function Scale (LOF: Hawk et al., 1975).

The MATRICS Consensus Cognitive Battery (MCCB: Nuechterlein et al., 2008) was administered to assess neuropsychological impairment in relation to 7 domains: processing speed (BACS Symbol Coding, category Fluency, Trail Making Test Part A), attention/vigilance (Continuous Performance Test-Identical Pairs), working memory (Spatial Span, Letter Number Span), verbal learning (Hopkins Verbal learning Test), visual learning (Brief Visuospatial Memory Test), reasoning/problem solving (NAB Mazes), and social cognition (MSCEIT Managing Emotions). The social cognition test (MSCEIT Managing Emotions subtest) requires participants to rate the effectiveness of alternative actions in achieving a result in situations where a person must regulate their emotions. This task is considered a measure of higher-order social cognition because it requires participants to make inferences about the mental states of others using knowledge that is not directly presented within the stimuli/items on the test.

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

2.3. Data analysis

One-way ANOVA examined group differences in plasma OT levels. MANOVA was used to evaluate group differences in the 7 MCCB domain scores. Pearson correlations were used to evaluate associations between plasma OT levels and the 7 MCCB domain scores in each group.

3. Results

SZ had significantly lower plasma OT levels than CN and demonstrated greater impairment than CN on all 7 MCCB domains (see Table 1).

In CN and SZ, lower OT levels were associated with poorer social cognition (see Fig. 1. In CN, the correlation with social cognition held when the one control with very high OT levels was excluded ($r = 0.44$, $p = 0.044$). In SZ, lower OT was also associated with poorer processing speed and working memory. Correlations between OT and other MCCB domains were nonsignificant (see Table 2). All of these correlations remained significant after applying the Benjamini and Hochberg (1995) correction for multiple comparisons (0.25 false discovery rate). Chlorpromazine equivalent dosage was not significantly associated with OT levels or MCCB performance in SZ.[1]

4. Discussion

The current study examined group differences in endogenous OT levels between SZ and CN groups, as well as associations between endogenous OT and measures of social cognition and general cognition in SZ. Contrary to hypotheses, SZ had lower endogenous OT than CN. These findings are consistent with a minority of studies indicating lower endogenous OT in SZ (Goldman et al., 2008, 2011), but contrary to several other studies reporting either higher OT levels in people with SZ (Beckmann et al., 1985; Strauss et al., 2015a; 2015b, 2015c), or no group differences (Rubin et al., 2010, 2011, 2013, 2014). Notably, we found the opposite results of our prior 3 studies (Strauss et al., 2015a; 2015b. 2015c), which used the same assay and were collected at similar time points and stored at similar temperatures. This may suggest that

[1] In males with SZ ($n = 22$), results indicated that OT was positively associated with processing speed ($r = 0.44$, $p = 0.041$), working memory ($r = 0.48$, $p = 0.023$), and social cognition ($r = 0.44$, $p = 0.041$). In females with SZ ($n = 8$), OT was not significantly correlated with MCCB scores, which was influenced by limited power. In male CNs ($n = 13$), OT was not significantly associated with MCCB domains. In female CN ($n = 8$), OT was significantly associated with processing speed ($r = 0.75$, $p = 0.031$), Reasoning and Problem Solving ($r = 0.75$, $p = 0.033$).

Table 2
Associations between MCCB and Endogenous OT in SZ and CN groups.

	SZ (n = 30)	CN (n = 21)
Processing speed	0.40*	−0.01
Attention/Vigilance	0.16	0.36
Working memory	0.43*	0.14
Verbal learning	0.07	0.08
Visual learning	−0.01	0.10
Reasoning/Problem solving	−0.01	0.22
Social cognition	0.37*	0.47*
Total Score	0.23	0.38

Note. *p < 0.05; SZ = schizophrenia group; CN = control group.

inconsistency in the literature does not primarily reflect assay related variables, but rather demographic (e.g., age, sex) or clinical factors (e.g., individual differences in symptoms, antipsychotics, percentage of polydipsic patients). Studies with large samples are needed to protect against false negative or false positive results. A meta-analysis could also shed light on the relative balance of group differences among all studies published and determine potential moderators.

