Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia

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Abstract

Background: Accumulating evidence indicates that oxytocin plays an important role in social interactions. Previous studies also suggest altered oxytocin function in patients with schizophrenia and depression. However, few studies have examined the central oxytocin levels in these disorders.

Methods: Cerebrospinal fluid (CSF) oxytocin levels were measured by ELISA in male participants consisting of 27 patients with schizophrenia, 17 with major depressive disorder (MDD), and 21 healthy controls.

Results: CSF oxytocin levels of patients with schizophrenia or MDD did not differ significantly with healthy controls. The antidepressant dose or the Hamilton depression rating scale score did not significantly correlate with the oxytocin levels in MDD patients. CSF oxytocin levels in schizophrenic patients significantly negatively correlated with second generation antipsychotic dose ($r =$ -0.49, $P =$ 0.010) but not with first generation antipsychotic dose ($r =$ -0.13, $P =$ 0.50). A significant correlation was observed between oxytocin levels and negative subscale of PANSS ($r =$ -0.38, $P =$ 0.050). This correlation remained

significant even after controlling for second generation antipsychotic dose (r = -0.47, P = 0.016).

Conclusions: We obtained no evidence of altered CSF oxytocin levels in patients with schizophrenia or those with MDD. However, lower oxytocin levels may be related to higher second generation antipsychotic dose and more severe negative symptoms in schizophrenia.

Keywords: schizophrenia; depression; oxytocin; cerebrospinal fluid; antipsychotics

1. Introduction

Oxytocin is produced in the supraoptic and paraventricular nuclei of

hypothalamus and is secreted into the blood stream from the posterior pituitary.

Its release is induced by a variety of stressful stimuli, including noxious stimuli,

conditioned fear, and exposure to novel environments (Onaka, 2004).

Accumulating evidence indicates that oxytocin plays an important role in social

interactions (Bartz et al., 2010; Lim and Young, 2006). Deficits in social

functioning observed in psychiatric disorders including schizophrenia (Couture et

al., 2006; Sparks et al., 2010) and mood disorders (Inoue et al., 2004; Montag et

al., 2010; Wolkenstein et al., 2011) imply the possible involvement of oxytocin in

the pathophysiology of these disorders.

Many studies have investigated the possible link between oxytocin and

psychiatric disorders. Some previous studies reported altered oxytocin function

in patients with schizophrenia (Beckmann et al., 1985; Linkowski et al., 1984;

Mai et al., 1993). Higher plasma oxytocin levels in schizophrenic patients were

associated with lower symptom severity (Rubin et al., 2010). A clinical study

showed that administration of this hormone ameliorated symptoms of

schizophrenia (Feifel et al., 2010). In a preclinical study, systemically

administered oxytocin reversed prepulse inhibition deficits induced by

amphetamine and the phencyclidine analog in rats (Feifel and Reza, 1999).

Oxytocin dysfunction has been implicated in the pathophysiology of depression

as well. Two studies have shown that peripheral oxytocin levels and depressive

symptoms were significantly correlated in patients with major depressive

disorder (MDD) (Cyranowski et al., 2008; Scantamburlo et al., 2007). Moreover,

oxytocin knock-out mice have shown dysregulated stress responses to

psychological stimuli (Mantella et al., 2005) and enhanced anxiety behaviors

(Mantella et al., 2003).

     Oxytocin secreted from the pituitary gland generally does not re-enter

the brain through the blood-brain barrier (Ermisch et al., 1985). Therefore, the

behavioral effects of oxytocin are likely to be due to the release from centrally

projecting oxytocin neurons. Since oxytocin in the nervous system can be

transported to blood (Durham et al., 1991), peripheral oxytocin levels may reflect

brain levels to some extent. However, central and peripheral oxytocin is

regulated independently, and the half-life of oxytocin is less than 5 minutes in the

blood (Ryden and Sjoholm, 1969) while that in the brain is 19.1 minutes

(Durham et al., 1991). Therefore, measurement in the CSF is necessary for the

direct assessment of central oxytocin levels.

