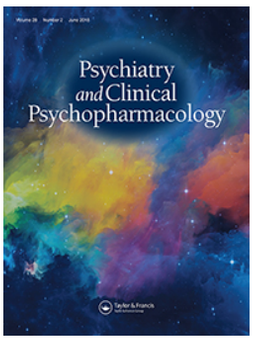

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Oxytocin and social cognition in patients with schizophrenia: comparison with healthy siblings and healthy controls

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ABSTRACT

Objective: There is substantial evidence from animal research indicating a key role of the neuropeptide oxytocin (OT) in the regulation of complex social cognition and behaviour. Social cognition is indispensable for social relationships for the whole of human society, and numerous studies have shown impaired social cognition in schizophrenia (SCH) and unaffected first-degree relatives also seem to be impaired, albeit to a lesser extent. Because of that, this study focuses on the role of OT in social cognition in SCH.

Methods: Twenty-seven patients with SCH, 27 healthy siblings (HS) of these patients, and 27 psychologically healthy controls (HC) were included in the study. Blood samples were collected through a peripheral venous catheter. Differences in the socio-demographical and WAIS-R were tested by chi-square and one way-ANOVA. To explore the relationships between social cognition and blood samples we performed Pearson correlations. MANCOVA (gender and WAIS-R as covariates) test was performed to investigate the effect of gender on blood levels of OT and WAIS-R on social cognition.

Results: Significant differences were found in neurocognitive and social cognitive capacity but not in OT levels. In the healthy control group, there was a positive correlation between blood OT levels and RMET. There is a statistically significant difference between high and low OT groups with regard to social cognition in all subtests of the RMET.

Conclusions: In the current study, we found that patients had deficits in social cognition and neurocognition. Lower endogenous OT levels are also predictive for poor social cognitive functioning in HS and HC.

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Oxytocin; schizophrenia; social cognition

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 behaviour [1] and these operations tend to be distinct from non-social cognition [2]. Unfortunately, while current antipsychotic medications are effective at ameliorating the positive symptoms, they are not very effective at treating the negative symptoms and cognitive dysfunction associated with schizophrenia (SCH), which tend to be more pervasive and persistent [3–5].

Several neurotransmitter and neuropeptide systems, in addition to dopamine, such as NMDA, GABA, and serotonin, have been implicated on the symptomatology of SCH [6–8]. Oxytocin (OT) is a neuropeptide that interacts with several of the aforementioned neurotransmitter and neuropeptide systems.

Since Bujanow raised the question whether OT might have antipsychotic properties in 1974 [9], a large number of studies have been conducted to explore the role of OT in SCH. Initial studies suggested enhanced concentrations of OT [10] and neurophysin II, the hypothalamic–pituitary carrier of OT [11,12], in patients with SCH compared to healthy controls (HC), whereas a follow-up study did not confirm these results [13]. The empirical evidence of neuropeptidergic functioning in SCH is limited and controversial, although recent studies in humans and animals suggest impairments of OT metabolism in SCH that might be related to impaired social cognitive functioning. Therefore, the subsequent studies have focused on the relationship between social cognition and OT in patients with SCH. For instance, Goldman and colleagues showed that blunted OT levels in SCH were associated with low performance in a facial affect rating task [14]. Another study investigating the effect of a trust-related interaction on peripheral OT levels revealed that patients with SCH lacked the interaction-induced increase in peripheral OT observed in HC [15].

A recent study found large effects of the administration of intranasal OT on high-level social cognition in patients with SCH and partially replicated previous

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findings in healthy individuals [16]. This particular effect of the administration of intranasal OT on high-level social cognition in SCH has been found independently by other groups [17] and remains significant after doubling sample size [18]. A recent study found that increases in key paternal parenting behaviours (e.g. touch, social gaze, social reciprocity) were paralleled by increases in infants' engagement behaviours (e.g. social gaze, exploration, social reciprocity) and peripheral OT levels, suggesting possible translational implications for an indirect neuropeptide treatment of infants at risk for social dysfunctions, such as siblings of children with autism spectrum disorders [19]. Lerer et al. performed family-based association test on all 18 identified single nucleotide polymorphisms within the OT receptor gene region in Israeli participants with autism spectrum disorders and their parents and unaffected siblings [20]. These data from autism spectrum disorders have led us to think that OT can be an endophenotype of social cognition. Therefore, we also included the healthy siblings (HS) of the patients with SCH in this study.

