

Reduced Levels of Vasopressin and Reduced Behavioral Modulation of Oxytocin in Psychotic Disorders

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Oxytocin (OT) and arginine vasopressin (AVP) exert robust influence on social affiliation and specific cognitive processes in healthy individuals. Abnormalities in these neuroendocrine systems have been observed in psychotic disorders, but their relation to impairments in behavioral domains that these endocrines modulate is not well understood. We compared abnormalities of OT and AVP serum concentrations in probands with schizophrenia ($n = 57$), schizoaffective disorder ($n = 34$), and psychotic bipolar disorder ($n = 75$); their first-degree relatives without a history of psychosis ($n = 61, 43, 91$, respectively); and healthy controls ($n = 66$) and examined their association with emotion processing and cognition. AVP levels were lower in schizophrenia ($P = .002$) and bipolar probands ($P = .03$) and in relatives of schizophrenia probands ($P = .002$) compared with controls. OT levels did not differ between groups. Familiarity estimates were robust for OT ($h^2 = 0.79$, $P = 3.97e-15$) and AVP ($h^2 = 0.78$, $P = 3.93e-11$). Higher levels of OT were associated with better emotion recognition ($\beta = 0.40$, $P < .001$) and general neuropsychological function ($\beta = 0.26$, $P = .04$) in healthy controls as expected but not in any proband or relative group. In schizophrenia, higher OT levels were related to greater positive symptom severity. The dissociation of OT levels and behavioral function in all proband and relative groups suggests that risk and illness factors associated with psychotic disorders are not related to reduced OT levels but to a disruption in the ability of physiological levels of OT to modulate social cognition and neuropsychological function. Decreased AVP levels may be a marker of biological vulnerability in

schizophrenia because alterations were seen in probands and relatives, and familiarity was high.

Key words: oxytocin/vasopressin/schizophrenia/bipolar disorder/emotion recognition

Introduction

Two phylogenetically ancient neuropeptides, oxytocin (OT) and arginine vasopressin (AVP), regulate specific social and cognitive processes that are abnormal in schizophrenia. Although OT is commonly known for its role in birth and lactation and AVP as an antidiuretic, both have widespread influences on emotion and cognition in healthy individuals.¹⁻⁵ Reciprocal interactions between OT and AVP facilitate shifts between positive socially oriented and defensive states. OT attenuates the stress response, improves emotion processing, and can have negative effects on verbal learning and memory in healthy individuals.^{1-3,6-8} In contrast, AVP amplifies reactivity to stressors and under some conditions can have beneficial effects on attention, verbal learning, and memory.^{1-3,6-8}

Several lines of evidence suggest that alterations in these endocrine systems may be involved in the pathophysiology of schizophrenia.^{9,10} First, some studies have reported differences in cerebrospinal fluid and peripheral levels of OT and AVP in schizophrenia.¹¹⁻¹⁷ Similar results have been reported recently in bipolar disorder.¹⁸ Second, there is notable overlap between the neurobehavioral functions modulated by OT and AVP in healthy

adults with those that are abnormal in schizophrenia, such as social cognition and memory.^{19–22} For example, AVP 1b knockout mice exhibit impairments in memory and social behavior.²³ Third, these hormones both regulate physiological activity in brain regions that have established functional and structural alterations in the disorder.^{24–28} OT receptor concentrations are highest within the hippocampus, septum, and amygdala²⁹ and the highest level of brain AVP 1b receptor expression is in the hippocampus,³⁰ which is an important brain structure for memory³¹ and is abnormal in schizophrenia.^{25,32} In preclinical models, haploinsufficient reeler mice, an animal model of neural deficits in schizophrenia, show reductions in OT receptors especially in the hippocampus and piriform cortex.³³ AVP-deficient Brattleboro rats also show several phenotypes of schizophrenia including sensorimotor gaiting and social cognitive deficits, some of which are reversed by antipsychotic drugs.^{34–36} Fourth, postmortem AVP concentrations are reduced in the temporal cortex of schizophrenia patients.³⁷

Although OT and AVP have been implicated in schizophrenia,^{14,38} the degree to which alterations in these hormone systems contribute to neurobehavioral deficits in schizophrenia and other psychotic disorders has not been systematically examined. Although supraphysiologic doses of OT modulate emotional and cognitive processes in healthy individuals^{20,21} and in some small-sample schizophrenia studies,^{39–46} it remains unclear whether there are altered physiological protein levels across these disorders and whether physiological levels of OT and AVP modulate neurobehavioral processes in schizophrenia and other psychotic disorders as in healthy individuals. Studies of endocrine levels and their neurobehavioral associations are needed to address these questions.

Different assay methods may contribute to the considerable variability in findings across previous studies. Enzyme immunoassay (EIA) without extraction provides greater sensitivity and specificity for OT and AVP⁴⁷ than commercially available radioimmunoassay. With regard to endocrine—neurobehavioral associations, 2 small-sample studies reported positive associations between peripheral OT levels and emotion processing in schizophrenia^{11,48} and trust-related interpersonal interactions have been reported to modulate peripheral OT levels in healthy individuals^{49,50} but not in schizophrenia.⁵⁰ In schizophrenia, disruptions in peripheral levels of AVP have been linked to poorer cognitive functioning and increased positive symptom severity.¹⁴ In addition to questions about abnormalities in peripheral hormone levels and their clinical associations, other questions of interest include whether alterations in endocrine levels and their associations are present across psychotic disorders and whether they are familial.