To our knowledge, two studies have previously examined the

cerebrospinal fluid (CSF) levels of oxytocin in patients with schizophrenia. One

reported elevated oxytocin levels in schizophrenia compared with controls

(Beckmann et al., 1985), while the other did not obtain such a finding (Glovinsky

et al., 1994). Only one study has examined the CSF levels of oxytocin in patients

with depression, in which no difference was found compared with controls (Pitts

et al., 1995). No study to date has examined the association of CSF oxytocin

levels with symptom severity of these disorders. Since symptom severity forms a

continuous spectrum ranging from mild to severe state, an association with the

severity of the disease would suggest that oxytocin levels reflect the state of the

disease.

In the present study, the oxytocin levels in the CSF of patients with schizophrenia and those with depression were measured and compared to that of healthy controls.   Furthermore, we investigated the correlation between CSF oxytocin levels and symptom severity of these disorders. From the findings of previous studies examining peripheral oxytocin levels (Rubin et al., 2010; Scantamburlo et al., 2007), we hypothesized that CSF oxytocin levels would be lower in patient groups compared to healthy controls and that symptom severity would be negatively correlated with the oxytocin levels.

2. Materials and methods

2.1. Subjects

Participants were 27 patients with schizophrenia (mean age (standard deviation): 42.6 (8.5) years), 17 patients with major depressive disorder (MDD) (age: 39.5 (8.0) years), and 21 healthy controls (age: 38.3 (15.3) years). Demographic and clinical characteristics of the subjects are summarized in Table 1. All subjects were males to avoid gender effects and were biologically

unrelated Japanese recruited from the outpatient clinic of the National Center of

Neurology and Psychiatry Hospital, Tokyo, Japan or through advertisements in

free local information magazines and by our website announcement. None of the

healthy controls were on psychotropic medication, while 70.6% of the patients

with MDD were treated with antidepressant medication at the time of the study.

Most of the schizophrenic patients were prescribed antipsychotic medication,

and all of those prescribed antipsychotics were on the medication for more than

3 years. Consensus diagnosis by at least 2 psychiatrists was made for each

patient according to the Diagnostic and Statistical Manual of Mental Disorders,

4th edition criteria (American Psychiatric Association, 1994), on the basis of

unstructured interviews and information from medical records. The controls were

healthy volunteers with no current or past history of psychiatric treatment and

were screened using the Japanese version of the Mini International

Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998) by a

research psychiatrist to eliminate the possibility of any axis I psychiatric

disorders. Participants were excluded if they had prior medical histories of

central nervous system diseases or severe head injury or if they met the criteria

for substance abuse or dependence or mental retardation. The study protocol

was approved by the ethics committee at the National Center of Neurology and

Psychiatry, Japan. After describing the study, written informed consent was

obtained from every subject.

2.2. Clinical measures

Schizophrenic symptoms and depressive symptoms were assessed

immediately after the lumbar puncture by an experienced research psychiatrist

using the Japanese version of the Positive and Negative Syndrome Scale

(PANSS) (Kay et al., 1987; Yamada et al., 1991) and the Japanese version of

the GRID Hamilton Depression Rating Scale, 17-item version (HAMD-17)

(Hamilton, 1967), which have both been demonstrated to show good inter-rater

reliability (Igarashi et al., 1998; Tabuse et al., 2007). Medication status at the

time of lumbar puncture was recorded. Daily doses of antipsychotics in patients

with schizophrenia and antidepressants in patients with MDD were converted to

chlorpromazine and imipramine equivalent doses, respectively, using published

guidelines (Inagaki et al., 1999).

2.3. Lumbar puncture and oxytocin assay

Lumbar puncture was performed with the subject in the left decubitus

position. CSF was withdrawn from the L3-L4 or L4-L5 interspace. After the

removal of 2 ml of CSF, a further 6 ml of CSF was collected and immediately

transferred on ice to be centrifuged at 4℃ and alliquoted for storage at -80℃

until assay. CSF oxytocin levels were analyzed using a commercial ELISA kit

(Enzo Life Sciences, INC., NY). Using the results from two separate runs of

standard concentrations, the inter-assay coefficient of variation (CV) was less

than 10%.

