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The relationship between oxytocin, vasopressin and atrial natriuretic peptide levels and cognitive functions in patients with schizophrenia

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between oxytocin (OXT), vasopressin (AVP) and atrial natriuretic peptide (ANP) levels and cognitive functions in schizophrenia as well as to compare the findings to those in healthy controls.

Method: Patients with chronic schizophrenia and ($n=63$) healthy controls ($n=60$) were evaluated with the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A-B (TMT), the Stroop Test, the Wechsler Memory Scale-Visual Production Subscale (WMS-V) and the Facial Emotion Recognition Tests. Blood samples were analysed by using ELISA. In the data analysis, the percentage distributions of the variables were obtained, the centrality and prevalence measures (mean, standard deviation) were calculated for the continuous variables, and the dependent and independent variables were evaluated using the chi-square test, the Student's *t*-test, and the Pearson correlation test. High score variables were determined by principal component analysis. For comparisons between groups; MANOVA applied.

Results: Serum OXT, AVP and ANP levels did not differ between the groups. In the healthy control group, subscales of the Stroop, WMS-V and TMT-B tests showed better scores and correlated with levels of OXT ($p < .05$). In the healthy controls, ANP levels and social cognition had a relationship with response times to happy facial expressions ($p < .05$). The correlations of OXT, AVP and ANP with the social and cognitive parameters were different between the control group and the schizophrenia group ($p < .05$).

Conclusion: The different correlations in the healthy controls and schizophrenia group suggest deteriorations in the interactions and functions of hormones in patients and highlights the need for new investigations into different neurodegenerative illness samples.

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Introduction

Understanding cognitive impairment in schizophrenia patients is extremely important for treatment, for plotting the course of the disease, and for improving quality of life. That said, it has yet to be investigated [1]. In patients with schizophrenia in remission, the prevalence of delusions and hallucinations (20–40%) and cognitive disorders has been identified (85%), suggesting that both further studies and clinical experience are required for determining frequency and management of cognitive impairment in schizophrenia [2]. Although there are still no conclusions about which areas are most affected in cognitive functions in schizophrenia, some researchers still believe that schizophrenia is a common disorder in all skill areas. Other researchers have reported more specific disorders in areas such as memory, attention, and problem solving, which are distinct from overall poor performance [3–5].

The main social cognitive skills are perceiving and recognizing facial expressions. The presence of

deficits in schizophrenic disorders has been demonstrated in many studies, but the underlying causes of these deficits have not yet been determined. That said, a relationship was found between the symptoms of schizophrenia and emotional perception, and, in general, patients with negative symptoms were found to be more deficient in recognizing facial expressions [6].

Many studies on the neurophysiological and molecular basis of schizophrenia have focused on dopamine, serotonin, noradrenaline, glutamate and GABA, and drugs used for the treatment of schizophrenia have been shown to be effective in altering the activity of these neurotransmitters. Although there is a wide range of treatment options, the goal of complete remission has not been achieved in the treatment of schizophrenia. The negative findings and limited effectiveness of antipsychotics on cognitive functions have led to the investigation of other molecules that may be involved in the aetiology of

schizophrenia. Oxytocin (OXT) and vasopressin (AVP) are among the neuropeptides of interest in recent years [7].

In recent studies, the effects of OXT on maternal behaviour, attachment attitudes, sexual behaviours and nutrition have been researched, and the importance of social communication has been emphasized [8]. There is much evidence to support the idea that oxytocinergic dysfunction occurs in schizophrenia [9–11]. OXT in humans reduces behavioural responses to stress and cortisol levels, encourages confidence [12] and facilitates attachment and social relationships [13]. OXT has been shown to have beneficial effects on schizophrenia symptoms, but the exact mechanism by which this effect occurs has not been fully clarified [14,15].

AVP has been shown to be effective for a variety of cognitions, including social cognition, non-spatial memory and attention [16]. The relationship between schizophrenia and AVP appears to involve several dimensions. In neuroanatomic examinations, the limbic structures containing the hypothalamus and hippocampus appear abnormal in schizophrenia, and these structures are involved in the regulation of the synthesis and release of AVP [17,18]. In neurochemical examinations, AVP release is directly regulated by dopamine and serotonin, the two most commonly studied neurotransmitters in schizophrenia [18]. When studies examining vasopressin levels in schizophrenia patients are examined, however, the results appear to be contradictory. This suggests that OT and AVP may conduce to changes in brain function and, as a result, contribute to disease-related behavioural changes, since brain regions that are modulated by these hormones in healthy individuals and known to be abnormal in schizophrenia patients are similar [19].

Atrial natriuretic peptide (ANP) suppresses the hypothalamohypophyso-adrenal (HPA) system in stress conditions [20,21]; however, it has been argued that ANP exerts a complex antistressor effect rather than acting as a general inhibitor of the HPA system, and that it works on the emotional components of stress [22]. Corticotropin releasing factor (CRF) with a very large localization in the CNS is similar to the localization of ANP [23–25]. These regions are responsible for behavioural activity and, additionally, for neuroendocrine and autonomous functions. This association supports the idea that ANP may play a neuromodulator role in olfactory/limbic information processing, which is also important in terms of the effectiveness of CRF and the formation of stress responses [26]. ANP, similar to OXT and AVP, suppresses the HPA system, raising the question of its anxiolytic effect, its effect on the serotonin, prolactin, dopamine systems, and its effects on cognitive functions due to its association with CRF neurons in the amygdala region.

The aim of the study was to compare the cognitive functions of schizophrenia patients with healthy controls and evaluate the relationship between neuropeptide levels and neurocognitive functioning (as evaluated by Rey Auditory Verbal Learning Test, RAVLT; Trail Making Test A and B, TMTA-B; Stroop Colour Word Test, SCWT; Wechsler Memory Scale-Visual Production, WMS-VP and Facial Emotion Recognition Test, ERT) in patients and healthy controls.

In this study, our hypothesis is that cognitive functions in schizophrenia patients differ from healthy controls, and blood OXT, AVP, ANP levels are associated with cognitive functions.

In this study, it was thought that ANP could be related to cognitive functions in schizophrenia; although its effect on schizophrenia has been shown, the mechanism is not fully understood and has not been studied previously for schizophrenia. In this study, the relationship between cognitive functions and OXT, AVP and ANP serum levels in patients in clinically stable periods was investigated.

