

# Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits

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## Abstract

Polydipsic hyponatremic schizophrenic patients (PHS) exhibit enhanced plasma arginine vasopressin (pAVP) and hypothalamic pituitary adrenal (HPA) axis responses to stress that appear attributable to anterior hippocampal dysfunction. Neuroanatomic and electrophysiologic studies indicate oxytocin activity in PHS patients should also be affected. Furthermore, oxytocin normally diminishes HPA responses to stress and facilitates cognitive and behavioral functions impaired in schizophrenia, suggesting that diminished oxytocin activity could contribute to this subsets' neuropsychiatric disorder. In the present study, we measured plasma oxytocin levels at intervals before and after stress induction in six polydipsic hyponatremic (PHS), four polydipsic normonatremic (PNS), five nonpolydipsic normonatremic schizophrenic (NNS) patients and seven healthy controls. Most of these subjects also completed studies measuring their medial temporal lobe volumes, their hippocampal-mediated HPA feedback and their ability to discriminate different facial emotions (an oxytocin-sensitive measure which is markedly impaired in schizophrenia). Results demonstrated that 1) plasma oxytocin levels were lower ( $p = .006$ ) in hyponatremic patients relative to the other three groups, whose levels were similar and did not change. Oxytocin levels across all subjects were 2) inversely correlated with anterior hippocampal ( $p = .004$ ) (but not posterior hippocampal or amygdala volumes), and 3) directly correlated with the integrity of hippocampal-mediated HPA feedback ( $p = .039$ ). Finally, 4) oxytocin levels predicted schizophrenic patients' ability to correctly identify facial emotions ( $p = .004$ ). These preliminary data provide further evidence that neuroendocrine dysfunction in PHS reflects anterior hippocampal pathology and contributes to a characteristic neuropsychiatric syndrome.

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## 1. Introduction

The frequent occurrence in chronically psychotic patients of polydipsia (Hoskins and Sleeper, 1933) and

unexplained impairments in water excretion (Targowla, 1923) was discovered in the early 1900s. The impaired water excretion was noted to worsen during psychotic exacerbations (Targowla, 1923), periodically culminating in life-threatening water intoxication (Barahal, 1938). Fifty years later it was confirmed that both the basal impairment and the transient worsening in water excretion were caused by enhanced plasma arginine vasopressin (pAVP) activity (Goldman et al., 1988, 1997). Systematic

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assessment of recognized and putative factors was initially unrevealing (Goldman et al., 1988, 1996a,b; Suzuki et al., 1992), except for the unexpected finding that polydipsic schizophrenic patients were relatively resistant to dexamethasone's effects on cortisol secretion (i.e. DST nonsuppressors) (Goldman et al., 1993).

Recent studies now indicate that both pAVP and hypothalamic–pituitary–adrenal (HPA) axis findings in polydipsic hyponatremic schizophrenic patients (PHS) are attributable to a circumscribed defect in hippocampal function (Herman et al., 2005; Nettles et al., 2000). Specifically, these patients do not exhibit the normal hippocampal-mediated constraint of pAVP and the HPA axis following stress (Goldman et al., 2007c) and exhibit blunted hippocampal-mediated glucocorticoid negative feedback (Goldman et al., 2007b; Tessner et al., 2007). Indeed, they also have smaller volumes of the hippocampal segment (i.e. anterior) which likely regulates neuroendocrine function (Goldman et al., 2007a). Furthermore, analogous findings are recreated in an animal model of schizophrenia which disrupts neurodevelopment of this hippocampal segment (Chrapusta et al., 2003; Mitchell and Goldman, 2004).