In the current study, we hypothesized that: (1) patients with SCH would have a deficit relative to their HS and a control group on social cognition; (2) patients with SCH would have a lower blood level of OT relative to their HS and a control group; and (3) there is a correlation between blood OT levels and social cognition. To examine these hypotheses, a group of patients with SCH was compared with their HS and a control group on a social cognition and neurocognition task. Then we compared the OT levels of three groups. After that we investigated the correlation between blood levels and social cognition. To examine this hypothesis, we carried out two analyses. Firstly, we correlated social cognition and blood levels of OT. Then we dichotomized the plasma OT levels using the group median: low and high OT groups. Lastly, we examined the differences of these groups in terms of social cognition.

Method

Participants

Twenty-seven patients with SCH (8 women and 19 men), ranging in age from 21 to 47 years (mean = 29.85, S.D. = 7.39), 27 HS of these patients (16 women and 11 men), ranging in age from 18 to 50 years (mean = 31.85, S.D. = 9.23), and 27 psychologically HC (15 women and 12 men), ranging from 18 to 48 years of age (mean = 30.59, S.D. = 6.97) were included in the study. Only patients with a verified DSM-IV diagnosis of SCH participated in the study. Diagnosis was confirmed by medical records and a psychiatrist using the Structured Clinical Interview for DSM-IV-Patient Edition [21]. Participants were outpatients who were being treated by the psychiatric unit of Celal Bayar University. Inclusion criteria included clinical stability as defined by no change in medication dosage in the past three months, and no hospitalization in the past six months before recruitment for the study. All of the patients with SCH received a second-generation antipsychotic medication. Mean chlorpromazine equivalent dosages (CPZ) were 604.62 ± 308.30 mg per day. For both groups, exclusion criteria were substance use disorder, intellectual disability, dementia, and being older than 65 years of age (in order to avoid possible confounders of cognitive deficits due to aging), use of hormone treatments, being in the menstruation period and hospitalization and pregnancy/lactation within the last year. The healthy control group and the HS group consisted of 27 persons each who did not have any psychiatric diagnosis (based on self-report and clinical interview done by an experienced psychiatrist).The current use medication for the chronic systemic disease, autonomic nervous and cardiovascular system, current clinical depression or other psychiatric disorder that could effect the levels of social cognition and blood OT level was the additional exclusion criteria for the HC and HS. All participants provided written informed consent. The study was approved by the local Institutional Review Board.

Instruments

Clinical measures

The patients with SCH were assessed by a clinical psychiatrist with validated clinical tests suitable for the severity of specific symptoms. The Positive and Negative Syndrome Scale (PANSS) is a 30-item scale developed to assess symptom severity in SCH [22]. The PANSS was designed to include three subscales for different types of symptoms: positive symptoms, negative symptoms, and general psychopathology. Higher scores indicate higher symptoms severity and impairment.

Wisconsin Card Sorting Test

This has often been cited as the most frequently used measure of executive functioning [23–26] and is regularly used by over 70% of neuropsychologists [27]. The Wisconsin Card Sorting Test (WCST) consists of 4 "Cards" shown on the computer screen were distinguished by the form of the objects (triangles, stars, crosses, and circles), the number of objects (from one to four), and the patterns inside the objects (solid, blank, dotted, and stippled). The participant selected a target card that matched a given trial card according to one feature. Feedback was given on the screen, and the next trial card was presented. After the participant correctly matched the cards in 10 consecutive trials (a "category"), the critical feature ("rule") changed

without warning or notification to the participant and the process was continued. The standard consisted of matching 128 trial cards or completing 6 categories, whichever came first. Three variables were used to measure performance at each level. "Categories achieved" was the number of times a participant correctly responded 10 times in a row. "Perseverative errors" was the number of total responses that would have been correct at a previous time in the test but were not correct at the time the participant made the response. "Number correct" was the total number of correct responses that occurred in runs; this variable is correlated with IQ.