Method

Participants

This study was conducted between August 2016 and April 2017 and sixty-three chronic schizophrenic patients at Sakarya University Educational and Research Hospital were admitted to the study, as were 60 healthy controls. IRB approval date of this study was 15/03/2016 and number 16214662/050.01.04/61. The inclusion criteria for patients were as follows: 1. Diagnosis of schizophrenia according to DSM-4 and DSM-5 criteria; 2. Between the ages of 18 and 65; 3. Be at least a primary school graduate; 4. Have been in remission for at least six months; 5. No admission to a psychiatric clinic in the six months prior to inclusion in the investigation; 6. Have received regular antipsychotic treatment for the last six months. The control group inclusion criteria were as follows: 1. According to DSM-IV and DSM-V criteria, no psychiatric diagnosis with regard to the participant or the participant's family; 2. Between the ages of 18 and 65; 3. Be at least a primary school graduate. Exclusion criteria for both groups were as follows: 1. Neurological/metabolic disease history affecting cognitive function (known); 2. Sensory impairment that may cause neurocognitive limitations (such as loss of hearing/blindness); 3. Mental retardation; 4. Alcohol or substance abuse; 5. History of electroconvulsive therapy in the last six months; 6. Pregnant and lactating; 7. Hypertension and known cardiovascular disease. The control group and the patient group were matched in terms of age, gender and duration of education, and care was taken to ensure that there was no significant difference in

terms of IQ scores. Individuals with an IQ score of 80 or higher in both groups were included in the study. The study received ethics approval and that consent was obtained from the subjects in the study.

Application

We measured neurocognition using the Rey Auditory Verbal Learning Test (VLT), the Trail Making Test A-B (TMT), the Stroop Test and the Wechsler Memory Scale-Visual Production Subscale (WMS-V), and to measure social cognition with the Facial Emotion Recognition Test. Before applying the tests, 10 mL of venous blood were taken from all participants and analysed using ELISA.

Instruments

Clinical measures

Structured clinical interview for DSM-IV (SCID-I)

SCID-I, which was developed as a semi-structured clinical diagnostic tool by Spitzer et al. in 1983, permits the investigation of first axis diagnosis according to DSM diagnostic criteria in the past and/or within the last month. In this study we used the Turkish version of the form, which was published by First et al. [27] and was adapted to the DSM-IV and published in 1999, validity and reliability study by Özkürkçügil Corapcioglu et al. [28].

Positive and negative syndrome Scale (PANNS)

The Positive and Negative Syndrome Scale (PANNS), developed by Kay et al. [29], is a semi-structured interview scale with a 30-point and seven-point severity assessment. Of the 30 psychiatric parameters evaluated by PANSS, seven belong to the positive syndrome subscale, seven to the negative syndrome subscale and the remaining 16 to the general psychopathology subscale.

Clinical Global Impression Scale (CGI)

This scale was developed by Guy [30] to evaluate the course of all psychiatric disorders of all ages for clinical research purposes. CGI is a three-dimensional (“severity of disease,” “recovery” and “severity of side effects”) scale, and is completed during semi-structured interviews to assess responses to treatment in people with psychiatric disorders.

Global assessment of functionality (GAF)

Using a single measure, the Global Assessment of Functionality (GAF) scale helps to monitor the clinical course of people with a general framework. While only psychological, social and occupational functionality is graded by the GAF scale, functionality distortions due to physical or environmental constraints cannot be evaluated separately. Assessment with a checklist

is completed by the clinician with a score of 1–100 for a period in the past, and the functionality of the subject is graded [31].

Neuropsychological tests

Trail making test A-B (TMT)

The Trail Making Test (TMT) was developed by Reitan in 1958 [32,33]. TMT consists of two parts (A and B). There is no time limit in the test. Completion times and error numbers are considered as points. The A section assesses psychomotor speed and attention, while section B measures the speed of visual scanning. Information on working memory is obtained from section B by subtracting the duration of section A (B-A).

Rey auditory verbal learning test (VLT)

A word list developed by Rey in 1941 is used in the Verbal Learning Test (VLT) [34,35]. The test consists of 15 unrelated words. VLT can distinguish between several parameters related to memory. The first is the immediate memory of the person; the second is the process of learning or acquiring information; and the third is remembering and recalling processes. After the first and second steps, the test is interrupted for approximately 40 min, and the third stage (long-term memory) is performed.

Wechsler memory scale–visual memory subscale (WMS-V)

This test was first developed by Wechsler in 1945 and evaluates visual learning and memory functions [36,37]. The WMS-V subtest consists of three cards on which geometric patterns are drawn. An immediate memory score and delayed spontaneous recall score are determined in the evaluation. In our study, only the immediate visual memory test was used.

Stroop test

The Stroop Test is a cognitive control test consisting of three parts that was developed by J. R. Stroop [38]. The test is associated with one of the frontal lobe functions: the ability to sustain attention despite distraction. Semantic perception and visual perception are evaluated. Each section is scored in three ways: (1) duration; (2) number of errors; (3) number of corrected reactions.

Facial emotion recognition test

In this study facial emotion recognition test which were developed by Ekman and Friesen in 1976 and happy, sad, frightened, angry, surprised, disgusted, 6 face emotion expressions and neutral face emotion expressions were used in a total of 56 photos of 8 models were used [39]. After the feelings represented in the facial expressions in the first seven photographs are shown to the person being tested, the test begins.

Participants are asked to correctly recognize the facial expressions in the photos and to do so as soon as possible. No time limitation is applied to the photos. During the test, participants' responses are noted by the researcher; at the same time, how much time is needed for each response is also recorded.

Biological sample collection and laboratory analysis

Ten ml of venous blood were taken into tubes without anticoagulants before test application (BD Vacutainer SST TM II Advance plastic tubes, Silica Gel, UK). Samples were collected between 11:00–15:00, when the plasma levels of the neurohormones being investigated were highest. Two hours were given for the completion of the coagulation process at room temperature. The samples were then centrifuged at 1000 xg for 15 min at 4 °C, and the serum samples were stored at –80 °C (Thermo Scientific, Centrifuge SL16R, UK). Once all patient samples were completed, the sera were removed from storage and prepared for biochemical analysis at room temperature (22–24°C). All reagents were stored at room temperature in accordance with the protocol before use. Serum oxytocin (Elabsience ELISA, Catalog No. E-EL-0029, Texas), AVP (Elabsience ELISA, Catalog No. E-EL-H0272, Texas) and ANP (Elabsience ELISA, Catalog No. E-EL-H0532, Texas) levels were evaluated by the ELISA method. The coefficient of variation for the assays are < %10.