Oxytocin is secreted from the same hypothalamic nuclei which regulate pAVP and the HPA axis, and neuroanatomic/electrophysiologic data indicate it is modulated by the same hippocampal projections which modulate pAVP and HPA axis activity (Herman et al., 2002; Risold and Swanson, 1996). Oxytocin and AVP are closely related neuropeptides with a long evolutionary history of modulating diverse responses to stress from cortisol release to social interactions (Carter, 1998; Carter et al., 2007; Keverne and Curley, 2004; Parker et al., 2005; Storm and Tecott, 2005). The actions of these two peptides, however, often oppose one another (Legros, 2001; Young and Wang, 2004). In humans, recent data indicate oxytocin diminishes both cortisol and behavioral responses to stress (Heinrichs et al., 2003), modulates neural responses to faces (Domes et al., 2007b), promotes trust (Kosfeld et al., 2005) and enhances the ability to accurately discriminate facial emotions (Domes et al., 2007a). In contrast, vasopressin makes faces appear more threatening (Thompson et al., 2006) and enhances stress responses.

Impaired ability to discriminate facial emotions and maintain appropriate levels of trust are robust deficits in persons with schizophrenia (Kohler et al., 2003, Kucharska-Pietura et al., 2005) and are closely linked to their social dysfunction (Addington et al., 2006; Brunet-Gouet and Decety, 2006). Recent studies demonstrate oxytocin ameliorates deficits in emotion discrimination in autism (Hollander et al., 2007) and reverses altered social behavior in animal models of

schizophrenia (Lee et al., 2007), while an older open-label study indicated it ameliorates symptoms in schizophrenia (Bujanow, 1974). These observations suggest that elevated vasopressin and diminished oxytocin could contribute to many aspects of these patients' neuropsychiatric disorder. Therefore, we hypothesized that oxytocin activity would be diminished in the subset of schizophrenic patients with polydipsia and hyponatremia (PHS). In the present study, we also explored the relationship of plasma oxytocin activity to medial temporal lobe volume, other indices of hippocampal-mediate neuroendocrine function, and accuracy of identifying emotions in faces.

## 2. Methods

### 2.1. Subjects

Six PHS, four polydipsic normonatremic schizophrenic (PNS), five nonpolydipsic normonatremic schizophrenic (NNS) subjects and seven healthy controls (HC) were selected from a previously studied sample based on the availability of plasma for assay and the number of associated studies they had completed. All psychiatric subjects were stabilized on clinically determined doses of antipsychotics and acclimated to the research setting in order to minimize the impact of novelty and other sources of uncontrolled stress. All but four patients were receiving haloperidol: one polydipsic and two hyponatremic patients were on risperidone, and one hyponatremic patient was taking ziprasadone. On separate occasions, fifteen of the 22 subjects completed an assessment of glucocorticoid feedback under conditions in which hippocampal influences are thought to predominate (Goldman et al., 2007b), 19 underwent a structural MRI scan, and 20 underwent testing of facial affect discrimination.

### 2.2. Design

#### 2.2.1. Cold pressor

All subjects completed a standard cold pressor test during the fifth week of admission in which they immersed their nondominant hand in ice water for 1 min (see Goldman et al., 2007c for details). The cold pressor was chosen because it is a reliable stressor in schizophrenia and likely increases neuroendocrine secretion as a consequence of its emotional impact (see Goldman et al., 2007c). The test was performed in the evening when the hypothalamic pituitary adrenal (HPA) axis is comparatively quiescent and hippocampal influences predominate (van Eekelen et al., 2003).

Briefly, two intravenous catheters were placed in forearm veins at 1800 h. Plasma osmolality then was normalized in each subject with a one-hour infusion of saline to control for effects of plasma osmolality on neuroendocrine responses. Blood sampling began at 1930 h. Thirty minutes following the onset of blood sampling (2000 h) the cold pressor occurred after which sampling continued at regular intervals for the next 45 min. Three samples were obtained in the 30 min prior to the cold pressor, and four in the subsequent 45 min. Six of the seven healthy controls were studied twice in randomized order, once immersing their hand in the ice water bath and once in a tepid water bath in order to more confidently characterize the effect of stress.