2.4. Statistical analysis

Statistical differences between groups were calculated using Student's

t-test, Welch's t-test, or one-way analysis of variance (ANOVA). Correlations

were assessed using Pearson's correlation coefficient. Since the CSF oxytocin

levels were not normally distributed, log transformation was applied prior to

statistical analyses to achieve normal distribution. Because previous studies

suggest that some antipsychotic and antidepressant medications increase

oxytocin secretion (Uvnas-Moberg et al., 1992; Uvnas-Moberg et al., 1999),

chlorpromazine and imipramine equivalent doses were examined as possible

confounders. Statistical analyses were performed using the Statistical Package

for the Social Sciences version 11.0 (SPSS Japan, Tokyo, Japan). All statistical

tests were two-tailed, and $P < 0.05$ indicated statistical significance.

3. Results

Figure 1 shows the CSF oxytocin levels in each diagnostic group. A

one-way ANOVA using the transformed oxytocin levels as the dependent

variable indicated no significant difference between diagnostic groups ($F = 1.08$,

$P = 0.35$). The transformed oxytocin levels showed no significant correlation with

age or body weight. Figure 2 and 3 show the relation of CSF oxytocin levels with

symptom severity and psychotropic dose, respectively. The antidepressant dose

or the HAMD-17 score did not significantly correlate with the transformed

oxytocin levels in patients with MDD (antidepressant dose: r = -0.15, P = 0.57;

HAMD-17: r = -0.19, P = 0.46). The transformed oxytocin levels were

significantly negatively correlated with negative subscale of PANSS (r = -0.38, P

= 0.050). Correlations between transformed oxytocin levels and other subscales

of PANSS were not statistically significant. The transformed oxytocin levels in

schizophrenic patients were significantly negatively correlated with

chlorpromazine equivalents of total antipsychotic dose (r = -0.51, P = 0.0064)

and second generation antipsychotic (SGA) dose (r = -0.49, P = 0.010) but not

with chlorpromazine equivalents of first generation antipsychotic (FGA) dose (r =

-0.13, P = 0.50). Those prescribed SGA had significantly lower CSF oxytocin

levels compared to those not prescribed SGA (Welch's t test: t = 2.6, df = 10.4, P

= 0.024). Comparison between patients prescribed and not prescribed FGA did

not yield significant difference (Student's t test: t = 1.1, df = 25, P = 0.27).

Although none of the subscales of PANSS were correlated with FGA, SGA, or

total chlorpromazine equivalent dose in the present study (all $P > 0.1$), a

previous study (Sim et al., 2009) reported an association between antipsychotic

dose and the severity of positive as well as negative symptoms of schizophrenia.

Therefore, we considered antipsychotic dose as a confounding factor for the

association between oxytocin levels and symptom severity. Thus, we also

examined the correlation between the oxytocin levels and PANSS scores

controlling for prescribed antipsychotic dose. Partial correlation between

transformed oxytocin levels and negative subscale of PANSS, removing the

linear effects of total antipsychotic dose, was statistically significant ($r = -0.39$, P

$= 0.047$). Removing the linear effects of SGA dose instead of total antipsychotic

dose also resulted in significant correlation of transformed CSF oxytocin levels

with negative subscale ($r = -0.47$, $P = 0.016$) as well as with total PANSS score

($r = -0.47$, $P = 0.016$). SGA dose-controlled partial correlations between

transformed oxytocin levels and other subscales of PANSS were not statistically

significant (positive subscale: $r = -0.24$, $P = 0.23$; general subscale: $r = -0.33$, $P =$

0.099).

4. Discussion

Consistent with some previous studies (Glovinsky et al., 1994; Pitts et al., 1995), CSF oxytocin levels did not significantly differ between healthy controls and patients with schizophrenia and MDD. However, the present results showed that higher levels of CSF oxytocin may be associated with less severe symptoms of schizophrenia.