Statistical analysis

In the study, the SPSS for Windows 22.0 package was used for statistical evaluation of the data. In the data analysis, the percentage distributions of the variables were obtained, the centrality and prevalence measures (mean, standard deviation) were calculated for the continuous variables, and the dependent and independent variables were evaluated using the chi-square test, the Student's *t*-test, and the Pearson correlation test. The authors used the tool "cocor" to compare correlations (<http://comparingcorrelations.org>). The significance level was set as $p < .05$. Analyses were formed with two tails.

All neurocognitive variables, and the patient and control groups were taken, and high score variables were determined by principal components analysis, and the correlation between neuropsychological variables and neuropeptides was evaluated. High score variables were determined by principal component analysis. For comparisons between groups; MANOVA applied.

Sociodemographic and clinical features

Of the patients, 55.6% were male, 44.4% were female and of the patient group, 40% (24 male) were male

and 60% (36 female) were female. The mean age was 40.94 ± 10.32 in the patient group and 40.55 ± 11.55 in the control group. The duration of educational training was 9.44 ± 3.43 years in the patient group and 9.67 ± 3.77 years in the control group. No statistically significant difference was found between the two groups in terms of gender, age and education (Table 1).

The relationship of clinical symptom severity to cognitive functions in patients

When the relationship between the tests indicating the clinical symptom severity of the patients and the neurocognition tests was examined, the long-term memory of the VLT scores ($p = .041$, $r = .258$) and the WMS were positively correlated with the mean score of the overall assessment of functionality ($r = .372$, $p = .003$); TMT-A and Stroop-1 were negatively correlated with time and number of errors in colour reading (respectively, $r = -.449$, $p = .000$; $r = -.379$, $p = .002$). When the relationship between the facial expressions shown in the Facial Emotion Recognition Test and the number of correct answers was examined, the correct number of sad, suprised, disgusted, neutral and total expressions was positively correlated with the general evaluation of the functionality (respectively, $r = .277$, $p = .028$; $r = .325$, $p = .009$; $r = .436$, $p = .000$; $r = .355$, $p = .004$; $r = .416$, $p = .001$). There was no statistically significant correlation between the time taken to answer the facial expressions questions and the tests used to measure clinical symptom severity ($p > .05$). There was a positive correlation between the correct number of "happy" expressions on the emotion recognition test and the PANSS negative subscale ($r = .362$, $p = .004$), and a negative correlation was found between the correct number of "scared" expressions ($r = -.312$, $p = .013$).

Neurocognitive test scores of the groups

In the patient group, the VLT-instant memory score was 4.19 ± 1.64 , the total learning score was 71.03 ± 22.64 , the highest learning score was 9.33 ± 2.82 , and the long-term memory score was 6.98 ± 2.99 . In the healthy control group, the instant memory score was 7.05 ± 2.32 , the total learning score was 95.73 ± 16.80 , the highest learning score was 11.43 ± 1.65 and the long-term memory score was 7.93 ± 1.95 . In all subgroups of the VLT test, the scores of the healthy control group were significantly higher than those of the patient groups ($p < .05$).

In the WMS-V subtest, patient scores were found to be 7.98 ± 3.57 ; healthy control group scores were found to be 11.93 ± 2.01 . Control group scores were significantly higher than those of the patient group ($p < .05$).

In the patient group completed; TMT-A: 78.88 ± 41.91 , TMT-B: 239.93 ± 173.73 s; the healthy control group completed TMT-A: 54.55 ± 26.14 , TMT-B:

Table 1. Sociodemographic and clinical characteristics of the patient and control groups in the study.

		Patient group		Control group		P
<i>Sociodemographic Characteristics (n = 123)</i>						
Sex	Male	35	55.6	24	40.0	.084
	Female	28	44.4	36	60.0	
Age	18–29	10	15.9	9	15.0	.815
	30–39	21	33.3	22	36.7	
	40–49	18	28.6	13	21.7	
	50–65	14	22.2	16	26.7	
Education (year)	0–5	17	27.0	19	31.7	.315
	6–8	13	20.6	9	15.0	
	9–12	25	39.7	18	30.0	
	>12	8	12.7	14	23.3	
Total		63	100.0	60	100.0	
Clinical features of schizophrenia patients (n = 63)						
Clinical features	Median	Mean	SD	MV	HV	
Duration of illness	15	14.13	9.31	1	32	
Number of hospitalizations	2	2.71	2.98	0	15	
Chlorpromazine Equivalent dose	800	876.19	370.14	200	2200	
PANSS Positive	12	12.10	3.03	8	22	
PANSS Negative	12	12.22	3.19	7	21	
PANSS General	25	26.06	9.33	18	92	
PANSS Total	50	50.38	11.74	35	122	
CGI	3	3.46	0.62	2	5	
GAF	55	53.10	8.10	30	70	

Note: SD: standard deviation, EKD: minimum value, EBD: highest value, PANSS: Positive and Negative Symptom Scale, CGI: clinical global impression, GAF: general assessment of functionality.

99.47 ± 40.86 s. The control group completed the tests in a shorter amount of time, and this difference was statistically significant ($p < .05$).

Stroop-2 and Stroop time difference parameters between the patient and control groups were statistically significantly worse in patients with schizophrenia (Stroop-2 patients: 115.05 ± 19.88; healthy controls: 86.48 ± 22.93) (Stroop difference patients: 64.87 ± 54.76; healthy control: 40.37 ± 15.35). Similarly, a statistically significant difference was found between the groups in Stroop-1 subtest on the number of word-reading corrections (patients: 3.08 ± 3.32; healthy controls: 1.87 ± 1.74) and word reading error (patients: 2.24 ± 3.93; healthy controls 0.80 ± 0.95). Also, in the Stroop-2 subtest in terms of the number of colour-identifying corrections (patients: 1.11 ± 1.70; healthy controls: 0.55 ± 0.96) schizophrenic patients had a significantly worse score ($p < .05$).

The number of correct answers for disgusted, neutral and total facial expressions was higher in the healthy control group ([disgusted] patients: 4.57 ± 1.98; [disgusted] control: 5.63 ± 1.40) ([neutral] patients: 5.22 ± 2.28; [neutral] control: 6.45 ± 1.23) ([total number of expressions] patients: 35.32 ± 388.14; [total number of expressions] control: 38.98 ± 5.86), and this difference was statistically significant ($p < .05$).