Wechsler Adult Intelligence Scale-Revised Vocabulary Subtest

This is an intelligence test for individuals between the ages of 16 and 90. The consistency is high and the test–retest reliabilities are between 0.70 (7 subscales) and 0.90 (2 subscales). The Inter-scorer coefficients are also high, all greater than 0.90 [28]. The test is structured into four scales, which consist of multiple subsets: Verbal Comprehension (similarities, vocabulary, information, comprehension), Perceptual Reasoning (block design, matrix reasoning, visual puzzles, Picture completion, figüre weights), Working Memory (digit span, arithmetic, letter-number sequencing), and Processing Speed (symbol search, coding, cancellation). We used only the Vocabulary subtest as it is often used as a Proxy measure of intelligence [29]. This exam consisted of 35 words that request a definition. Points are awarded based on how close the participant's definition is the definition that is predetermined on a scale of 0–2 [28]: 0 being obviously incorrect, 1 being incorrect but showing some knowledge of content, and 2 showing the understanding of proper synonym and use. Scores on this test range from 0 to 70.

"Reading the Mind from the Eyes" Test Turkish version

To assess social cognitive ability the "Reading the Mind from the Eyes" Test (RMET) is used. The revised version of the Eyes Test is an advanced theory of mind task in which 36 photographs depicting only the eye region of the face are presented along with 4 complex mental state words [30]. Participants are asked to identify which Word best describes the thought or feeling expressed in the photograph. Half of the photos depict females and half depict males, and all involve complex cognitive and emotional states. A glossary of words was provided in the case that participants were unaware of the meaning of words. Scoring consisted of tallying the number of correct responses. The Turkish version's validity and reliability studies made by Yildirim and consists of 32 items [29].The Eyes Test has enjoyed wide use and has demonstrated reduced test performance in patients with SCH [30]. All in all, findings from this widely used test show it to be sensitive for detecting specific Theory of Mind impairments in populations that have been found to have deficits in other Theory of Mind tests [31]. Because the RMET was originally developed to measure severe impairments in mind reading capability in adults with autism spectrum disorders, we circumvented possible ceiling effects in healthy participants by dividing the 32 items into two subsets of easy and difficult items. These subsets were generated based on the median of item difficulty derived from the value of healthy control group's data.

Assessment of blood samples

Blood samples were collected through a peripheral venous catheter only. To measure basal OT levels, five cubic centimetres of blood was collected before the beginning of the experiment to EDTA tubes containing the polypeptide aprotinin (EDTA-Aprotinin Tubes, Greiner Bio-One GmbH, Germany) and centrifuged at 4°C at 4000 g for 20 min after which plasma was separated into two tubes. Plasma was stored in a freezer at –80°C until the assessment day and assayed as duplicate. For the analyses, considering the debate on the plasma extraction procedure [32], we preferred to use a novel commercially available extraction-free Elisa kit (Bachem S-1176.0001 OT EIA Kit, High Sensitivity, Extraction-free CE-marked). For human serum or plasma samples, typical sensitivity (Av. IC50) was 0.15 ng/ml with a range of 0–10 ng/ml.

Statistical analyses

Thirty-four patients with SCH, their HS and 34 psychologically HC were included. Similar to previous studies [33,34], due to high variability in plasma OT levels, data outside two standard deviations above or below each participant's mean score were removed. Statistical analysis was performed with the remaining 27 patients with SCH, their HS, and 27 psychologically HC. Analyses were conducted using SPSS Statistics 21.0 (IBM Corp., Armonk, NY) and p values $\leq .05$ were accepted as significant. In the preliminary step, variables were checked for the assumptions of parametric statistical testing by the visual analyses of distribution plots and Wilks–Shapiro tests. Differences in the socio-demographical and WAİS-R were tested by chi-square and one way-ANOVA. To explore the relationships between social cognition and blood samples we performed Pearson correlations. MANCOVA (gender and WAIS-R as covariates) test was performed to investigate the effect of gender on blood levels of OT and WAIS-R on social cognition. OT data were divided into low (<400 pg/ml) and high (>400 pg/ml) categories, based on the distribution of the data and corroborated by previous reports on

OT [35,36]. Differences between low and high OT group were tested by *t*-tests and chi-square.

