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Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression

L. VAN LONDEN,[1] J. G. GOEKOOP, A. H. ZWINDERMAN, J. B. K. LANSER, V. M. WIEGANT AND D. DE WIED

From the Departments of Psychiatry, Medical Statistics and Neuropsychology, Leiden University; and the Rudolf Magnus Institute for Neurosciences, Department of Medical Pharmacology, Utrecht University, The Netherlands

ABSTRACT

Background. The aim of the study was to search for the existence of, and define, a possible relationship between performance in neuropsychological tests and baseline concentrations of plasma cortisol, vasopressin and oxytocin in medication-free patients with a major depressive episode.

Methods. Measures of depression and anxiety were obtained and a neuropsychological battery was presented. Blood for neuropeptide analysis was drawn by venepuncture at 8.00, 16.00 and 23.00 h.

Results. The melancholic patients performed less well on the neuropsychological battery than did the non-melancholic patients, but these differences could be accounted for by the severity of the illness. Global intellectual functioning was negatively correlated with mean baseline plasma concentrations of cortisol. Patients with high mean plasma vasopressin concentrations remembered more auditory presented words in the delayed recall test and produced more intrusions in the visual word learning list than did patients with low or normal mean plasma vasopressin concentrations. No association was found between neuropsychological performance and plasma concentrations of oxytocin.

Conclusions. Our findings support the hypothesis that elevated baseline plasma cortisol concentrations are related to cognitive impairment in depressed patients and the hypothesis that the neuropeptide vasopressin independently enhances memory, directly or indirectly through increasing arousal and attention.

INTRODUCTION

Depressed patients have been reported to have impaired concentration, learning and memory (Reus, 1984). The learning and memory impairments are dependent on the degree of effort required by the task, the severity of the depression and the valence of the stimulus material (Hartlage *et al*. 1993). Hypercortisolaemia, Cushing's disease, short-term administration of glucocorticoids, as well as dexamethasone non-suppressor status were shown to be associated with this cognitive impairment in major depression (Winokur *et al*. 1987; Wolkowitz *et al*. 1990; Mitchell, 1995). Others could not confirm the relation between dexamethasone suppressor status and cognitive impairment (Caine *et al*. 1984; Wauthy *et al*. 1991).

In addition to the demonstration of a steroid-related cognitive decline, peptide hormones such as vasopressin and oxytocin have also been shown to have effect on memory and learning (De Wied *et al*. 1988). It is still unclear whether or not vasopressin acts directly on the neural substrates of memory, or indirectly, for example, by enhancing arousal (Ettenberg *et al*. 1983; De Wied *et al*. 1988). Beneficial effects of different

[1] Address for correspondence: Dr L. Van Londen, Department of Psychiatry, Leiden University, PO Box 1251, 2340 BG Oegstgeest, The Netherlands.

vasopressin fragments on both short-term and long-term memory processes were found in healthy volunteers (Weingartner *et al.* 1981; Beckwith *et al.* 1990*a*; Bruins *et al.* 1990, 1992). Others, however, have failed to demonstrate a clear effect in humans (Fehm-Wolfsdorf *et al.* 1988; Beckwith *et al.* 1990*b*). Positive effects of peripherally administered vasopressin on the performance of depressed patients in memory tests have been demonstrated (Gold *et al.* 1981; Weingartner *et al.* 1981).

In experimental animals, oxytocin injected centrally into the ventricles was found to exert effects opposite to those of vasopressin. Oxytocin attenuates memory and learning performances (Argiolas & Gessa, 1991; De Wied *et al.* 1993). Women receiving oxytocin as part of the treatment to induce therapeutic abortion show impairment in recall from long-term memory (Ferrier *et al.* 1980; Kennett *et al.* 1982). No oxytocin effects on delayed recall were found in healthy volunteers (Fehm-Wolfsdorf *et al.* 1988; Bruins *et al.* 1992). No significant correlation between increased oxytocin plasma concentrations and memory or attention were found in peripartal women (Silber *et al.* 1990), or in women with a significant increase in plasma oxytocin while they were taking oral contraceptives (Silber *et al.* 1987).