It was found that the patient group recognized the most happy facial expressions, followed by angry and neutral expressions. Patients were able to recognize the fewest frightened facial expressions, followed by disgusted and sad facial expressions (happy > angry > neutral > surprised > disgusted > sad > frightened). Similarly the healthy controls, the most happy facial expressions were recognized, followed by neutral, angry, disgusted, surprised, sad and frightened facial

expressions (happy > neutral > angry > disgusted > surprised > sad > frightened) ($p > .05$).

When the difference between the facial expression response time in the patient and control groups was examined, the average response times for all facial expressions in the healthy control group were found to be shorter than those of the patients ([happy time] patients: 2.42 ± 1.45 s; [happy time] control: 1.33 ± 0.33 s) ([sad] patients: 4.22 ± 2.79 s; [sad] control: 2.02 ± 0.73 s) ([angry] patients: 3.77 ± 2.92 s; [angry] control: 2.06 ± 0.56 s) ([surprised] patients: 3.62 ± 2.53 s; [surprised] control: 1.96 ± 0.59 s) ([frightened] patients: 3.91 ± 2.41 s; [frightened] control: 2.17 ± 0.54 s) ([disgusted] patients: 3.76 ± 2.55 s; [disgusted] control: 1.96 ± 0.54 s) ([neutral] patients: 3.37 ± 2.50 s; [neutral] control: 1.58 ± 0.59 s) ([total expression] patients: 25.08 ± 15.66 s; [total expression] control: 13.09 ± 3.17 s). This situation was statistically significant ($p < .05$).

Serum hormone levels of the groups

Blood oxytocin levels in the patient group were 32.87 ± 14.47 pg/mL, while vasopressin levels were 43.12 ± 28.37 pg/mL and atrial natriuretic peptide levels were 240.02 ± 95.61 pg/mL. In the healthy control group, blood OXT levels were found to be 35.00 ± 20.89 pg/mL, while AVP levels were 44.97 ± 19.55 pg/mL and ANP levels were 250.39 ± 83.53 pg/mL. Although the levels of oxytocin, vasopressin and atrial natriuretic peptide were higher in the healthy control group, there was no statistically significant difference between the groups (Figure 1).

There was no significant correlation between PANSS positive, negative, general and total scores, GAF, CGI scores of patients and serum AVP, OXT

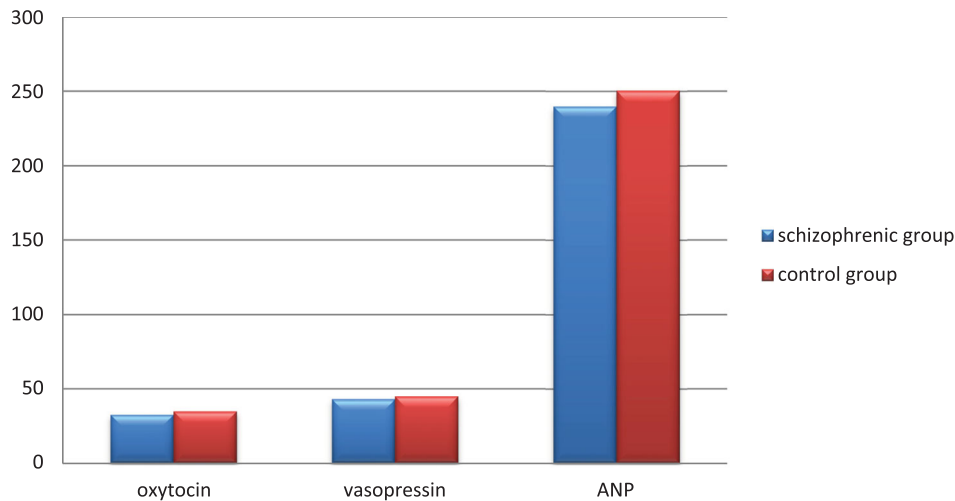


Figure 1. Levels of oxytocin, vasopressin and atrial natriuretic peptide.

and ANP hormone levels. Also, there was no significant correlation between VLT-immediate memory scores, total learning scores, high learning scores and hormone levels. There was a significant negative correlation between ANP and long-term memory scores with a moderate power ($r = -.321$, $p = .010$).

The WMS-V subtest was not associated with blood OXT, AVP or ANP levels ($p > .05$).

When TMT-A and TMT-B test completion times were examined, the ANP level had a positive correlation, with a moderate power with TMT-B ($r = .268$, $p = .046$). In the patient group, there was no correlation between the Stroop tests and hormone levels ($p > .05$).

The Relationship between Hormone Levels and Neurocognitive Tests in the Healthy Control Group (Table 2).

In the healthy control groups, a negative correlation was found between vasopressin levels and instantaneous memory scores ($p < .05$) (Table 2). There was a significant difference between the correlations of instantaneous memory scores and OXT and AVP hormone levels between patient and healthy control group ($p = .0335$, $p = .0149$) (Table 3).

In the healthy control group, a moderate significant correlation was found between the visual instant memory score and OXT hormone levels ($p < .05$). (Table 2) There was a significant difference between the correlations of

Table 2. Relationship of neurocognitive test scores with blood hormone levels.

Neurocognitive tests	Patient group (n = 63)			Control group (n = 60)			r
	Oxytocin	Vasopressin	ANP	Oxytocin	Vasopressin	ANP	
Stroop 1 (word reading)	0.123	-0.174	0.143	-0.165	0.347**	0.062	r
	0.336	0.172	0.264	0.209	0.007	0.639	p
Stroop 2 (colour reading)	0.044	-0.109	0.198	-0.090	0.215	0.046	r
	0.735	0.396	0.119	0.495	0.099	0.725	p
Stroop difference	0.041	-0.068	0.163	-0.021	0.047	0.017	r
	0.751	0.598	0.203	0.874	0.721	0.896	p
Word reading correction	0.013	0.000	-0.041	-0.301*	0.001	0.011	r
	0.922	0.999	0.750	0.019	0.993	0.932	p
Word reading mistake	-0.088	0.031	0.145	-0.189	-0.003	-0.015	r
	0.493	0.812	0.256	0.149	0.984	0.911	p
Colour reading correction	0.119	-0.116	0.048	-0.281*	0.182	0.041	r
	0.352	0.367	0.707	0.030	0.163	0.753	p
Colour reading mistake	0.089	-0.051	0.087	-0.087	0.014	0.080	r
	0.490	0.693	0.496	0.507	0.916	0.545	p
TMT-A completing duration	0.012	-0.066	0.111	-0.314*	0.058	-0.092	r
	0.925	0.605	0.385	0.015	0.660	0.484	p
TMT-B completing duration	0.177	-0.053	0.268*	-0.216	0.130	-0.071	r
	0.193	0.701	0.046	0.097	0.321	0.591	p
Visual instant memory score (WMS)	-0.173	0.130	-0.162	0.314*	-0.211	0.201	r
	0.176	0.309	0.205	0.015	0.106	0.123	p
Instant memory score (VLT)	-0.219	0.173	-0.180	0.169	-0.269*	0.142	r
	0.085	0.176	0.158	.196	0.038	0.280	p
Total learning score (VLT)	-0.071	0.019	-0.235	0.190	-0.189	0.119	r
	0.578	0.883	0.063	0.146	0.149	0.363	p
Highest learning score (VLT)	-0.023	-0.050	-0.246	0.159	-0.064	0.233	r
	0.858	0.698	0.052	0.226	0.630	0.073	p
Long-term memory score (VLT)	-0.082	-0.022	-0.321*	0.179	-0.104	0.043	r
	0.523	0.863	0.010	0.170	0.427	0.746	p