### 2.2.2. *Glucocorticoid negative feedback*

Studies were completed during the sixth week of admission in the evening after treatment with two doses of metyrapone (500 mg PO) to reduce basal cortisol levels. Levels were then restored with an infusion of cortisol (0.03 mg/Kg/h) for 150 min. Plasma adrenocorticotropic hormone was sampled at 20 min intervals from 40 min prior to the infusion until 90 min after it was completed. See Goldman et al., 2007b for further details.

### 2.2.3. *Structural imaging*

Whole brain images were obtained during the fourth week of admission on a 3.0 T-GE Signa LX scanner (GE Medical Systems, Milwaukee, WI). Two different sequences were obtained. 3D T<sub>1</sub> weighted images, using a spoiled gradient-recalled echo sequence, were acquired with the following parameters: echo time (TE)=min-full; repetition time (TR)=20 ms; 1.5 mm coronal slices, flip angle=30°, field of view (FOV)=160 mm, matrix=256×256. T<sub>2</sub> weighted images were acquired using a fast spin-echo sequence with the following parameters: TE=85 ms, TR=4800 ms, 1.8 mm coronal slices, FOV=160 mm, matrix=256×256, echo train length=8, spacing=interleave. Standard work-up consisted of spatial normalization through alignment of T<sub>1</sub> images along the AC/PC line and interhemispheric fissure; re-sampling to yield 1 mm contiguous coronal slices; alignment of the T<sub>2</sub> weighted images to the spatially normalized T<sub>1</sub> image; and tissue classification through the use of a discriminant analysis method.

Hippocampal traces contained the entire hippocampus proper and subiculum, and boundaries were determined entirely by internal landmarks (intra-class correlation coefficient (ICC)=0.72.). The anterior–posterior division (boundary slice) was subsequently made at the posterior extent of the uncus (ICC of 0.86). See Goldman et al., 2007a for further details.

### 2.2.4. *Facial affect discrimination*

During the third week of admission, subjects rated 36 photos of actors exemplifying one of six a priori-defined emotions as well as three photos of neutral expressions. Pictures were a subset of those from Ekman and Friesen (1976) previously used to demonstrate altered responses in facial affect discrimination in patients with amygdala pathology (Adolphs et al., 1999), autism (Baron-Cohen et al., 2001) and schizophrenia (Addington et al., 2006). Subjects viewed each photo on a computer screen and assigned it a number on a five-point scale for intensity of fear, happiness, sadness, surprise, disgust, and anger (six ratings/photo) (Adolphs et al., 1999). In order to address the possibility that findings could be a result of a generalized impairment in recognizing faces, subjects also completed The Benton Facial Discrimination Test (Benton et al., 1983).

### 2.3. *Laboratory analysis*

Unextracted samples were analyzed by enzyme immunoassay (Assay Designs, Ann Arbor, MI). Intra-assay coefficient of variation was 2.1%. Inter-assay CV was 3.5% and 9.5% for high and low controls respectively. Validity of the assay was established by multiple methods including demonstrating that a) values were parallel to those obtained by RIA; b) measurable oxytocin only occurred in the HPLC fraction which contained spiked oxytocin (and there was no cross reaction with spiked vasopressin); c) plasma spiked with various physiologic amounts of oxytocin were parallel to the standard curve, and d) that values varied reliably as a function of the menstrual cycle, the use of oral contraceptives and massage (Carter et al., 2007).

### 2.4. *Data analysis*

The reciprocal of oxytocin concentration was calculated in order to normalize the data. A mixed effects linear regression model was chosen because this approach handles missing data, intra-subject correlation, and time-varying covariates in a more flexible and realistic manner (Hedeker and Gibbons, 1996). We formulated the analysis of the group effects as three a priori orthogonal (Helmert) contrasts. The 1st contrast, i.e. PHS versus the other three groups tested our main hypothesis. Because plasma oxytocin, per se, seems rarely to be affected by acute stress (Altemus et al., 2001a; Taylor et al., 2006), whereas basal levels are often inversely correlated with indices of the stress response (Light et al., 2004), we predicted oxytocin levels would be lower in PHS. The other two contrasts

compared PNS to NNS and HC; and the NNS to HC. We hypothesized that oxytocin activity would be  $PNS < NNS + HC$ , and  $NNS > HC$  based on the corresponding pAVP and HPA responses in these groups (Goldman et al., 2007b,c).