Results

Socio-demographical differences between groups

There was a statistically significant difference between the groups in terms of gender $\chi^2(2) = 5.63$, $p = .05$), but the age ($F = 0.43$, df = 2.78, $p = .64$) and education status ($F = 0.39$, df = 2.78, $p = .67$) of both samples did not differ significantly. Significant differences on WAIS-R were found between groups. In *post hoc* Tukey analysis, statistical significance in WAIS-R was between the healthy control group and patients with SCH ($F = 3.29$, df = 2.78, $p = .04$). Mean duration of disease in patients was 10.18 ± 7.47 years, mean age of onset was 19.66 ± 3.47. Mean PANSS scores were 21.55 ± 4.40 in PANSS-Negative, 12.29 ± 4.65 in PANSS-positive, and 38.00 ± 8.70 in PANSS-General.

Group differences in neuropsychological and social cognitive capacity and blood OT levels

MANCOVA analysis was performed to compare the blood OT levels, WCST, and RMET of the groups. Due to the observed group differences, gender and WAIS-R were treated as covariate in this step and the univariate statistical results were presented following the Bonferroni correction. There were not any significant effects of gender (Wilks Lambda; F (6,71) = 1.76; $p = .11$; $\eta_p^2 = 0.13$), and WAİS-R (Wilks Lambda; F (6,71) = 1.89; $p = .09$; $\eta_p^2 = 0.12$) on the groups.

A statistically significant difference was found between the groups in the scores of RMET Easy İtems, RMET Total Scores, WCST's Categories achieved, Perseverative errors, and Number of correct. All results between the groups are presented in Table 1.

Correlations between social cognitive and neurocognitive capacity and OT levels

In healthy control group, there was positive correlation between blood OT levels and RMET's difficult items subtest ($r = .461$, $n = 27$, $p = .01$), total score subtest ($r = .415$, $n = 27$, $p = .03$), and WCST's categories achieved ($r = .416$, $n = 27$, $p = .03$). In other groups, no statistical significance was found. When all participants were evaluated, a statistically significant correlation was found between blood OT levels and all subtests of RMET [easy items subtest ($r = .272$, $n = 81$, $p = .01$), difficult items subtest ($r = .216$, $n = 81$, $p = .05$), total score subtest ($r = .281$, $n = 81$, $p = .01$)]. Correlations are presented in Table 2.

The differences between high and low OT groups

There is a statistically significant difference between high and low OT groups with regard to social cognition in all subtests of the RMET. Group differences are presented in Table 3. When participants were divided into three groups as patients with SCH, HS, and control group, only a statistically significant difference was observed in the control group in all subtests of the RMET [RMET Easy items($t = 2.01$, df = 25, $p = .05$), RMET Difficult items($t = 4.07$, df = 25, $p < .01$), RMET Total score($t = 3.09$, df = 25, $p < .01$)]. In HS, there was a statistically significant difference in easy items subtest ($t = 2.03$, df = 25, $p = .05$) and total score subtest ($t = 2.19$, df = 25, $p = .03$). No statistically significant difference was found in the patient group.

Discussion

In the current study, we found that patients had deficits in social cognition and neurocognition. Interestingly, we found no differences between patients and their HS in terms of social cognition. Numerous studies have shown impaired social cognition in SCH [37–39] and unaffected first-degree relatives also seem to be impaired, albeit to a lesser extent [40]. In a meta-analysis, Kohler et al. have found that patients with SCH were seriously unsuccessful compared to healthy participants in emotion detection tasks [41]. Eack et al. have identified similar impairment in emotion recognition in patients with SCH and their first-degree relatives [42]. When siblings of patients with SCH are considered to be healthy, it is expected

Table 1. Group comparison of RMET, WCST, and OT showing means and the results from a MANCOVA analysis.