Note: * $p < .05$, ** $p < .001$; r: Pearson correlation ratio; VLT: Verbal learning Test; TMT: Trail Making Test; WMS: Weschler Memory Scale. The significance for bold values is p values under 0.05.

Table 3. Comparison of correlations between neurocognitive tests and oxytocin, vasopressin and ANP level in patient and healthy controls.

Neurocognitive tests	Oxytocin		Vasopressin		ANP	
	<i>p</i>	CI	<i>p</i>	CI	<i>p</i>	CI
Stroop 1 (word reading)	.117	−0.0723 0.6231	.004	−0.8295 −0.1702	.658	−0.2730 0.4288
Stroop 2 (colour reading)	.468	−0.2251 0.4811	.076	−0.6550 0.0351	.403	−0.2021 0.4944
Stroop difference	.737	−0.2952 0.4137	.534	−0.4636 0.2437	.425	−0.2104 0.4906
Word reading correction	.080	−0.0385 0.6411	.996	−0.3557 0.3538	.779	−0.4042 0.3047
Word reading mistake	.577	−0.2512 0.4442	.854	−0.3221 0.3872	.384	−0.1981 0.5047
Colour reading correction	.027	0.0440 0.7224	.104	−0.6320 0.0620	.969	−0.3473 0.3610
Colour reading mistake	.219	−0.1045 0.4469	.725	−0.4165 0.2921	.969	−0.3456 0.3595
TMT-A completing duration	.069	−0.0256 0.6515	.502	−0.4720 0.2350	.271	−0.1572 0.5454
TMT-B completing duration	.031	0.0344 0.7179	.320	−0.5263 0.1766	.062	−0.0172 0.6678
Visual instant memory score (WMS)	.007	−0.8001 −0.1336	.062	−0.0183 0.6707	.047	−0.6909 −0.0037
Instant memory score (VLT)	.035	−0.7136 −0.0293	.015	0.0857 0.7610	.079	−0.6542 0.0380
Total learning score (VLT)	.154	−0.5975 0.0983	.256	−0.1499 0.5476	.052	−0.6826 0.0043
Highest learning score (VLT)	.322	−0.5244 0.1765	.939	−0.3405 0.3669	.008	−0.7945 −0.1232
Long-term memory score (VLT)	.155	−0.5978 0.0987	.656	−0.2747 0.4311	.042	−0.6884 −0.0119

Note: VLT: Verbal learning Test; TMT: Trail Making Test; WMS: Weschler Memory Scale CI: Confidence interval.

Visual Instant Memory Score (WMS) and OXT and ANP hormone levels between patient and healthy control groups ($p = .0069$, $p = .0471$) (Table 3).

Also there was a significant difference between the correlations of ANP hormone levels and Highest Learning Score (VLT) and Long-term Memory Score (VLT) between patient and healthy control group ($p = .0083$, $p = .0422$) (Table 3).

When TMT-A and TMT-B times were examined, a significant negative correlation was found between the TMT-A test and OXT hormone levels in the healthy control group ($p < .05$) (Table 2). There was a significant difference between the correlations of TMT-B Completing Duration and oxytocin hormone levels between patient and healthy control group ($p = .0313$) (Table 3).

In the Stroop Test, a moderate significant correlation was found between OXT and word-reading correction and colour-reading correction ($r = -.301$, $p = .019$; $r = -.281$, $p = .030$, respectively). There was a moderate positive correlation between AVP and Stroop duration 1, and AVP was found to worsen Stroop-1 performance in healthy controls ($p < .05$) (Table 2). There was a significant difference between the correlation of AVP levels and Stroop-1 and Stroop-2 tests between patient and healthy control group ($p = .0036$, $p = .0763$) (Table 3).

In the patient group, there was no correlation between the scores of correct answers for facial expressions and levels of AVP, OXT and ANP ($p > .05$).

There was a positive correlation between OXT levels and happy, sad, disgusted and neutral response times when the response time for the facial expressions in the Facial Emotion Recognition Test was examined groups ($p < .05$).

In the healthy control group, when the relationship between AVP, OXT and ANP was evaluated, a positive correlation was found between oxytocin levels and the number of correct answers for sad, angry and frightened facial expressions on the emotion recognition test (respectively, $p = .006$, $p = .001$, $p = .018$) (Table 4).

When the relationship between AVP, OXT and ANP correlation between patient and healthy control groups,

there was a difference between OXT levels and the number of correct answers for angry facial expressions on the emotion recognition test between groups ($p = .0293$). There was also significant difference between the correlations of ANP levels and the number of total correct answers for facial expressions between patient and healthy control groups ($p < .001$) (Table 5).

Vasopressin and ANP did not correlate with the correct response numbers in the Facial Emotion Recognition Test.

When the response times for the facial expressions in the Facial Emotion Recognition Test were examined in the healthy control group, a negative correlation was found between OXT levels and the response times for all expressions ($p < .001$) (Table 4). There was a significant difference between the correlations of OXT levels and happy, sad, angry, surprised, frightened, disgusted, neutral, total response times on the between patient and healthy control group ($p < .001$) (Table 5).

There was a statistically significant negative correlation between ANP levels and happy and total expression response times (respectively, $p = .029$, $p = .043$) (Table 4). There was a significant difference between the correlations of ANP levels and happy, sad, neutral, total response times on the emotion recognition test between patient and healthy control group (respectively, $p = .0084$, $p = .0042$, $p = .0189$, $p = .0169$) (Table 5).