This study was designed to examine alterations in OT and AVP levels and the relation of endocrine levels to behavior and cognition in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder

and in their first-degree family members. Our first study aim was to compare peripheral OT and AVP levels across the patient groups and their relatives. We hypothesized that patients and their relatives would show atypical OT and AVP levels, compared with controls. Our second aim was to evaluate whether peripheral OT and AVP levels were associated with clinical symptoms, emotion processing, and cognitive functioning. We predicted that higher physiologic levels of OT, which we found previously,⁵¹ would be associated with less severe symptoms and better emotion processing and cognitive functioning, whereas higher AVP levels would be associated with more severe symptoms and poorer emotion processing and cognitive functioning.

Methods

Participants

This study included participants from the Chicago site of the Bipolar and Schizophrenia Network on Intermediate Phenotypes (BSNIP) consortium.⁵² Written informed consent was provided by all participants (participant assent and parental consent for those <18 years). Participants included probands with schizophrenia ($n = 57$), schizoaffective disorder ($n = 34$, 76% bipolar type), psychotic bipolar disorder ($n = 75$), their first-degree relatives without a history of psychosis ($n = 61$, 43, and 91, respectively), and healthy controls ($n = 66$; [tables 1 and 2](#)). DSM-IV diagnoses were made at consensus meetings using all available information including findings from the Structured Clinical Interview for DSM-IV Axis I Disorders.⁵⁴ First-degree relatives were administered the Structured Interview for DSM-IV Personality (SIDP-IV).⁵⁵ Healthy comparison subjects had no history of a psychotic disorder or recurrent depression and no known immediate family history of these disorders.

Exclusion criteria included history of head injury with loss of consciousness >10 minutes; pregnancy; positive urine toxicology screen for common drugs of abuse on the day of testing; diagnosis of substance abuse in the past 30 days or substance dependence in the past 6 months; history of systemic medical or neurological disorder affecting mood or cognition; or age-corrected Wide-Range Achievement test reading test standard score ≤ 65 . A full description of subject recruitment and clinical assessment is available.⁵²

Measures

Clinical Symptoms and Global Functional Status. Clinical symptom assessments included the Positive and Negative Syndrome scale,⁵⁶ Montgomery Asberg Depression Rating scale,⁵⁷ and Young Mania Rating scale.⁵⁸ Community functioning was assessed with the Birchwood Social Functioning scale.⁵⁹

Emotion Processing and Cognition. The Penn Emotion Recognition-40 test (PENN ER-40)^{60–62} assesses the ability to accurately recognize specific emotions conveyed

in pictures of faces. Stimuli are 40 faces (half female) expressing 1 of 4 emotions (happiness, sadness, anger, fear) or a neutral expression (8 faces per expression). The primary outcome measure was the accuracy of affect identification. The Brief Assessment of Cognition in Schizophrenia (BACS) battery assessed global neuropsychological function via a composite score.^{63,64}

Serum Hormone Assays. Blood samples were drawn in the morning when possible (89% blood draws before noon). The percentage of participants drawn before noon did not differ across groups ($P = .21$). Samples were stored in plain tubes, spun at 4°C, divided into 300 ul aliquots, and stored at -80°C. Samples were batched, diluted in an assay buffer to give reliable results within the linear portion of the standard curve (OT 1:4; AVP 1:2), and completed in duplicate using unextracted plasma. OT and AVP were quantified with an EIA kit (Enzo Life Sciences/Assay Designs).⁴⁷ These EIAs are highly sensitive (minimal detection levels < 12 pg/ml OT; 4 pg/ml AVP) and specific with cross-reactivity between OT and AVP < 0.04%. Samples were assayed blind to subject information. All samples from a given subject were run at the same time. OT values > 2000 pg/ml and AVP values > 400 pg/ml were re-run to confirm sample accuracy. OT samples consistently remaining higher (10 samples) were set at 2000 pg/ml, and AVP samples constantly remaining higher (6 samples) were set at 400 pg/ml for statistical analyses. Intra-assay coefficients of variation were <10% for both assays.

Statistical Analyses

Hierarchical linear modeling (HLM) with SAS (version 9.2, SAS Institute Inc, Cary, NC) was used to examine group differences in peripheral hormone levels, with family membership treated as a random effect because participants were nested within families. To test hypotheses most firmly supported by prior studies, planned comparisons were performed to test for group differences starting with schizophrenia patients, their relatives, and healthy controls. To determine if pedigrees with psychotic bipolar disorder and schizoaffective disorder probands showed similar patterns to schizophrenia families, planned comparisons were performed to test for differences between these groups. We evaluated whether hormonal effects varied depending on whether patients were taking first- or second-generation antipsychotic medications or anticonvulsant/mood stabilizers; associations were minimal ([supplementary table 1](#)). Next, multivariable linear regression modeling was used to examine the degree to which endocrine levels were associated with emotion processing, cognition, clinical symptoms, and global functional status. When investigating hormone-behavior associations, OT and AVP were examined in the same multivariable models, so we could measure the contribution of OT controlling for AVP and vice versa because OT and AVP levels were

modestly correlated across groups (r 's ranged between .25 and .43; [supplementary table 2](#)). Because these exploratory correlational analyses were performed for heuristic purposes to examine the potential clinical significance of group differences and clinical associations, we did not correct for multiple comparisons. All analyses were adjusted for age, race, and sex. Significance was set at $P < .05$; trends at $P \geq .05$ and $P < .10$ are reported.