The observed negative correlation between antipsychotic dose and CSF oxytocin levels points to the possibility that antipsychotic medication lowers oxytocin levels. A recent study suggests that an inhibitory feedback loop may exist between prolactin-secreting lactrophs and oxytocinergic paraventricular neurons (Sirzen-Zelenskaya et al., 2011). Therefore, the disinhibition of prolactin secretion due to the D_2 receptor blockade by antipsychotics may have resulted in the suppression of oxytocin secretion. This, however, does not explain the stronger correlation of SGA dose compared to FGA dose. Kiss et al (2010) showed that SGAs have a more potent influence than haloperidol on the activity

of oxytocin magnocellular neurons. This also seems contradictory to the present

finding that SGA is negatively correlated with oxytocin levels. An alternative

explanation for this negative correlation is that patients with low oxytocin levels

may respond poorly to antipsychotic medication, and thus, higher dose was

prescribed to such patients. Nevertheless, despite the relatively strong

correlation with the antipsychotic dose, the cross-sectional design of the present

study hinders any causal inferences. One previous study (Glovinsky et al., 1994)

demonstrated that CSF oxytocin levels were unchanged by antipsychotic

medication. Thus, further investigation is necessary to elucidate the effects of

antipsychotic medication on oxytocin levels.

The present results showed that the negative symptoms of

schizophrenia were negatively correlated with CSF oxytocin levels. The

correlation coefficient between CSF oxytocin levels and total PANSS score was

also significant, controlling for SGA dose. Rubin et al. (2010) reported that higher

peripheral oxytocin levels were associated with more prosocial behaviors in

female patients with schizophrenia. Furthermore, previous studies have

demonstrated improvement of social behaviors with administration of intranasal

oxytocin (Macdonald and Macdonald, 2010; Pedersen et al., 2011). Since strong

relationships between negative symptoms and social difficulties have been

demonstrated in schizophrenia (Weinberg et al., 2009), the present finding

associating higher CSF oxytocin levels with lower negative subscale is in accord

with what has previously been described for peripheral oxytocin. Whether the

peripheral oxytocin levels reflect the CSF oxytocin levels, or whether a different

mechanisms of action in the brain and the peripheral result in a similar effect,

remains to be explored.

Previous studies examining CSF oxytocin levels in patients with

schizophrenia (Beckmann et al., 1985; Glovinsky et al., 1994) and depression

(Pitts et al., 1995) showed mean oxytocin levels of less than 10 pg/ml, which is

lower than that in the present study (> 20 pg/ml). Such outcome may have

resulted from some of the methodological differences between previous studies

and the present one. Previous three studies measured oxytocin levels using

radioimmunoassay (RIA), while the present study used a commercially available

ELISA kit. A recent study that used the same ELISA kit to measure CSF oxytocin

levels (Heim et al., 2009) also demonstrated higher levels of oxytocin (mean

oxytocin levels of 17 pg/ml in women without a history of emotional abuse)

compared to the previous studies using RIA. Thus, the different measurement

techniques may have influenced the values.

A number of other methodological differences exist between the present

study and previous ones examining CSF oxytocin levels (Beckmann et al., 1985;

Glovinsky et al., 1994; Pitts et al., 1995). One of the major differences was that

the present study did not require fasting prior to lumbar puncture, while

Beckmann et al (Beckmann et al., 1985) collected CSF in patients with

schizophrenia after 12 hours fasting. Although a previous study (Challinor et al.,

1994) reported that peripheral oxytocin levels were not affected by 20 hours of

fasting, the influence of fasting on CSF levels is unknown. Furthermore,

Beckmann et al used Research Diagnostic Criteria to select a patient group

consisting entirely of paranoid schizophrenia. Such difference in composition of

participants may have affected the outcome of the study by Beckmann et al

(1985), which showed significantly higher CSF oxytocin levels in schizophrenic

patients compared to healthy controls. The findings by Glovinsky et al (1994)

and Pitts et al (1995) were consistent with the present study in that no significant

difference in CSF oxytocin levels were found between patients and controls.

However, participants in these studies also differed from that of the present

study in that both genders were included. Furthermore, MDD patients in the

study by Pitts et al (1995) all scored 18 or above on the HAMD-17, while the

MDD patients in the present study included those in a remitted state. These

differences in composition of study samples should be carefully considered

when comparing findings across studies.