	SCH		HS		HC		Stats.			
Group	Mean	S.D.	Mean	S.D.	Mean	S.D.	*F*	sig	η_p^2	*Post hoc* analysis
RMET – Easy items	9.37	2.49	10.81	3.06	11.29	2.99	3.30	0.04	0.07	HC > SCH $p = .04$
RMET – Difficult items	8.00	2.16	9.11	2.40	9.18	1.96	2.49	0.08	0.06	
RMET – Total score	17.37	3.80	19.92	4.89	20.48	4.48	3.81	0.02	.08	HC > SCH $p = .03$
WCST number correct	78.37	21.24	88.40	15.94	93.51	13.62	5.39	<0.01	0.12	HC > SCH $p < .01$
WCST perseverative error	28.22	14.14	19.51	8.80	18.44	8.86	6.53	<0.01	0.13	SCH > HS $p = .01$ SCH > HC $p < .01$
WCST categories achieved	4.25	3.27	5.85	2.21	6.66	2.14	5.99	<0.01	0.14	HC > SCH $p < .01$
Oxytocin	397.64	202.51	421.81	206.30	411.23	158.09	0.11	0.89	0.00	

Notes: RMET: Reading the Mind from the Eyes Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WCST: Wisconsin Card Sorting Test; SCH: schizophrenia patient; HS: healthy sibling; HC: healthy control. Gender and WAIS-R were treated as covariate.

Table 2. Correlations between social cognitive and neurocognitive capacity and OT levels.

		RMET – Easy items	RMET – Difficult items	RMET – Total score	WCST number correct	WCST perseverative error	WCST categories achieved
BLOOD OXYTOCİN LEVEL	SCH	.240	−.118	.091	.014	−.236	−.058
	HS	.272	.348	.342	−.221	.038	−.272
	HC	.319	.461*	.415*	.359	−.334	.416*
	AP	.272*	.216*	.281*	.023	−.177	.000

Notes: RMET: Reading the Mind from the Eyes Test; WCST: Wisconsin Card Sorting Test; SCH: schizophrenia patient; HS: healthy sibling; HC: healthy control; AP: all participants.

that the siblings should show a higher social cognitive performance compared to patients. However, controversially to the literature, we could not found such a difference. Considering the genetic and neurodevelopmental origins of the disease, it can be said that social cognitive performance is associated with the genetic and neurodevelopmental process as well as the destructive nature of the disease. On the other hand, as a limitation of our study healthy sibling group ranges between ages 18 and 65. Since 18 is below the modal age of onset of SCH, it cannot be ruled out that some of these siblings are in fact not "healthy," but may be in fact in a prodromal phase of SCH. Although the RMET is the best predictor of theory of mind, the lack of any other scale used to evaluate social cognition is the other limitation which can affect the results.

In the neurocognitive assessment, we found that there was a statistically significant difference in all domains of the WCST between the patient and control groups, but there was statistically significant difference in only WCST perseverative error scores between patients and HS. It was found that patients made more recurrent errors than HS. Theory of mind is one of the sub-fields of the social cognition. Studies conducted with HC showed that cognitive functions such as working memory and executive functions are associated with the performance in theory of mind tests [43–48]. Although HS had a better score in RMET, there was no statistically significant difference between the patients and HS. The difference in WCST perseverative error could explain the difference in RMET scores. These findings seem to support, as usually accepted, that neurocognition has a significant impact on the development of social cognitive capacity, but it is not a determinant by itself.

We did not find any statistically significant difference between these three groups with regard to blood OT levels. Studies conducted in recent years demonstrated strong evidence that OT has a role in the etiology of mental disorders leading to difficulties in social communication [49]. In a recent study, a negative correlation between the severity of the symptoms of SCH and basal OT levels is shown [50]. It has also been demonstrated that low doses of nasal OT increase social cognitive skills in SCH [50–52]. However, there exist controversial studies [53]. Contrary to previous studies, we did not find any statistically significant difference in blood OT levels. The inconsistencies in endogenous OT levels among our study and the other studies may reflect differences in evaluating peripheral vs. cerebrospinal fluid levels, sample-related differences in demographics (e.g. sex, age, race), the proportion of participants taking different antipsychotics, differences in disease chronicity, and the proportion of participants displaying neuroendocrine dysfunction (e.g. polydipsia). Difficulties in the measurement of OT from peripheral blood, including the short half-life of OT, the failure to reflect the central levels of OT, and being effected by the circadian ritm are the limitations of this study as with other studies.