There was a statistically significant positive correlation between AVP and happy and neutral response times (respectively, $p = .042$, $p = .004$) (Table 4). There was a significant difference between the correlations of AVP levels and happy, neutral, total response times on the emotion recognition test between patient and healthy control group (respectively, $p = .0059$, $p = .002$, $p = .0256$) (Table 5).

There was a significant difference between patient and control groups when considered jointly on the selected neurocognitive variables Pillai's Trace=0.390, $F(8,114) = 9.117$, $p < .001$, partial eta squared= 0.39. In the MANOVA analysis, since the Box's M test is

Table 4. The relationship between oxytocin, vasopressin and atrial natriuretic peptide levels and responses to facial expressions in the facial expression test in the patient and healthy group.

Neurocognitive tests	Patient group (n = 63)			Control group (n = 60)			
	Oxytocin	Vasopressin	ANP	Oxytocin	Vasopressin	ANP	
Responding time for happy expression	0.287* 0.023	-0.234 0.065	0.195 0.126	-0.496** 0.000	0.264* 0.042	-0.282* 0.029	r p
Responding time for sad expression	0.332** 0.008	-0.208 0.102	0.211 0.097	-0.422** 0.001	0.127 0.334	-0.305* 0.018	r p
Responding time for angry expression	0.221 0.082	-0.198 0.120	0.047 0.716	-0.375** 0.003	0.172 0.189	-0.218 0.095	r p
Responding time for surprised expression	0.235 0.064	-0.181 0.157	0.143 0.263	-0.450** 0.000	0.178 0.173	-0.160 0.222	r p
Responding time for frightened expression	0.241 0.057	-0.223 0.079	0.104 0.418	-0.505** 0.000	-0.079 0.550	-0.217 0.096	r p
Responding time for disgusted expression	0.259* 0.040	-0.184 0.149	0.195 0.125	-0.409** 0.001	0.100 0.449	-0.142 0.280	r p
Responding time for neutral expression	0.332** 0.008	-0.188 0.139	0.245 0.053	-0.403** 0.001	0.363** 0.004	-0.182 0.163	r p
Total responding time for expressions	0.292* 0.020	-0.16 0.089	0.171 0.181	-0.530** 0.000	0.191 0.143	-0.263* 0.043	r p
Correct number of happy expression	-0.024 0.851	0.178 0.163	-0.018 0.888	0.076 0.562	0.038 0.775	0.191 0.145	r p
Correct number for sad expression	0.089 0.486	0.159 0.213	-0.025 0.849	0.353** 0.006	-0.113 0.389	-0.036 0.785	r p
Correct number for angry expression	0.036 0.780	0.084 0.515	0.157 0.220	0.413** 0.001	-0.125 0.340	0.015 0.907	r p
Correct number for surprised expression	0.112 0.382	0.001 0.994	0.005 0.968	0.242 0.062	-0.180 0.168	-0.045 0.731	r p
Correct number for frightened expression	0.217 0.087	-0.098 0.446	0.054 0.672	0.305* 0.018	0.128 0.328	0.251 0.053	r p
Correct number for disgusted expression	0.086 0.503	0.003 0.979	-0.072 0.573	0.175 0.182	0.007 0.956	-0.011 0.932	r p
Correct number for neutral expression	-0.111 0.386	0.232 0.067	-0.152 0.234	-0.164 0.210	-0.036 0.785	-0.100 0.449	r p
Total correct number of expressions	0.093 0.469	0.102 0.425	-0.025 0.844	0.357** 0.005	-0.047 0.719	0.081 0.536	r p

* $p < .05$, ** $p < .001$. Note: The significance for bold values is p values under 0.05.

<0.001, the homogeneity of variance approach is not performed, so Pillai's Trace is used (Table 6).

Discussion

In this study, the cognitive functions of schizophrenic patients were compared with those of healthy controls, and the relationship between cognitive functions, OXT, AVP and ANP was investigated in patient and healthy controls. In the data obtained, it was seen that OXT, AVP and ANP behaved differently in the schizophrenia

group in some cognitive domains than in the control group. Here, we will briefly review the results of neuropsychological tests in the schizophrenia and control groups, which the results in the literature have been confirmed; then, the relationship between the hormones, which are the specific results of this study, will be discussed.

Cognitive and social functions in the schizophrenia and control groups

Our study, both the cognitive functions and social cognition tests showed poor results in the schizophrenia

Table 5. Comparison correlations between facial emotion recognition test and oxytocin, vasopressin and ANP in patient and healthy controls.

	Oxytocin		Vasopressin		ANP	
	p	CI	p	CI	p	CI
Happy expression	<.001	0.4545 1.0550	.006	-0.8111 -0.1431	.008	0.1219 0.7921
Sad expression	<.001	0.4188 1.0315	.067	-0.6657 0.0243	.004	0.1628 0.8263
Angry expression	.001	0.2491 0.8954	.043	-0.6975 -0.0108	.147	-0.0929 0.6000
Surprised expression	.001	0.3473 0.9713	.049	-0.6876 0.0005	.099	-0.0573 0.6369
Frightened expression	<.001	0.4163 1.0228	.425	-0.4847 0.2071	.079	-0.0380 0.6522
Disgusted expression	<.001	0.3264 0.9576	.121	-0.6194 0.0758	.066	-0.0226 0.6677
Neutral expression	<.001	0.3976 1.0156	.002	-0.8558 -0.2020	.019	0.0696 0.7484
Total responding time for expressions	<.001	0.4992 1.0876	.026	-0.7306 -0.0487	.017	0.0773 0.7539
Correct number of happy expression	.588	-0.4492 0.2582	.443	-0.2151 0.4840	.253	-0.5485 0.1488
Correct number for sad expression	.131	-0.5877 0.0787	.139	-0.0883 0.6087	.953	-0.3441 0.3649
Correct number for angry expression	.029	-0.6911 -0.0371	.257	-0.1512 0.5507	.439	-0.2146 0.4870
Correct number for surprised expression	.467	-0.4677 0.2186	.323	-0.1764 0.5224	.787	-0.3067 0.4021
Correct number for frightened expression	.609	-0.4166 0.2474	.219	-0.5665 0.1344	.274	-0.5327 0.1551
Correct number for disgusted expression	.624	-0.4335 0.2636	.983	-0.3586 0.3510	.741	-0.4124 0.2955
Correct number for neutral expression	.770	-0.2980 0.3988	.141	-0.0889 0.6031	.775	-0.3998 0.2992
Total correct number of expressions	.129	-0.5872 0.0781	.419	-0.2102 0.4952	<.001	-1.0915 -0.5627

Note: CI: Confidence interval. The significance for bold values is p values under 0.05.