Some limitations must be considered when interpreting the results of this

study. First, the effects of medication could not be fully controlled due to the

variability in types and doses. Future studies should examine oxytocin levels in

untreated patients to elucidate the role of oxytocin in the pathophysiology of

schizophrenia and depression. Treatment duration may also affect oxytocin

levels. However, since all of the schizophrenic patients that were prescribed

antipsychotics were on chronic treatment with the medication, treatment duration

is unlikely to have confounded the main findings of the present study. Secondly,

as mentioned above, the cross-sectional design did not allow for any definitive

conclusions regarding the causal relationship between the CSF oxytocin levels,

psychotropic medication, and symptom severity. Thirdly, only male participants

were included in the present study. Previous studies suggest that effects of

peripheral and intranasal oxytocin may differ between men and women (Domes

et al., 2010; Rubin et al., 2011; Rubin et al., 2010). Therefore, the present

findings cannot be generalized to women. Finally, the risk of type II error was

high due to the small sample size. The sample size in the present study was

comparable to those of the previous studies that examined CSF oxytocin levels

in patients with schizophrenia and depression (Beckmann et al., 1985; Glovinsky

et al., 1994; Pitts et al., 1995). However, the power to detect a moderate

difference (effect size of 0.50) in CSF oxytocin levels between patients and

controls was relatively low (schizophrenia: 39%; MDD: 32%; calculated by

G*Power 3.1.3 (Faul et al., 2007)). A larger sample may be necessary to detect

small to moderate change in CSF oxytocin levels in psychiatric disorders.

In conclusion, we obtained no evidence of altered CSF oxytocin levels in patients with schizophrenia or those with MDD. However, lower CSF oxytocin levels may be related to higher SGA dose and more severe negative symptoms in schizophrenia, which is in line with the possibility that central oxytocin may ameliorate the severity of some symptoms of schizophrenia by improving social functioning.

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Figure legends

Figure 1: Cerebrospinal fluid oxytocin levels as a function of group

The cerebrospinal fluid oxytocin levels in healthy controls and patients

with schizophrenia and major depressive disorder are shown. Solid bars indicate

median values and the dotted lines indicate interquartile range. No significant

difference was observed between the diagnostic groups.

Figure 2: Relationship between cerebrospinal fluid oxytocin levels and symptom

severity

The association between cerebrospinal oxytocin levels and symptom

severity is shown. Oxytocin levels are shown in logarithmic scale. Solid lines

indicate fitted regression lines, unevenly dashed lines indicate 95% confidence

intervals, and evenly dashed lines indicate 95% prediction intervals.

(†): Correlation at significance level of $P < 0.05$

PANSS: Positive and Negative Syndrome Scale,

HAMD-17: Hamilton Depression Rating Scale, 17-item version,

95%CI: 95% confidence interval, 95%PI: 95% prediction interval

Figure 3: Relationship between cerebrospinal fluid oxytocin levels and dose of

psychotropics

The association between cerebrospinal oxytocin levels and dose of

psychotropics is shown. Oxytocin levels are shown in logarithmic scale. Solid

lines indicate fitted regression lines, unevenly dashed lines indicate 95%

confidence intervals, and evenly dashed lines indicate 95% prediction intervals.