Subject and time were entered as random effects in the model. The three group contrasts and their interactions with time, were entered as fixed effects. The significance of other factors was assessed by reducing them to a single outcome measure and then including them in the above model. For example, to assess the relationship of oxytocin activity to hippocampal-mediated glucocorticoid negative feedback, we calculated the cumulative drop (i.e. AUC) in adrenocorticotropin (ACTH) for the 240 min during and after the infusion compared to the 40 min prior to the infusion for each subject (see Goldman et al., 2007b for details). The association of oxytocin to the ACTH, cortisol and AVP responses during the cold pressor was determined

in an analogous manner. Left and right sides of each brain structure were added to each other and corrected for whole brain volume, and then entered as covariates in the model as described above. For the facial affect discrimination task, the accuracy of each patient's ratings for each emotion was determined as described by Adolphs et al. (1999). Briefly, subjects' ratings of the intensity of each emotion were correlated with the mean intensity of 12 concurrently studied healthy controls. This regression coefficient was then normalized and averaged for all emotions in each subject, and then entered in the model.

The significance of the added covariate (expressed as a Z score) thus indicates whether the factor in question was associated with oxytocin activity across subjects when controlling for group and time effects. Only the first two contrasts and their interactions with time were included in models restricted to patients. All *p* values reflect two-tailed tests.

Table 1  
Clinical parameters and basal laboratory values in three schizophrenic subject groups and controls

Measure	Polydipsic hyponatremic (PHS, <i>n</i> =6)	Polydipsic normonatremic (PNS, <i>n</i> =4)	Nonpolydipsic normonatremic (NNS, <i>n</i> =5)	Healthy controls (HC, <i>n</i> =7)	Significant contrasts <sup>a</sup> ( <i>p</i> <0.05)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Male	4 (66%)	3 (75%)	2 (40%)	4(57%)	None
Schizoaffective	1 (16%)	0 (0%)	1 (20%)	–	None
Atypical antipsychotic	3 (50%)	1 (25%)	0 (0%)	–	None
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (yr)	44.7±2.4	43.5±9.2	34.2±8.9	34.7±10.1	PHS vs others
Dose antipsychotic-(mg/day) <sup>b</sup>	437±413	512±295	700±264	–	None
Age of onset (yr)	22.6±9.4	23.0±5.3	20.0±4.6	–	None
Duration of illness (yr)	23.0±9.9	22.7±5.1	10.0±6.0	–	None
PANSS total	70.4±23.8	45.06±7.8	66.8±18.4	–	None
PANSS positive	16.8±3.8	12.1±4.7	18.6±5.0	–	None
PANSS negative	22.7±7.8	10.1±2.3	15.5±5.1	–	PHS vs others
Plasma osmolality (–120 min) (mosmol/kg)	278.5±6.6	289.7±6.0	289.9±3	289.1±3	PHS vs others
Baseline oxytocin (–30 min) (pg/ml)	100±35	266±309	301±338	240±224	None
<i>Other outcome measures</i>					
Anterior hippocampal volume (ccs)	2.07±.20	2.23±.48	1.98±.45	2.37±.59	None
Posterior hippocampal volume (ccs)	3.41±.22	3.62±.80	3.43±.62	3.81±.58	None
Amygdala volume (ccs)	3.33±.42	3.61±.54	3.04±.80	3.44±.53	None
Whole brain volume (ccs)	1275±141	1223±113	1078±132	1203±133	None
Mean accuracy facial affect rating ( <i>r</i> ) <sup>c</sup>	.542±.139	.659±.188	.680±.151	–	None
Benton facial recognition	37.7±6.9	42.6±3.8	45.0±2.0	49.1±1.4	PHS vs others NNS vs HC

<sup>a</sup> We limited ourselves to three contrasts 1) PHS vs other three groups, 2) PNS vs NNS and HC, and 3) NNS vs HC. Analyses by ANOVA or ordinal regression.