Thereafter, we studied the correlation between blood levels of OT and social cognition. We found a positive correlation between social cognition and blood level of OT in the control group, but not in patient or healthy sibling groups. Finally, we dichotomized the plasma OT levels using the group median, resulting in two groups: a low OT group and a high OT group. We found that there is a statistically significant difference between the high and low OT groups in terms of social cognitive capacity. In previous studies, it was found that lower endogenous OT levels are also predictive of poor social cognitive functioning and greater severity of positive and negative symptoms [14,50,54,55]. It can be concluded that the level of OT is a decisive influence on the social cognitive functions.

The amygdala, the prefrontal cortex, and dopaminergic systems have a mediator role in oxytocinergic

Table 3. The differences between high and low OT groups on social cognition.

	Groups	*N*	Mean	Std. deviation	*t*	df	Sig. (2-tailed)
RMET easy items	High oxytocin	40	11.4	2.5	2.85	79	<0.01
	Low oxytocin	41	9.6	3.0	2.86	76.6	<0.01
RMET difficult items	High oxytocin	40	9.4	2.1	2.85	79	<0.01
	Low oxytocin	41	8.0	2.0	2.85	78.7	<0.01
RMET total score	High oxytocin	40	20.8	4.0	3.27	79	<0.01
	Low oxytocin	41	17.7	4.5	3.28	78.1	<0.01

Note: RMET: Reading the Mind from the Eyes Test.

system [56,57]. It is also known that the patients with SCH have a deficit in the amygdala, the prefrontal cortex and the dopaminergic systems [56,57]. The lack of correlation between the blood levels of OT and social cognitive capacity in patients with SCH, in our study, can be explained by the deficits in these systems. Furthermore, we did not find any correlation between the blood OT levels and social cognitionin HS group. Thus, both patient and healthy sibling groups differ from the control group in terms of having a correlation between social cognitive performance and blood OT levels. This suggests that the system which is mediating the role of OT is impaired in HS group. The lack of a statistically significant difference in social cognitive capacity of patient and healthy sibling groups supports our hypothesis.

A number of studies have been carried in the past out to compare patients with HC. Epidemiological studies related to SCH show that siblings of patients with SCH have a higher incidence of SCH than general society. Therefore, HS defined as a risk group should also be investigated. Although social cognitive capacity in HS is lower than the HC, the absence of disease in HS supports that the idea there is not only one cognitive factor effecting the disease occurrence. Most of the earlier studies indicate that the impaired social cognitive capacity is associated with a decrease in the blood OT levels in patients with SCH. However, our study did not show this correlation. With the data obtained from earlier studies and this study, it can be said that there is a relationship between social cognitive performances and blood OT levels. In the last step of our study, regardless of the disease, an association between social cognitive performance and blood OT levels was determined.

The way of understanding the inefficacy of OT in patients with SCH, is to focus on quality of OT, rather than its quantity. In other words, the structure of OT may be disturbed in these patients. There are many studies about the disruption of protein structure of OT in autism spectrum disorders. Modahl et al. found lower mean OT plasma levels in children with autism, compared with age-matched HC. Elevated OT levels were associated with higher scores on the Vineland Adaptive Behavior Scale (VABS) for the typically developing children, but with lower scores for the children with autism [58]. A follow-up study of individuals with autism demonstrated that decreased plasma OT level was associated with increased extended peptide inactive forms of OT derived from the same pro-hormone, indicating a defect in peptide processing of OT [59].

These studies suggest that there may be a dysfunction in OT processing associated with ASD, and that there may be developmental changes associated with the OT system over the lifespan of individuals with ASD. Further longitudinal studies or larger studies of broader age range are necessary to confirm this finding, along with an adequate control for intellectual development across age groups [60]. Regardless of the basal blood levels of OT, social cognition has improved in patients who were administered nasal OT [61]. These data support our belief about disruption of the protein structure. We conclude that future studies should also focus on the disruption of protein structure.

Disclosure statement

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