(‡): Correlation at significance level of $P < 0.01$

CP equivalent: chlorpromazine equivalent,

95%CI: 95% confidence interval, 95%PI: 95% prediction interval

Table 1: Demographic and clinical characteristics

	Controls (N = 21)	Schizophrenia (N = 27)	Depression (N = 17)	Analysis
Age (years)	38.3 (15.3)	42.6 (8.5)	39.5 (8.0)	ANOVA: $F = 0.97$, n.s.
BMI	23.9 (4.1)	26.0 (6.2)	23.9 (4.5)	ANOVA: $F = 1.06$, n.s.
Duration of illlness (years)		16.3 (9.8)	7.7 (7.3)	t-test: $t = 2.8$, $P < 0.01$
Treatment duration (years)		15.5 (9.1)	5.8 (6.9)	t-test: $t = 3.4$, $P < 0.01$
Medication status				
on antipsychotic medication				
first generation (%)	0	59.3	11.8	
second generation (%)	0	66.7	23.5	
first and/or second generation (%)	0	96.3	35.3	
on antidepressant medication (%)	0	25.9	70.6	
on benzodiazepine medication (%)	0	81.5	76.5	
on mood stabilizer medication (%)	0	14.8	5.9	
CP equivalent dose				
first generation (mg/day)		361.8 (445.0)		
second generation (mg/day)		402.4 (498.3)		
total (mg/day)		764.2 (591.6)		
IMI equivalent dose (mg/day)			167.2 (141.5)	
PANSS				
Positive symptoms score		12.5 (3.8)		
Negative symptom score		16.0 (5.8)		
General symptom score		6.8 (1.3)		
Total score		55.6 (12.6)		
HAMD-17 score			13.4 (9.6)	

Values are shown as mean (standard deviation).

BMI: body mass index; CP: chlorpromazine; IMI: imipramine;

PANSS: Positive and Negative Syndrome Scale; HAMD-17: 17 item Hamilton Rating Scale for Depression

ANOVA: anaylsis of variance; n.s.: not significant

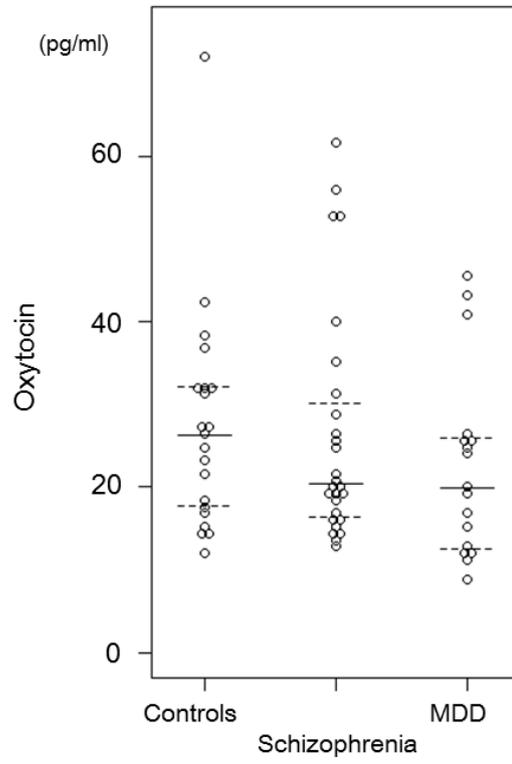CSF Oxytocin levels as a function of group

Figure 1

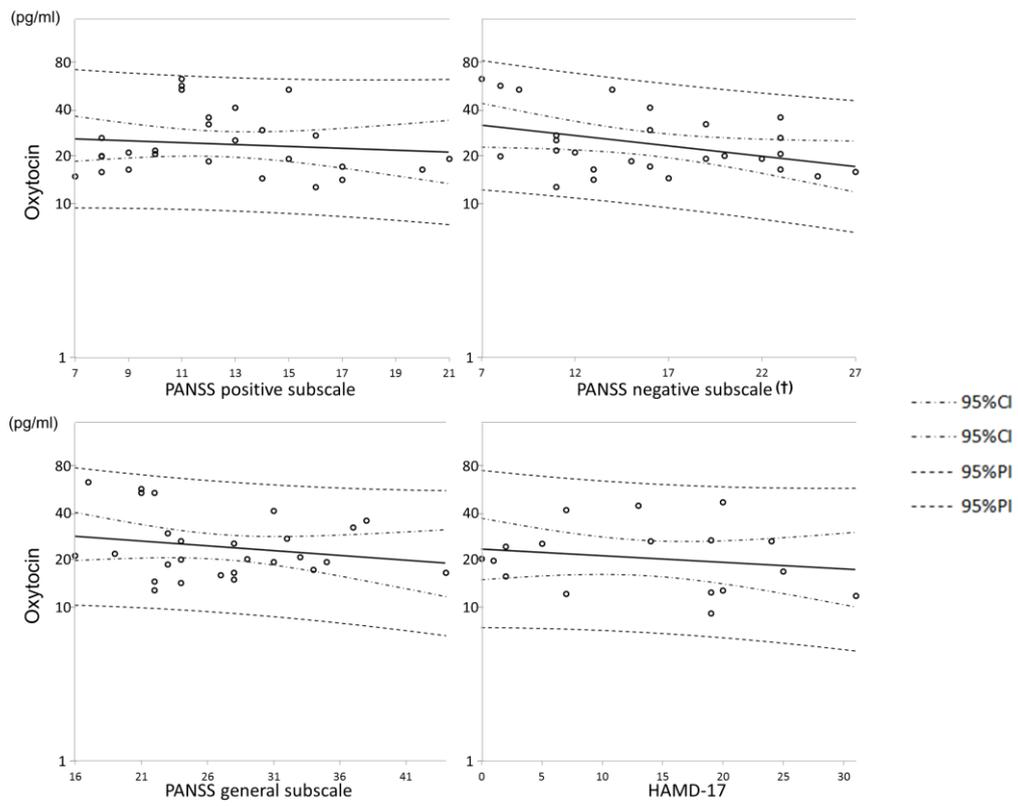# Relationship between CSF oxytocin levels and symptom severity