<sup>b</sup> Milligrams of chlorpromazine equivalent per day estimated as 1 mg/day haloperidol or risperidone, or 2.5 mg/day of olanzapine=50 mg chlorpromazine.

<sup>c</sup> Determined by correlating each patient subject's ratings with 12 concurrently studied healthy controls. See Methods.

### 3. Results

#### 3.1. Healthy controls: cold pressor versus tepid water condition

Plasma oxytocin levels appeared to vary because of episodic spikes which occurred in most healthy controls (Table 2). Levels otherwise were remarkably consistent within, although they varied greatly between, subjects. Analysis using mixed effects regression demonstrated no significant condition ( $p=.55$ ), time ( $p=.87$ ) or interaction ( $p=.90$ ) effects. Exclusion of the spikes (i.e. levels 2 S.D.>subject's mean level) did not alter this conclusion.

#### 3.2. All groups: demographics

Total PANSS scores, positive PANSS symptoms of psychosis, and antipsychotic doses were similar across patient groups, while negative PANSS symptoms were

more prominent in PHS (Table 1). The PHS group was older than the other three groups who did not differ significantly from each other on these variables, while duration of illness was marginally greater ( $p=.08$ ) in PNS than the PNN group. Prior to the saline infusion, plasma osmolality, as expected, was lower in PHS, but after correction was similar across groups (data not shown). Because of the group difference in age, age effects were examined in all the subsequent analyses by including it as an additional covariate in the analyses.

#### 3.3. Four groups: cold pressor effects and impact of demographic variables

Basal oxytocin levels (−30 min) were nonsignificantly lower ( $p=.07$ ) in PHS (Table 1). Like healthy controls, PHS and PNS psychiatric patients exhibited episodic spikes, though none were observed in NNS (Table 2). Mixed effects linear regression confirmed the

Table 2  
Oxytocin levels (pg/ml) prior to and following a cold pressor test<sup>a</sup>

Group (id)	Gender	Condition	Time of sample relative to cold pressor						
			−30	−15	−10	5	10	30	45
Healthy control a	Male	Tepid	689	734	734	722	610	700	541
Healthy control b	Male	Tepid	Missing	Missing	272	238	317	1035	265
Healthy control c	Female	Tepid	704	100	104	105	94	150	127
Healthy control d	Female	Tepid	246	Missing	181	293	158	180	192
Healthy control e	Female	Tepid	159	155	142	166	1177	162	163
Healthy control f	Male	Tepid	121	146	147	135	123	126	124
Healthy control a	Male	Ice	725	1678	755	653	681	745	917
Healthy control b	Male	Ice	291	294	332	384	288	334	282
Healthy control c	Female	Ice	132	144	1172	147	146	120	139
Healthy control d	Female	Ice	173	197	191	163	194	179	175
Healthy control e	Female	Ice	191	189	153	165	212	239	154
Healthy control f	Male	Ice	81	87	91	87	92	80	86
Healthy control	Male	Ice	91	109	72	82	83	91	67
Nonpolydipsic schizophrenic	Female	Ice	140	129	106	132	108	109	118
Nonpolydipsic schizophrenic	Male	Ice	995	880	917	950	985	882	830
Nonpolydipsic schizophrenic	Female	Ice	127	127	169	170	133	94	127
Nonpolydipsic schizophrenic	Female	Ice	161	185	150	132	174	164	155
Nonpolydipsic schizophrenic	Male	Ice	86	125	100	96	107	116	109
Polydipsic schizophrenic	Female	Ice	208	176	162	199	176	136	176
Polydipsic schizophrenic	Male	Ice	82	Missing	91	113	Missing	89	Missing
Polydipsic schizophrenic	Male	Ice	56	266	60	46	59	62	62
Polydipsic schizophrenic	Male	Ice	720	473	437	369	341	452	400
Hyponatremic schizophrenic	Male	Ice	56	48	71	75	60	78	72
Hyponatremic schizophrenic	Female	Ice	91	95	95	84	93	80	114
Hyponatremic schizophrenic	Male	Ice	88	78	75	81	89	99	1035
Hyponatremic schizophrenic	Male	Ice	106	105	744	Missing	Missing	Missing	127
Hyponatremic schizophrenic	Male	Ice	102	101	120	91	Missing	Missing	Missing
Hyponatremic schizophrenic	Female	Ice	162	127	126	105	87	89	112