Estimates of familiarity (h^2) represent the portion of the phenotypic variance accounted for by family membership and were obtained using sequential oligogenic linkage analysis routine.⁶⁵ To test for the significance of familiarity, a maximum likelihood ratio test compared a model in which phenotypic variation was explained by family membership to one not considering variation explained by familial factors. Because families were recruited through the identification of a psychotic proband and not as a representative community sample, a correction was applied to account for this ascertainment bias.⁶⁶

Results

Baseline Differences in Cognition, Social Functioning, and Emotion Recognition

Consistent with multisite BSNIP consortium findings,^{52,53} there were significant group differences on the BACS composite and in community functioning (P 's < .001; [Tables 1 and 2](#)). All proband groups performed worse than healthy controls on both measures (P 's < .001). Schizophrenia probands also performed worse than bipolar probands on both measures (P 's < .05). On the PENN ER-40, schizophrenia probands ($P < .001$) performed worse than healthy controls and bipolar probands ($P = .04$). Differences between relatives and healthy controls were not significant.

Group Differences and Familiarity Estimates for Peripheral Concentrations of OT and AVP

HLM analyses yielded significant group differences in AVP for schizophrenia probands and their relatives compared to controls, but not OT levels ([figure 1](#)). Schizophrenia probands ($B = -0.44$, $SE = 0.14$, $P = .002$) and their relatives ($B = -0.37$, $SE = 0.12$, $P = .002$) showed lower AVP but not OT levels, compared with controls. Bipolar probands ($B = -0.27$, $SE = 0.13$, $P = .03$) also had lower levels of AVP but not OT, compared with controls. Relatives of bipolar probands showed a trend for lower levels of AVP but not OT, compared with controls ($B = -0.20$, $SE = 0.11$, $P = .07$). Among the smaller sample of schizoaffective families, probands ($M = 4.24$, $SE = 0.14$) showed a trend toward lower levels of AVP, compared with controls ($M = 4.51$, $SE = 0.09$; $B = -0.26$, $SE = 0.16$, $P = .09$), similar in magnitude to the reduction seen in bipolar probands. Post hoc comparisons yielded no significant differences in peptides between proband groups or first-degree relative groups. All proband and relative groups showed a higher proportion

Table 1. Demographics and Clinical Characteristics for Health Comparison Subjects and Probands with Schizophrenia, Schizoaffective Disorder, and Psychotic Bipolar Disorder

| | Schizophrenia Group ^a (<i>n</i> = 57) | Schizoaffective Group ^b (<i>n</i> = 34) | Psychotic Bipolar Group ^c (<i>n</i> = 75) | Healthy Comparison Group ^d (<i>n</i> = 66) | Post Hoc ^e |
|------------------------------------|--|---|---|--|-----------------------|
| | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | |
| Age (y) | 35.31 (12.92) | 37.50 (14.12) | 32.97 (13.61) | 37.18 (12.65) | — |
| Education (y) | 12.86 (2.49) | 13.67 (2.89) | 14.11 (2.58) | 15.36 (2.44) | d > a, b, c; c > a |
| WRAT | 94.24 (15.67) | 100.00 (16.63) | 103.93 (15.09) | 103.33 (12.37) | b, c, d > a |
| BACS composite | -1.39 (1.42) | -1.11 (1.20) | -0.77 (1.31) | 0.14 (1.14) | d > a, b, c; c > a |
| PENN ER-40 (% correct) | 76.75 (11.43) | 79.77 (9.85) | 80.25 (8.46) | 82.64 (7.37) | d, c > a |
| SFS | 126.07 (19.74) | 125.53 (19.81) | 140.05 (20.21) | 162.57 (14.65) | d > a, b, c; c > a, b |
| PANSS | | | | | |
| Positive subscale | 19.41 (5.66) | 19.59 (4.71) | 12.84 (3.89) | — | a, b > c |
| Negative subscale | 20.21 (7.02) | 17.38 (6.60) | 13.68 (4.53) | — | a, b > c |
| YMRS | 7.86 (6.48) | 8.26 (5.57) | 5.62 (6.21) | — | a, b > c |
| MADRS | 9.80 (7.26) | 15.32 (9.85) | 10.83 (9.31) | — | b > a, c |
| | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | |
| Male | 35 (61) | 15 (44) | 24 (32) | 28 (42) | a > b, c, d |
| Race | | | | | |
| Caucasian | 25 (44) | 18 (53) | 58 (77) | 37 (56) | c > a, b, d |
| African American | 24 (42) | 15 (44) | 11 (15) | 18 (27) | a, b > c, d |
| Other | 8 (14) | 1 (3) | 6 (8) | 11 (17) | d > b |
| Blood draw ≤ noon | 49 (86) | 32 (94) | 67 (89) | 63 (95) | — |
| Medication class ^f | | | | | |
| Antipsychotic | | | | | |
| First generation | 12 (21) | 5 (15) | 3 (4) | — | a, b > c |
| Second generation | 43 (75) | 25 (73) | 51 (68) | — | — |
| Anticonvulsant/ mood stabilizer | 10 (17) | 22 (65) | 53 (71) | — | b, c > a |
| Lithium | — | 2 (6) | 22 (29) | — | c > a, b |
| Valproic acid | 6 (10) | 7 (20) | 13 (17) | — | — |
| Antidepressant | 20 (35) | 21 (62) | 35 (47) | — | b, c > a |
| Sedative/anxiolytic | 15 (26) | 13 (38) | 22 (29) | — | — |
| Stimulant | 5 (9) | 2 (6) | 11 (15) | — | — |
| Anticholinergic | 5 (9) | 1 (3) | 4 (5) | — | — |