Table 6. Correlation of neuropsychiatric variables and neuropeptides obtained by principal component analysis.

		Patient group (n = 63)			Control group (n = 60)		
		Oxytocin	Vasopressin	ANP	Oxytocin	Vasopressin	ANP
Total responding time for expressions	<i>r</i>	0.292	-0.216	0.171	-0.530	0.191	-0.263
	<i>p</i>	0.020	0.089	0.181	<0.001	0.143	0.043
Total correct number of expressions	<i>r</i>	0.093	0.102	-0.025	0.357	-0.047	0.081
	<i>p</i>	0.469	0.425	0.844	0.005	0.719	0.536
Correct number for frightened expression	<i>r</i>	0.217	-0.098	0.054	0.305	0.128	0.251
	<i>p</i>	0.087	0.446	0.672	0.018	0.328	0.053
Correct number for disgusted expression	<i>r</i>	0.086	0.003	-0.072	0.175	0.007	-0.011
	<i>p</i>	0.503	0.979	0.573	0.182	0.956	0.932
Stroop-difference	<i>r</i>	0.041	-0.068	0.163	-0.021	0.047	0.017
	<i>p</i>	0.751	0.598	0.203	0.874	0.721	0.896
Stroop 1 (word reading)	<i>r</i>	0.123	-0.174	0.143	-0.165	0.347	0.062
	<i>p</i>	0.336	0.172	0.264	0.209	0.007	0.639
Total learning score (VLT)	<i>r</i>	-0.071	0.019	-0.235	0.190	-0.189	0.119
	<i>p</i>	0.578	0.883	0.063	0.146	0.149	0.363
Highest learning score (VLT)	<i>r</i>	-0.023	-0.050	-0.246	0.159	-0.064	0.233
	<i>p</i>	0.858	0.698	0.063	0.226	0.630	0.073

Note: The significance for bold values is *p* values under 0.05.

group compared to the control group, although this group was composed of patients with schizophrenia who were in remission. In a meta-analysis of 70 studies investigating memory functions in schizophrenia, patients with a diagnosis of schizophrenia reported significant impairment in memory functions as compared to healthy individuals [40]. In this study, it was observed that memory, attention, executive functions, sustained selective attention and processing speed/response time under a disruptive effect, mental flexibility from executive functions, resistance to a disturbing effect, and more significant impairment in response inhibition abilities determined in the patient group were in accordance with the literature. One of the main social cognitive skills is to perceive and recognize facial expressions. In a meta-analysis conducted by Kohler et al. [41], it was found that patients with schizophrenia were significantly more unsuccessful in perception of feeling tasks than healthy individuals. In addition, schizophrenic patients reported that their rate of response to emotion recognition was slower than in normal controls [42]. In our study, we found that the correct response time of the patient group was slower than that of the control group in accordance with the literature, and it was also significantly lower regarding the correct number of disgusted, neutral and total expressions.

Clinical symptoms of schizophrenia

Although the positive and negative symptoms of schizophrenia vary throughout the course of the disease, cognitive deficits persist and have been shown to be related to functional loss rather than to clinical symptoms [43]. In this study, there was no relationship between the neurocognitive test scores of cognitive functions, such as attention, executive functions and working memory and PANNS scores, which determine the severity of the disease, and the CGI disease severity subscale; while the GAF scale we used to measure

functionality was found to have a statistically significant relationship with long-term memory, visual momentary memory, TMT-A, Stroop-1, the number of colour-reading errors. This demonstrates that cognitive functions are related to functionality rather than to disease severity, in accordance with the literature.

Studies have shown that as the severity of illness increases, emotion recognition ability decreases [44,45]. In particular, there is a negative correlation between negative symptoms and emotion recognition skills [44]. In our study, recognition of the correct number of disgusted facial expressions and CGI disease severity were significantly correlated. In addition, there was a significant negative correlation between negative PANNS scores and the right number of frightened facial expressions. According to our results, as the severity of the disease increases, emotion recognition deficits increase [44,45], suggesting a relationship between negative symptoms and emotion recognition skills, thereby confirming results from previous studies [46,47]. When the relationship between the emotion recognition processes which are directly related to social interaction and functionality in our study was examined, a statistically significant correlation was shown between the correct number of sad, confused, disgusted, neutral and total expressions and GAF, in accordance with previous studies.

The Relationship Between Cognitive and Social Functions and Clinical Symptoms of Posterior Pituitary Hormones.

The lack of a complete remission target in schizophrenia treatment, especially in light of negative findings and the limited efficacy of antipsychotics in cognitive functions, has led to the investigation of molecules other than dopamine and serotonin that may be involved in the aetiology of schizophrenia. For this reason, OXT and AVP have become of increased research interest in recent years. Studies investigating blood and OXT and AVP levels in patients and healthy controls have yielded contradictory findings. In a study

of 27 patients and 17 controls, no difference was found between CSF oxytocin levels of schizophrenics and healthy controls [48]. In another study, 27 patients, 27 healthy controls and 27 healthy siblings did not differ in terms of blood OXT levels [7]. In contrast, other studies have shown that blood OXT levels are lower in patients with schizophrenia [9,49]. Some studies have shown no significant decrease in levels of AVP in schizophrenia patients compared to controls [50,51]. In our study, no statistically significant difference was found between serum OXT, AVP and ANP levels of schizophrenic patients and healthy controls. However, only schizophrenia patients in the remission period were evaluated, and thus values in the acute period were not recorded. In a study of patients in the acute phase, OXT levels were significantly higher in patients with acute schizophrenia, while ANP levels have been reported to be found to be relatively lower [52]. In the process of remission, OXT, AVP and ANP values may return to normal limits, and the absence of differences may be related to the patient's clinical features. In order to evaluate this situation, studies comparing acute phase patients, remission patients and a control group are needed.

OXT and AVP are neuropeptides associated with social cognition. However, in a limited study of cognitive functions, OXT was shown to have a positive effect on recall and free recall, although it did not change performance on tests measuring working memory [53]. Previously, a negative correlation between AVP and motor activity in patients with depression was found, and a positive correlation with memory functions was reported [54]. In contrast, in a study on rats, AVP was shown to have negative effects, especially on immediate memory (short-term memory) [55]. In our study, we found that OXT was associated with a statistically significant improvement in the sub-parameters of the WMS, TMT-B and Stroop tests in healthy controls, whereas AVP was associated with a decrease in Stroop-1 and instant memory performance in healthy controls. In addition, the long-term memory scores in Rey VLT tests and TMT-B completion times of the ANP level were statistically lower in the patient group. Previously, this effect of ANP has been shown to reduce anxiety and decrease the positive effect of anxiety on learning by suppressing anxiety [56]. A similar mechanism may have been introduced in our study.