<sup>a</sup>Six of the seven healthy controls were studied twice, and are identified as subjects a–f. Oxytocin spikes are identified in shaded cells (see text for definition).

visual impression that oxytocin levels were on average lower throughout the study in PHS compared to the other three groups (1st group contrast  $Z=2.72$ ,  $p=.006$ ) (Fig. 1). While levels in the other groups did not appear to change, levels rose in PHS over the course of the study (1st group by time interaction  $Z=2.47$ ,  $p=.013$ ). A single spike following the cold pressor in the PHS appeared, however, to account for this group by time finding (Table 2) and indeed exclusion of spikes from the analysis eliminated the finding ( $p=.27$ ), but not the significant group effect ( $Z=2.06$ ,  $p=.03$ ). Neither time, the other two group contrasts or their interactions with time approached significance, though oxytocin levels appeared, as predicted, to be lower in PNS than in NNS and HC (Fig. 1).

Neither age (covariate  $p=.53$ ) nor gender ( $p=.61$ ) could account for the difference in oxytocin between PHS and the other groups. Antipsychotic dose in chlorpromazine equivalents was highly correlated with the oxytocin response (covariate  $Z=2.70$ ,  $p=.006$ ), but including it in the model only increased the significance of the previously noted findings (i.e. 1st group contrast:  $p=.0004$ , 1st group by time interaction  $p=.010$ ). PANSS negative ratings showed a slight trend toward being higher in those with low oxytocin ( $Z=1.35$ ,  $p=0.17$ ). Positive, total and general PANSS ratings were unrelated (all  $p$  values  $>0.60$ ), as were other demographic factors listed in Table 1.

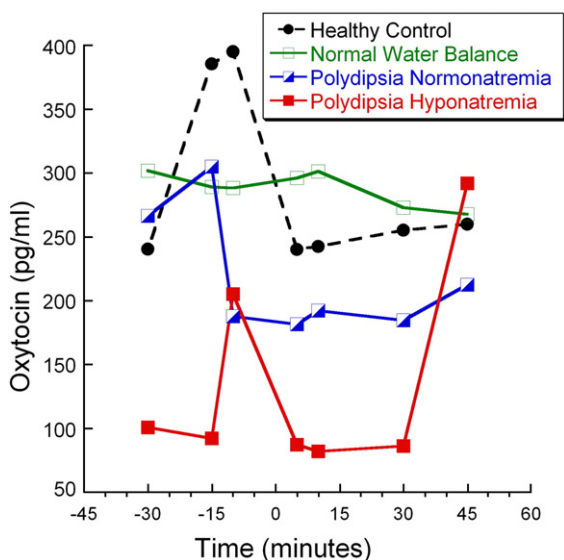


Fig. 1. Oxytocin levels before and after a cold pressor in schizophrenic patients with and without water balance and healthy controls.