Note: WRAT, Wide-Range Achievement Test-IV: reading test; BACS, Brief Assessment of Cognition in Schizophrenia race-adjusted composite (higher = better functioning); PENN-ER-40, Penn Emotion Recognition-40 test; SFS, Social Functioning scale (higher = better functioning); PANSS, Positive and Negative Syndrome scale; YMRS, Young Mania Rating scale; MADRS, Montgomery Asberg Depression Rating scale.

a, b, c and d—all differences noted are at *P* < .05.

^ePost hoc tests were computed when the omnibus *F* test was significant at *P* < .05.

^fConsistent with Tamminga et al.⁵² and Hill et al.⁵³

of individuals with lower levels of AVP (ie, <1 *SD* from controls), compared with controls using the Lambda^{67,68} statistic (supplementary table 3). Additionally, there were more schizophrenia probands than bipolar probands with low levels of AVP (*P* = .04). The same pattern was demonstrated when comparing relatives of schizophrenia to relatives of bipolar probands (*P* = .05).

Familiarity estimates were highly significant for both OT (*h*² = 0.79, *SE* = 0.08, *P* = 3.97e-15) and AVP (*h*² = 0.78, *SE* = 0.10, *P* = 3.93e-12) in the pooled data of proband families. Correlations between relative and proband's OT and AVP levels were also robust (figure 2).

Comparable familiarity estimates were observed in schizophrenia and bipolar pedigrees (supplementary table 4). In probands, chlorpromazine equivalents of antipsychotic treatment⁶⁹ were not associated with hormone levels. Excluding first-degree relatives taking psychiatric medications from the HLM analysis did not change the pattern of results.

Hormone-Behavior Associations

Emotion Processing. Higher levels of OT were associated with better emotion recognition accuracy in healthy

Table 2. Demographics, History of Psychosis, and Personality Traits for Healthy Comparison Subjects, First-Degree Relatives of Probands With Schizophrenia, Schizoaffective Disorder, and Psychotic Bipolar Disorder

| | Relatives of Schizophrenia Probands ^a (<i>n</i> = 61) | Relatives of Schizoaffective Probands ^b (<i>n</i> = 43) | Relatives of Bipolar Probands ^c (<i>n</i> = 91) | Healthy Comparison Group ^d (<i>n</i> = 66) | Post Hoc ^e |
|------------------------------------|---|---|--|---|-----------------------|
| | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | <i>M</i> (<i>SD</i>) | |
| Age (y) | 42.77 (15.83) | 39.79 (16.39) | 41.01 (15.47) | 37.18 (12.65) | — |
| Education (y) | 13.97 (2.38) | 14.40 (2.86) | 15.19 (2.64) | 15.36 (2.44) | c, d > a, b |
| WRAT | 98.82 (14.67) | 105.29 (15.37) | 104.15 (13.88) | 103.33 (12.37) | — |
| BACS composite | -0.11 (1.03) | 0.26 (1.02) | 0.17 (1.12) | 0.14 (1.14) | — |
| PENN ER-40 (% correct) | 81.08 (6.22) | 81.18 (7.05) | 82.27 (7.52) | 82.64 (7.37) | — |
| SFS | 150.84 (18.33) | 148.11 (20.55) | 152.46 (18.41) | 162.57 (14.65) | d > a, b, c |
| | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | <i>n</i> (%) | |
| Male | 15 (24) | 14 (33) | 32 (35) | 28 (42) | — |
| Race | | | | | |
| Caucasian | 33 (54) | 27 (63) | 78 (86) | 37 (56) | c > a, b, d |
| African American | 22 (36) | 13 (30) | 10 (11) | 18 (27) | a, b, d > c |
| Other | 6 (10) | 3 (7) | 3 (3) | 11 (17) | d > b |
| Blood draw ≤ noon | 53 (87) | 42 (98) | 79 (87) | 63 (95) | — |
| Medications | | | | | |
| No medications | 53 (87) | 33 (77) | 62 (68) | — | — |
| Antipsychotic | | | | | |
| Second generation | 2 (3) | 2 (4) | 4 (4) | — | — |
| Anticonvulsant/ mood stabilizer | — | 4 (9) | 7 (7) | — | — |
| Lithium | — | 1 (2) | 1 (1) | — | — |
| Valproic acid | 1 (2) | 2 (5) | 1 (1) | — | — |
| Antidepressant | 7 (11) | 7 (16) | 21 (23) | — | — |
| Sedative/anxiolytic | 3 (5) | 2 (5) | 8 (9) | — | — |
| Stimulant | — | 3 (7) | 4 (4) | — | — |