In studies investigating the effect of OXT on social cognition in schizophrenia patients, the level of OXT in schizophrenia patients was thought to be a predictor of high social cognition [9]. There are studies emphasizing the importance of internal OT levels as a biological determinant of social cognition in control and schizophrenia patients [57]. It has also been shown to have a relationship with trust related interactions [10]. In addition, the social cognitive skills of

schizophrenic patients treated with intranasal oxytocin were increased [8,53,58]. It has been observed that OXT causes the development of the theory of mind, a subgroup of social cognition. In a study performed on 20 patients with schizophrenia, it was shown that the intranasal OXT group showed significant improvement in the theory of mind, which is a part of social cognition in which antipsychotics are ineffective [58]. In another study involving 23 patients with schizophrenia spectrum disorder and 25 healthy controls, it was shown that administration of intranasal OXT dose of 40 IU increased right temporo-parietal junction activation and accuracy for theory of mind [59]. But, on the contrary, there are also studies showing no effect of OXT on social cognition in schizophrenia patients [60,61]. In addition, no relationship was found between OXT and social cognition in schizophrenia patients, and there were also similar findings in the study of healthy volunteers [7,62]. In a randomized double-blind study with intranasal 20 IU OXT administered twice daily, no difference was found between the treatment and placebo groups after 3 weeks in terms of social cognition [63]. In our study, there was no correlation between the correct number of emotion recognitions and OXT in the patient group, but a positive correlation was found between OXT and the social cognition subscales in healthy controls. It was found that OXT increased the number of both face recognitions and face recognition response times in the healthy group. The beneficial effect of OXT on social cognition is thought to be related to modification of mesolimbic dopamine pathways and amygdala activation [15]. These pathways are known to be affected by schizophrenia; the change in the neurophysiological integrity level in these regions may explain the difference between the groups.

The limited number of studies investigating the effects of AVP on social cognition have been contradictory. In a double-blind placebo-controlled trial with 34 patients with schizophrenia, no difference in emotion recognition between AVP and a placebo was found [64]. Goldman et al. [65] measured elevated plasma AVP levels in patients with osmotic dysregulation, such as polydipsia and hyponatremia, and schizophrenics who exhibited typical psychiatric symptoms and social impairment. In addition, increased plasma AVP levels were demonstrated in patients with acute psychotic disorder, regardless of whether they had used antipsychotic treatment [66]. Furthermore, in a double-blind placebo-controlled study of 34 schizophrenic patients that investigated the relationship between ANP and emotion recognition, no difference in emotion recognition was observed between AVP and the placebo. However, it has been observed that AVP reduces the recognition of angry faces in male patients and improves the recognition of fearful faces while reducing the recognition of sad faces in women

[64]. In our study, there was no significant relationship between social cognition and AVP in the patient group, but it was found that vasopressin increased the time needed to respond to happy and neutral facial expressions in the healthy controls. Although these findings confirm that there is a relationship between vasopressin and social cognition, there is a need for further studies to understand the direction and details of this relationship.

ANP plays an active role in circulatory hemodynamics and emotional stress-sensitive processes in CNS [67]. ANP show an anxiolytic effect by suppressing the HPA system, similar to OXT and AVP. There is no previous study in the literature on ANP and emotion recognition, and we found that ANP in healthy controls significantly increased performance on happy and total expression response times, such as OXT, and healing effect in recognizing other facial expressions. This suggests that ANP, like OXT, may have a positive effect on social cognition. Theoretically, this effect may be due to the presence of the regulatory effects of ANP on serotonin, prolactin and dopamine, as well as the effects on CRF neurons in the amygdala region. It is not surprising that the hormone ANP, a neuropeptide with effects on the limbic system-amygdala, which has a very wide distribution in the brain, is effective in social cognition. This is the first study to examine the relationship between ANP and social cognition, and more studies on this subject are warranted.

There were some limitations to our study. Considering the prevalence of schizophrenia, the higher number of participants in the study may increase the strength of the results of the study. Only schizophrenia patients in the remission period were evaluated, and thus values in the acute period remain unknown. Additionally, a limited number of tests on cognitive functions were used. For this reason, it was not possible to comment on certain areas of cognitive functions. It is important to repeat the study with the results of the tests performed by evaluating different areas of neuroscience and social cognition.

The strengths of our study include a relatively strong sample size compared to other studies in the literature. In this study, groups were sociodemographically similar. Individuals with IQ 80 and above were included. In addition, the mixing effect of sex variables, which has been shown to have an effect on IQ, education and blood OXT levels, which are known to be effective on cognitive functions, was eliminated. In addition, this study included different types of neurocognitive tests, the diagnosis of schizophrenia was confirmed by an experienced psychiatrist according to both diagnostic systems (DSM-IV, DSM V), and confounding factors, such as substance use and physical diseases, were excluded. This was one of the first studies in the field for OXT and AVP and the first study in the field for ANP, and therefore presents important data about

the relationship between neurohypophysis hormones and cognition in schizophrenia and healthy controls.

Conclusion

Main results of this study were that neuropeptide levels did not differ significantly between groups, correlations between neuropeptides and social and cognitive functioning differed significantly between controls and patients with schizophrenia, SCWT, WMS-VP, TMT-B scores were significantly elevated in controls and correlated with OXT levels, TMT-B, RAVLT (long-term memory) scores were significantly decreases in patients with ANP levels. Although ERT scores improved with oxytocin in patient and healthy group, oxytocin was found to be more effective in subtest in healthy group. ANP in controls correlated with reaction times to happy faces in ERT.

In this study, cognitive and social functioning tests showed significant results in different areas in the schizophrenia and control groups. Cognitive dysfunctions continued in the remission period in the schizophrenia patients, and a positive correlation was found between these functions and OXT and ANP levels. Unlike in other studies, the results of ANP's association with social cognition and other cognitive functions were presented here. The different correlations in the healthy controls and schizophrenia group suggest deteriorations in the functions and interactions with cognition of hormones in patients. Further studies, however, are needed to support the data generated in our study.

Disclosure statement

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