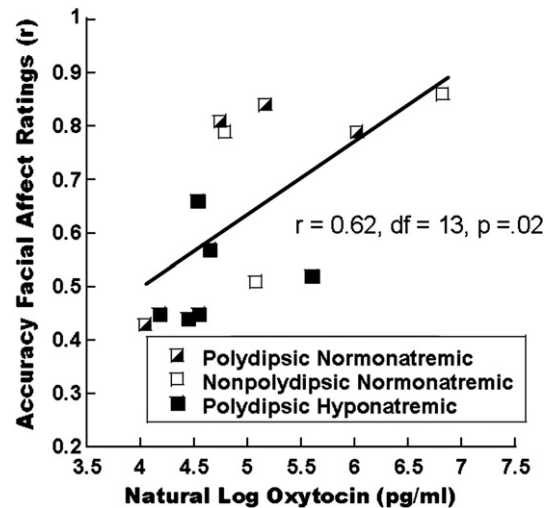


Fig. 2. Relationship of patients' accuracy for rating intensity of facial affects and mean level of plasma oxytocin before, during and after the cold pressor study. The natural log of oxytocin was taken to normalize the data. In contrast, facial discrimination (Benton rating) per se was not correlated with mean oxytocin levels ( $r=0.30$ ,  $p=.32$ ,  $df=13$ ). See Methods section for details.

### 3.4. Relationship of oxytocin levels to neuroendocrine, brain structural and affective data

Other neuroendocrine responses to the cold pressor were not associated with the oxytocin response (ACTH:  $p=.81$ , cortisol:  $p=.14$ , AVP:  $p=.52$ ). In contrast, the drop in ACTH during and following infused cortisol (i.e. HPA negative feedback) was significantly associated (covariate  $Z=2.05$ ,  $p=.039$ ). Furthermore, anterior hippocampal (covariate  $Z=2.82$ ,  $p=.004$ ), but not posterior hippocampal ( $p=.95$ ), amygdala ( $p=.68$ ) or whole brain volumes ( $p=.13$ ) was also significantly associated with higher oxytocin levels across all groups. None of the demographic measures in Table 1 could account for these effects.

Ability to accurately assess the intensity of facial emotions and the ability to recognize faces were similar across patient groups, though PHS appeared to be more impaired (Table 1). Greater accuracy of rating all facial emotions was significantly associated with higher oxytocin levels in the patient groups (Fig. 2) (covariate  $Z=2.83$ ,  $p=.004$ ). The association was extremely high for correctly identifying happy expressions ( $Z=4.88$ ,  $p=0.00001$ ) and was modestly to marginally significant for each of the other emotions (sad  $p=.025$ ; surprise  $p=.041$ ; disgust  $p=.065$ ; angry  $p=.069$ ; fear  $p=.093$ ). In contrast to facial affect discrimination, the measure of facial recognition was not associated with oxytocin activity ( $p=.23$ ), and its addition, as well as that of the other

demographic measures shown in Table 1, to the model could not account for the association between plasma oxytocin and accuracy of facial emotion ratings.

#### 4. Comment

Plasma oxytocin levels are lower in PHS patients than other schizophrenic subgroups or healthy controls. Moreover, across schizophrenic subgroups oxytocin activity is highly correlated with anterior hippocampal volumes, other neuroendocrine measures of hippocampal function, and facial emotion processing deficits closely linked to schizophrenia and known to be modulated by oxytocin. These associations with oxytocin activity occurred despite the absence of significant group differences on these measures, and after accounting for group differences in oxytocin activity. Thus they do not appear attributable to group differences per se, suggesting that grouping is one of many outcomes of oxytocin (and related neuroendocrine) dysfunction, and not a cause of the findings.

While the lower level of oxytocin activity in PHS and associated findings were predicted, the relative rise in oxytocin in PHS following the cold pressor was not. As noted above, this finding is attributable to a single spike in PHS, and when all spikes were omitted from the analysis this finding disappeared. Table 2 shows that none of the other groups had a spike in oxytocin following the cold pressor (there were two spikes in healthy controls following tepid water). Thus it is possible that this difference is either a chance occurrence, or alternatively PHS may not appropriately suppress oxytocin spikes following stress (Ueda et al., 1994). This speculation is based on the analogous deficits in HPA and pAVP activity in these patients as well as the supranormal suppression of HPA and pAVP in NNS who showed no spikes in oxytocin (Fig. 1). Clearly this findings must be replicated and more information gathered about the physiologic regulation of oxytocin spikes (Stock et al., 1994; Wang and Hatton, 2005), in particular during stress (Altemus et al., 2001a, b; Grewen et al., 2005), before this question can be definitively addressed.