Figure 2

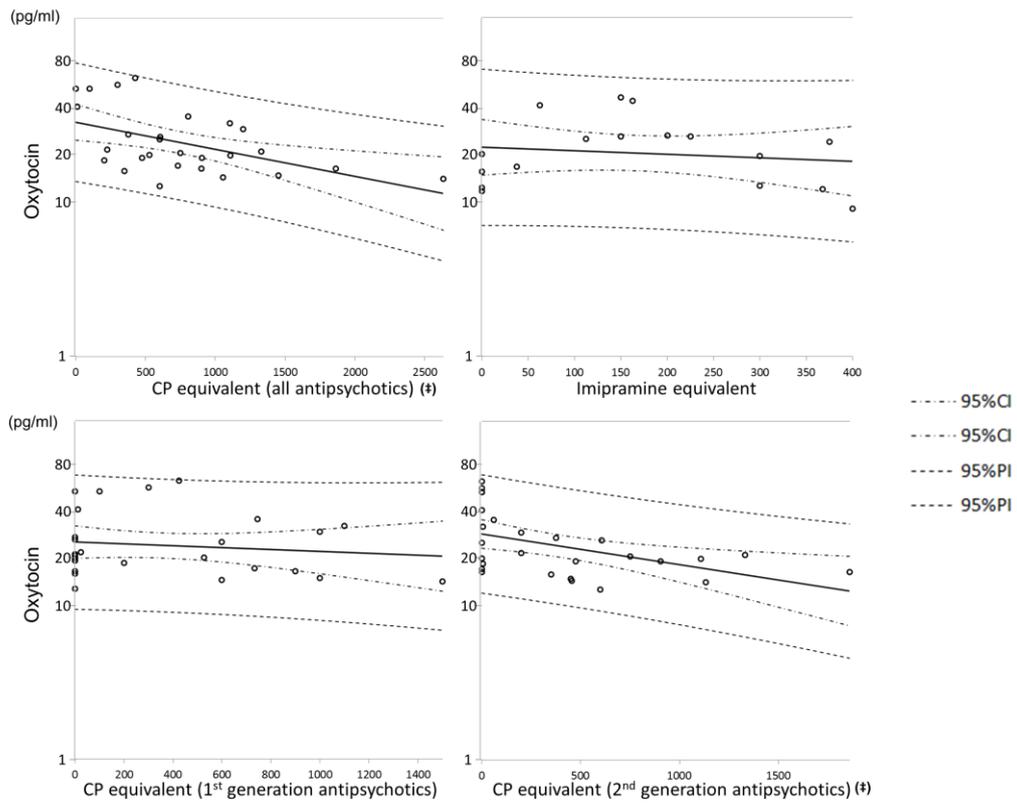# Relationship between CSF oxytocin levels and dose of psychotropics

Figure 3