Note: WRAT, Wide-Range Achievement Test-IV: reading test; PENN-ER-40, Penn Emotion Recognition-40 test; SFS, Social Functioning scale (higher = better functioning); BACS, Brief Assessment of Cognition in Schizophrenia race-adjusted composite score (higher = better functioning); medication class consistent with Tamminga et al⁵² and Hill et al.⁵³

a, b, c and d—all differences noted are at $P < .05$.

^ePost hoc tests were computed when the omnibus F test was significant at $P < .05$.

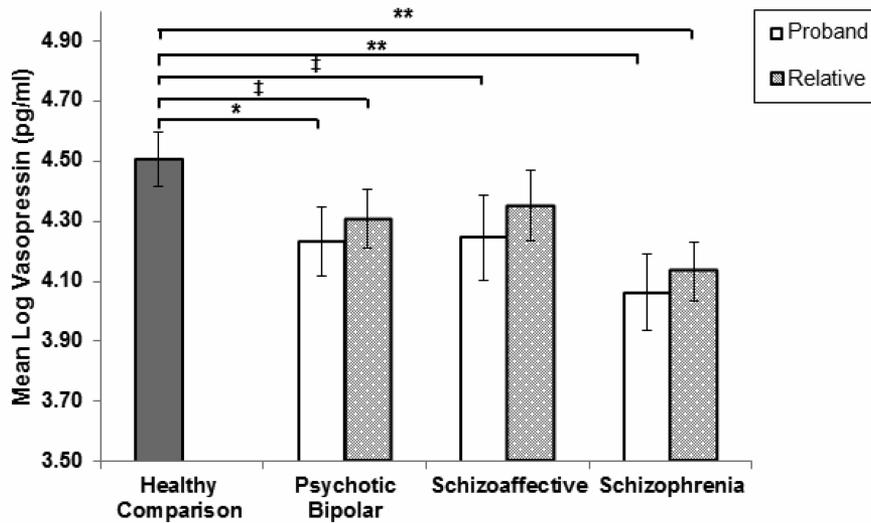
controls ($\beta = 0.40$, $B = 3.76$, $SE = 1.13$, $P < .001$) but not in patients with schizophrenia or their relatives (Figure 3). Higher levels of OT in healthy individuals were associated with better emotion recognition of neutral ($\beta = 0.35$, $B = 7.17$, $SE = 2.64$, $P < .01$), happy, ($\beta = 0.27$, $B = 1.44$, $SE = 0.69$, $P = .04$), and sad faces ($\beta = 0.26$, $B = 6.03$, $SE = 2.96$, $P = .04$). OT levels also were not associated with emotion recognition in bipolar or schizoaffective probands or their relatives (figure 3). All associations were significantly reduced relative to controls (Fisher's r to z transformations, P 's $< .05$) except for the smaller schizoaffective relative group for whom the difference was at the trend level ($P = .10$). AVP levels were not significantly associated with emotion recognition in any group.

Cognition. Similar to the emotion recognition results, higher levels of OT were associated with better global

neuropsychological performance in healthy controls ($\beta = 0.26$, $B = 0.36$, $SE = 0.17$, $P = .04$) but not in any proband or relative group. AVP levels were not associated with overall neuropsychological performance in any group.

Clinical Symptoms. In schizophrenia, higher levels of OT, but not AVP, were associated with more severe positive symptoms ($\beta = 0.32$, $B = 2.67$, $SE = 1.17$, $P = .02$). Because the sample was clinically stable for at least 1 month at the time of the study, this may reflect a relation between higher OT levels and the presence of more significant residual or treatment nonresponsive symptoms. There was a trend for higher levels of OT to be associated with more severe negative ($\beta = 0.31$, $B = 2.36$, $SE = 1.33$, $P = .08$) and manic symptoms ($\beta = 0.32$, $B = 2.03$, $SE = 1.06$, $P = .06$) in schizoaffective probands. In schizoaffective probands, those with

(a) Mean Vasopressin Levels:



(b) Mean Oxytocin Levels:

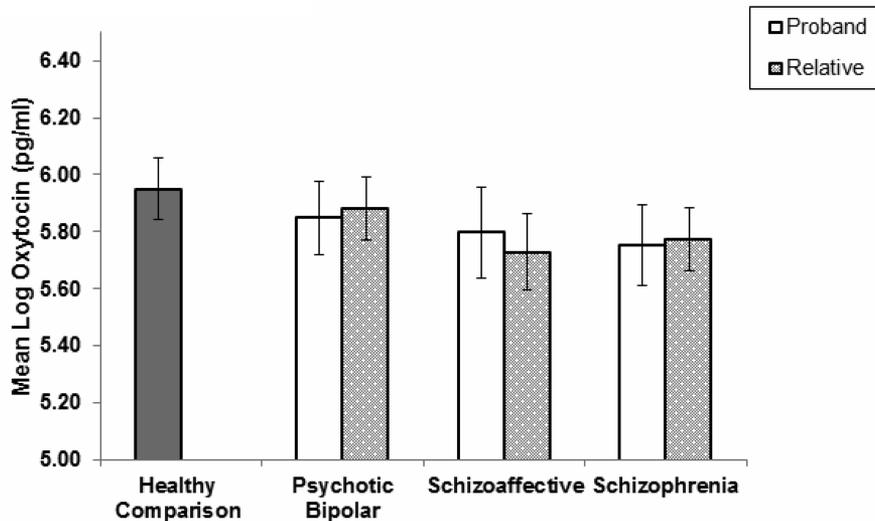


Fig. 1. Comparison of serum vasopressin (a) and oxytocin levels (b) between the healthy comparison group, psychotic probands, and their first-degree relatives. ** $P < .01$; * $P < .05$; ‡ $P \leq .09$. Serum values were adjusted for age, race, sex, and first and second generation antipsychotic medication use.

lower AVP levels had more severe manic ($\beta = -0.50$, $B = -4.06$, $SE = 1.29$, $P = .002$) and positive symptoms ($\beta = -0.40$, $B = -2.68$, $SE = 1.12$, $P = .02$). Levels of OT and AVP were not related to symptom severity in bipolar probands. Across all relatives, regardless of proband diagnosis, those with a Cluster A (psychosis spectrum) personality disorder had lower levels of AVP than those without a Cluster A diagnosis ($\beta = -0.17$, $B = 0.55$, $SE = 0.23$, $P = .02$).

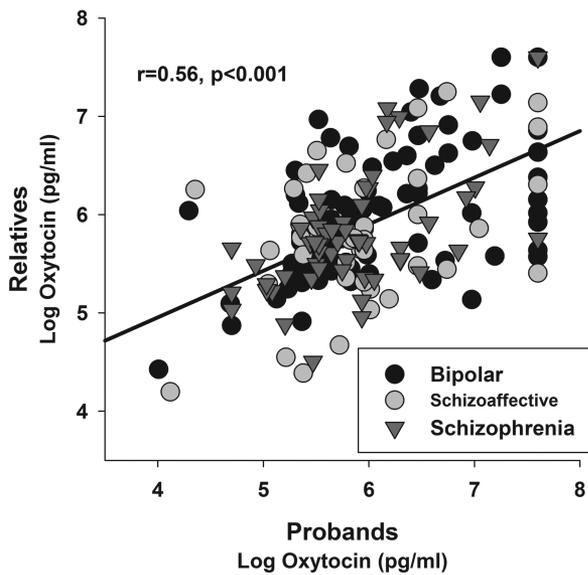
Community Functioning and Sex Differences. OT and AVP were not associated with community functioning in any group. There were no significant sex by group

interactions in hormone levels, and there were no sex differences in any hormone-behavior relationships.

Discussion

The results of this study demonstrate abnormalities of serum AVP and in the modulatory function of OT on emotion processing and cognitive functioning among individuals with psychotic disorders and their first-degree relatives. Both schizophrenia patients and their relatives showed decreased levels of AVP compared with the healthy comparison group; similar findings were seen in bipolar patients and their relatives albeit to a less

(A) Oxytocin



(B) Vasopressin

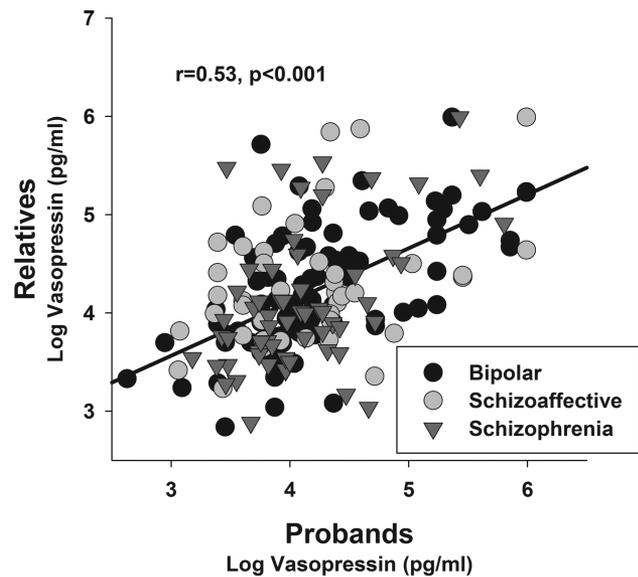


Fig. 2. Relationship between oxytocin and vasopressin levels in relatives and probands. Values for each relative are plotted relative to their family member proband. Data represents 203 pedigrees and 144 probands. Maximum levels for oxytocin and vasopressin were used as described in the text.

prominent degree, and AVP levels were highly familial. Additionally, relatives with a psychosis spectrum personality disorder showed lower AVP levels than other relatives. Thus, reduced AVP levels have several characteristics of a promising endophenotype across psychotic disorders.