Consistent with hypotheses and prior studies, lower endogenous OT was associated with poorer social cognition in SZ. This effect was also observed in CN, highlighting the importance of individual differences in endogenous OT levels as a biological predictor of social cognition, irrespective of clinical status. Our results extend prior studies, which have found an association between lower OT and performance on lower-level social cognition tasks (Goldman et al., 2008; Rubin et al., 2011; Strauss et al., 2015a; 2015b, 2015c) by finding an association with higher-order social cognition on a task that requires inferential processes and knowledge not directly presented in social stimuli. Given that endogenous OT is significantly associated with measures of higher-order and lower-level social cognition in SZ, one might expect that augmenting OT levels via exogenous administration might enhance performance on these domains. However, intranasal administration of OT appears to predominantly benefit higher-order, but not lower-level social cognition (Bürkner et al., 2017). It is possible that dosing, pharmacodynamics, and OT receptor density may play a role in determining whether differential OT effects are observed on these domains (Bürkner et al., 2017); additional studies are needed that directly manipulate these variables, while concurrently testing whether endogenous OT moderates treatment response.

A second major finding was the association between lower endogenous OT and poorer processing speed and working memory in participants with SZ. This positive correlation is consistent with results of Rubin et al. (2015), but opposite of Rubin et al. (2017) who found a negative correlation between cognition and endogenous OT. Exogenously administered OT has also been found to enhance verbal learning/memory (Feifel et al., 2012) and working memory (Michalopoulou et al., 2015) in SZ. Beneficial effects on social and general cognition may reflect a broad distribution of OT receptors in areas such as the amygdala, medial prefrontal cortex, anterior cingulate, and insula that are activated when participants perform both types of cognitive tasks (Adolphs, 2009; Bethlehem et al., 2013). OT seems to contribute to the maturation of hippocampal circuits, selective GABA excitation, and long-term potentiation in the medial prefrontal cortex in animal models (Chini et al., 2014), suggesting that it may have specific inhibitory and excitatory roles in learning and memory.

These findings also have important implications for studies administering exogenous OT as a treatment for social cognitive deficits in SZ. Future acute challenge and multi-dose clinical trials should measure endogenous OT levels and determine whether endogenous OT moderates treatment response. One study suggested that individual differences in endogenous OT did not explain changes in symptoms in a multi-dose study (Lee et al., 2016); however, social cognition was not evaluated (however see Parker et al., 2017 for evidence that baseline OT levels predict response to intranasal OT in autism). It is possible that endogenous OT levels could serve as a biomarker for study inclusion criteria, with only participants falling below a certain level of endogenous OT entered into clinical trials, analogous to what is commonly done in studies with symptom entry criteria. Furthermore, given that a past study (Goldman et al., 2011) showed dose-dependent effects of OT in polydipsic participants with SZ who have ultra-low levels of endogenous OT, it may be important for future trials to tailor dosing to endogenous OT or OT receptor density.

Certain limitations should be considered. First, the sample size was too small to permit examination of sex-specific correlations (see footnote 1). Our sample had a preponderance of males. Given that prior studies have indicated stronger associations between OT and social cognition in women than men, our sample may not have been ideal for optimally testing the sex-driven OT effects (Rubin et al., 2011, 2015; 2017; Strauss et al., 2015c). Second, although chlorpromazine equivalent dosage was not significantly correlated with OT levels or MCCB performance, the lack of significant associations does not rule out a potential effect of antipsychotics on OT levels. Chlorpromazine equivalents are a gross measure that may lack the sensitivity needed to detect antipsychotic effects. Antipsychotics are known to suppress secretion of OT, potentially due to effects on prolactin release (Sirzen-Zelenskaya et al., 2011), and patients with lower OT levels respond more poorly to antipsychotics and thus require higher doses (Sasayama et al., 2012). It is therefore possible that antipsychotics have an unexpected mediating or moderating effect on the associations reported in the current study, but these cannot be detected due to insensitivity of dose-equivalent metrics. Third, individuals with SZ are more likely to smoke than CN (Goff et al., 1992), and smoking may affect endogenous OT levels (Napierala et al., 2017). Smoking status was not recorded to test this possibility. Fourth, although no subjects met criteria for current substance use disorders in the past 6 months, substance use on day of testing was not measured and therefore may have unknowingly influenced results. Fifth, the MCCB tasks are purely behavioral measures and neural correlates cannot be reasonably inferred. Sixth, a single measure of social cognition was used and conclusions are restricted to the content covered by the MSCEIT subtests in the MCCB. Seventh, plasma OT levels reflect peripheral, rather than central nervous system concentrations and the extent to which correlations are influenced by central vs. peripheral nervous system function is unclear. Finally, OT receptor density was not measured and the relationship between receptor sensitivity and circulating OT levels is unclear.

Conflicts of interest

The authors have no conflicts of interest relevant to the current manuscript.

Acknowledgements

This research is supported in part by the US National Institute of Mental Health Grant P50-MH082999 (WT Carpenter) and a U.S. Department of Veterans Affairs Mental Illness Research Education Clinical Centers VISN 5 pilot grant (GP Strauss).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.017.

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