The findings do not appear attributable to recognized or putative factors, though not all were addressed. In particular, no effort was made to control for phase of the menstrual cycle or sexual activity both of which have been reported to influence oxytocin (Carter et al., 2007; Salonia et al., 2005). While PHS were older than the other groups and initially had lower plasma osmolalities, inclusion of age in the model did not alter the findings and osmolality was normalized prior to sampling.

Neither factor has been clearly associated with oxytocin, though as noted oxytocin regulation has been inadequately studied. Higher doses of antipsychotic medication were associated with lower levels of oxytocin in our study, but accounting for this only appeared to increase the significance of the results. Antipsychotics are not known to alter oxytocin function, though dopamine and oxytocin may work together to facilitate social behaviors modulated by the nucleus accumbens (Liu and Wang, 2003).

The lower levels of plasma oxytocin in PHS and the significant association with anterior hippocampal volume and hippocampal-mediated HPA feedback across subjects implicate anterior hippocampal pathology as mediating the neuroendocrine dysfunction in PHS. The absence of an intrasubject association between oxytocin and other neuroendocrine responses to the cold pressor argues against this interpretation, but this in turn may be attributable to basal differences in hormone activity which significantly determine subsequent responses. In contrast, basal activity was normalized in the study of hippocampal-mediated HPA feedback (Goldman et al., 2007b) thereby enhancing power to detect intrasubject associations.

The highly significant link between facial affect discrimination and plasma oxytocin raises the possibility that altered neuroendocrine dysfunction in PHS directly contributes to their psychiatric disorder. This highly speculative interpretation is based on data showing 1) schizophrenics demonstrate marked impairments in facial affect discrimination (Kohler et al., 2003, Kucharska-Pietura et al., 2005) which, in turn, are closely associated with their social dysfunction (Addington et al., 2006); 2) central oxytocin modulates facial affect processing in humans (Domes et al., 2007a,b); 3) peripheral and central oxytocin release are regulated in tandem (Ludwig and Leng, 2006), 4) analogous cognitive deficits in autistic patients have been linked to diminished peripheral oxytocin levels (Modahl et al., 1998) and improve with supplemental oxytocin (Hollander et al., 2007) and 5) supplemental oxytocin also diminishes repetitive behaviors in autism (Hollander et al., 2003) which closely resemble polydipsia and other behaviors seen in PHS (and PNS) (Shutty et al., 1995). On the other hand, the data do not support a strong link between emotional deficits per se and oxytocin, in so far as PANSS negative scores, while lower in PHS, were only marginally associated with oxytocin levels, and inclusion of these scores in the statistical model did not eliminate the association with facial affect discrimination. While many of these observations require confirmation, and the association between central and peripheral oxytocin secretion is

not established, our data suggest that a trial of intranasal oxytocin in schizophrenia, especially in PHS, is warranted.

Our findings and conclusions must be interpreted with caution because of the small sample size, the preliminary nature of this study, and limited knowledge about oxytocin regulation and pharmacokinetics. The apparent absence of explanatory factors must also be taken with caution given our low power to identify real associations. Furthermore, the differences in group demographics may not be correctable by statistical adjustment, and the associational analyses do not establish causality. The assessment of facial affect discrimination relied on the accuracy of twelve concurrently studied healthy controls, though one might anticipate that this limitation would underestimate the real true associations in patients. Thus while potentially highly significant in 1) linking schizophrenia to recognized brain circuitry and neuropathology, and in 2) suggesting a novel therapy, these findings must be replicated in a larger sample and more knowledge gathered about oxytocin regulation before their significance can be judged.

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#### Contributors

MB Goldman, I Torres, and Marlow O'Connor designed the study and participated in the data analysis. CS Carter oversaw laboratory analyses and assisted in data interpretation. All authors contributed to and have approved the final manuscript.

#### Conflicts of interest

None of the authors has a conflict of interest.

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