Findings with OT were notably different. OT levels were not reduced in any proband or relative group even though familiarity was highly significant across psychotic disorders. Rather, findings with OT were most notable in their association with clinical symptoms and reduced association with neurobehavioral functions. First, OT levels in schizophrenia and schizoaffective probands were associated with higher rather than lower clinical symptom levels. Second, the positive association between OT levels and better social cognition and general neuropsychological function observed in our healthy controls and widely reported in the literature^{3,4} was not seen in any proband or relative group. This finding suggests a dissociation between OT levels and behavioral function in both probands with psychotic disorders and their unaffected relatives, such that hormone levels appear to have a reduced capacity to modulate affective and neuropsychological functioning. This pattern suggests alterations in downstream processes at the level of OT receptors, signal transduction, or in the neurophysiological integrity of brain regions dense with OT receptors that may be impacted by illness and risk rather than an abnormality in OT peptide levels.

Our findings are consistent with previous studies demonstrating AVP dysregulation in schizophrenia.^{14,15,17,38,70}

Of note, however, the direction of effects in prior work has been mixed, perhaps in relation to state of illness and assays used. For example, in contrast to our clinically stable patients with schizophrenia showing lower levels of AVP, studies of unmedicated acutely ill first-episode patients show higher levels of AVP, compared with healthy controls in 2 of 3 studies.^{14,15,17} Higher AVP levels in acutely ill patients maybe the result of a dysregulated biological stress response system.⁷¹

The present findings extend prior work by demonstrating a similar pattern of abnormality in psychotic bipolar disorder and schizoaffective probands. There was a similar trend in the relatives of bipolar probands, and all relative groups had a higher percent of individuals with AVP levels 1 *SD* below healthy controls. Also, we observed that findings in family members were greater in those with psychosis spectrum personality traits. These findings suggest that alterations in AVP occur across psychotic disorders rather than selectively in schizophrenia. Medications could be confounding factors in our proband data because they varied based on clinical indication. However, statistical associations of effects with medication treatments were not significant, and AVP alterations in untreated relatives were similar to those seen in the patient probands. This pattern of effects is more consistent with disease-related rather than treatment-induced abnormalities.

In contrast to effects seen in serum AVP, we did not find significant alterations in OT levels in probands with psychotic disorders or their first-degree relatives. This is consistent with our previous studies of schizophrenia

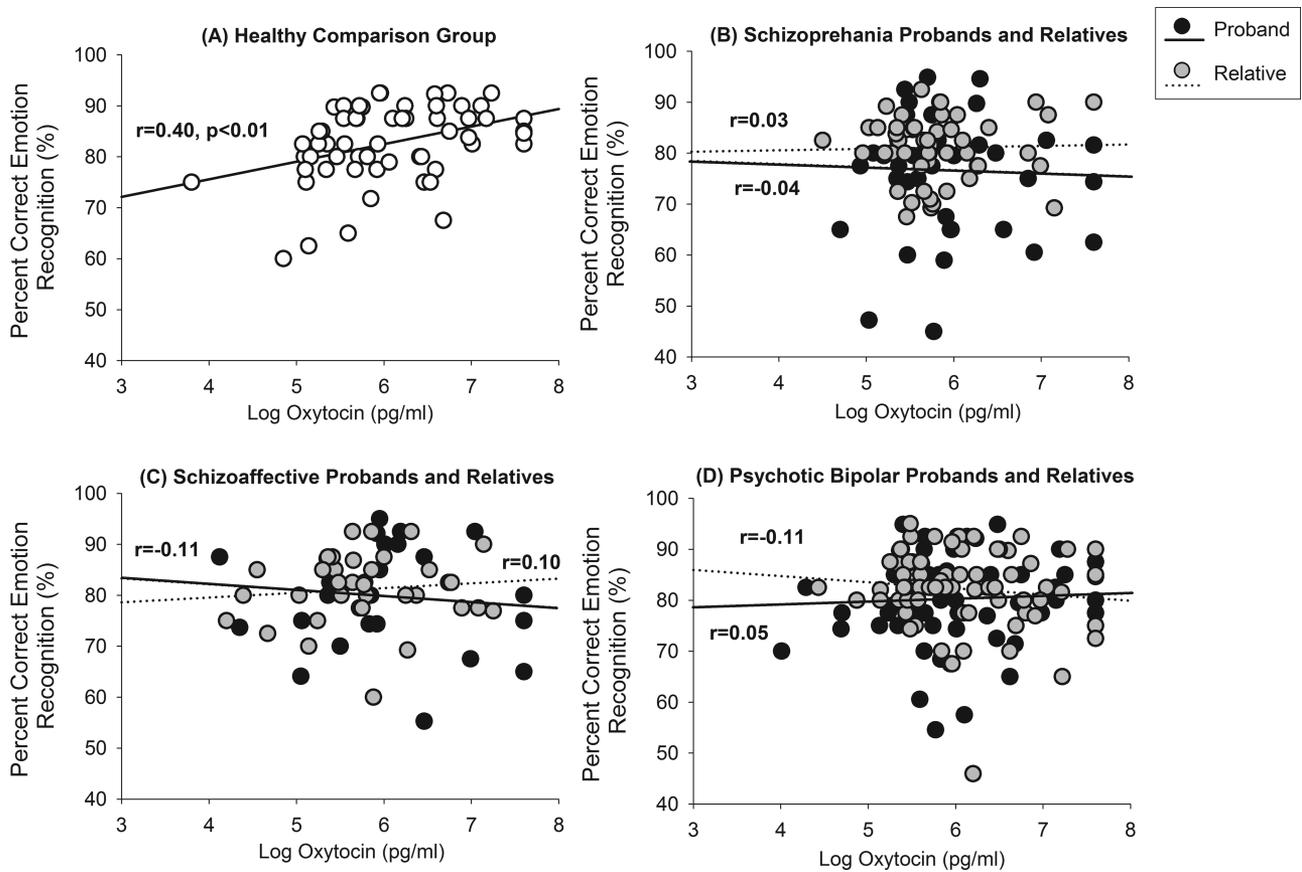


Fig. 3. Raw correlations showing (A) Higher serum levels of oxytocin are associated with better performance on a facial emotion recognition test in the healthy comparison group but not in (B) schizophrenia probands and their first-degree relatives, (C) schizoaffective probands and their first-degree relatives, or (D) psychotic bipolar and their first-degree relatives.

patients.^{14,51} The only other study to date using the same assay methodologies showed lower levels of peripheral OT in schizophrenia patients with polydipsia hyponatremia.¹¹

In contrast to our previous findings,⁵¹ OT levels were associated with higher clinical symptom levels. At least 3 factors might have contributed to these differences. First, schizophrenia probands in this study were recruited from the community rather than a clinic and exhibited higher levels of positive symptoms than our previous study of chronic patients.⁵¹ Second, given our larger sample sizes we were able to examine OT-symptom associations separately for schizophrenia and schizoaffective probands. Analyses in our previous study combined both disorders. Third, OT levels were higher in probands in the present study. One possibility is that OT may have a protective or beneficial effect when the range of OT values is lower, but detrimental effects when OT values are higher. Alternatively, it is possible that higher OT levels in probands may have been a compensatory response and thus be mitigating symptoms that might otherwise be even higher.

With respect to clinical associations, relationships between OT and clinical symptoms were stronger in schizophrenia spectrum disorders than bipolar probands. Thus, the clinical significance of OT levels may be greater in

psychotic disorders with higher levels of persistent positive and negative symptoms and poorer community functioning. The implications of this study for the use of exogenous OT as a treatment are indirect but worthy of note. While treatment-induced supraphysiological levels may have direct positive effects or reset responsivity of brain systems to OT modulation,^{40,44} the absence of abnormal physiological OT levels, the lack of association between OT levels and social cognition, and the positive relationship between OT levels and symptom severity do not in themselves offer support for this therapeutic strategy.

Concentrations of both peripheral hormone levels were highly familial, and recent investigations suggest that variations in genes for OT (*OXT*) and AVP (*V1aR*) show associations with schizophrenia, symptom severity, and treatment response to clozapine in schizophrenia patients.⁷²⁻⁷⁵ Hence, the presence of alteration in family members and its familiarity suggest that OT and AVP genes or other factors influencing the impact of these hormones on brain and behavioral function may contribute to psychosis vulnerability.

Limitations of this study include a cross-sectional study design, and a single measurement of hormone levels. The study was designed to assess trait-like alterations

rather than clinical state relationships, so the range of symptom severity was limited by design. Thus, relations of hormones to active symptoms may be underestimated, or different patterns of alterations might be seen during acute episodes of illness. Experimental approaches, such as administration of intranasal OT or agents that affect the AVP system are needed to assess therapeutic implications and complement studies of peripheral hormone levels. In addition, it has been suggested that perturbations of the hypothalamic-pituitary-adrenal axis may be a risk factor for the development of psychotic disorders.⁷¹ This and other hormones merit study in order to examine patterns and specificity of hormone alterations associated with psychotic disorders. Finally, although neuropeptides in the peripheral circulation do not readily cross the blood-brain barrier, most peripheral OT and AVP are synthesized within the brain and released into the periphery via the posterior pituitary. Animal data indicate that central and peripheral levels of OT are correlated.⁷⁶ While central nervous system implications of peripheral measures are uncertain, peripheral hormone levels, both at baseline and in reaction to social stimuli have been associated in numerous studies with multiple behavioral parameters that indicate the relevance of peripheral measures of neurobehavioral functions.^{77,78}

Overall, our findings extend previous work in schizophrenia to suggest that OT and AVP may be involved in pathophysiology across psychotic disorders and that they may be involved in the vulnerability to schizophrenia as indicated by findings in first-degree relatives. The reduced modulation of relevant neurobehavioral functions by OT even in the context of normal peripheral hormone levels suggests that a downstream alteration in OT receptors or relevant limbic and neocortical systems where the receptors are densely expressed, rather than an alteration in hormone levels, may contribute to social cognition deficits in psychotic disorders.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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