Evidence of an increased number of vasopressin-immunoreactive and oxytocin-immunoreactive neurons in the paraventricular nucleus of the hypothalamus in depressed patients was found recently (Purba *et al.* 1996). Also, in depressed patients, mean plasma concentrations of vasopressin, but not of oxytocin, were higher than those in healthy controls (Van Londen *et al.* 1997). Concentrations of plasma vasopressin in the melancholic group of patients were higher than in the non-melancholic group. Our main aim in the present study was thus to search for and define possible relationships between neuropsychological performance and baseline levels of plasma vasopressin, oxytocin and cortisol in medication-free depressed patients. As far as we know, this is the first study in which this was done. We sought answers to the following questions: (1) Do melancholic patients differ from non-melancholic patients with respect to neuropsychological performance?; (2) Are high cortisol and oxytocin levels in plasma associated with neuropsychological impairment?; and (3) Are high plasma concentrations of vasopressin related to better neuropsychological performance?

The data are based on the same sample of 56 patients, that we have reported on in previous papers (Van Londen *et al.* 1997, 1998).

METHOD

Subjects (Table 1)

Fifty-six patients from the Endegeest Psychiatric Hospital and the Jelgersma Out-patient Clinic participated in the study. All patients fulfilled DSM-III-R criteria for a major depressive episode. Exclusion criteria for entering the study were: endocrine disease, orthostatic hypotension, and diseases or medication that might affect plasma levels of vasopressin, oxytocin or cortisol. All patients were in good physical health and underwent routine blood analysis. They had been completely drug-free for 2 weeks before the start of the study, except for eight patients who took a maximum of 10 mg clorazepate, oxazepam or temazepam a day on an irregular basis in case of severe anxiety or insomnia. None presented clinical evidence of dementia or other cognition-impairing disease beyond the depressive episode. Of these 56 patients seven had to be excluded from the study; two patients were lost due to missing neuropeptide assessments; one patient had to be excluded for alcohol abuse; one patient developed multiple sclerosis in the year following the index episode; one patient was excluded because he was not a sufficiently fluent Dutch speaker; two patients were excluded because severe agitation or psychomotor retardation precluded neuropsychological testing. Complete sets of data for neuropeptide- and neuropsychological measures were obtained for the remaining 49 patients (21 men and 28 women; mean age 44·6 years (S.D. 13·7, range 22–77). This sample consisted of eight bipolar depressed, five psychotic depressed and 36 non-psychotic unipolar depressed patients. There were 33 out-patients and 16 in-patients. It was the first episode of major depression for 23 patients. There were 23 smokers and 26 non-smokers.

Clinical and biological evaluation

Patient assessment according to the DSM-III-R criteria for a major depressive episode was made

by a psychiatrist (L. Van L.). She saw the patient after referral by the psychiatric staff who had earlier independently reached the diagnosis. If there was a discrepancy between the assessments the patient was not admitted to the study. The Comprehensive Psychopathological Rating Scale (CPRS, Åsberg *et al.* 1978) was used in the diagnostic interview. The diagnostic criteria for melancholic subtype (according to the DSM-III-R) were met by 27 patients. Severity of depression and anxiety were assessed by means of the Montgomery & Åsberg Depression Rating Scale (MADRS, Montgomery & Åsberg, 1979) and the Brief Anxiety Scale (BAS, Tyrer *et al.* 1984). Scores of at least 20 on the MADRS were required before entry. The Salpêtrière Retardation Rating Scale (SRRS, Widlöcher, 1983) was used to measure psychomotor retardation. All subjects underwent a routine blood analysis. Three blood samples, 50 ml each, were drawn by venepuncture on the same day at 08.00, 16.00 and 23.00 h. Plasma vasopressin and oxytocin were determined in duplicate by radioimmunoassay (RIA) following extraction of peptides from plasma (efficiency approximately 100%). A rabbit antiserum (coded W1E) with the following cross-reactivities: vasotocin 100%; [Cyt^6]vasopressin-(3–9) 50%; [pGlu^4,Cyt^6]vasopressin-(4–9) 25%; [Cyt^6]vasopressin-(5–9) 13%; vasopressin-(1–8), vasopressin-(1–7) and oxytocin undetectable, was used for RIA of vasopressin. The detection limit was 0·5 pg/tube, yielding a sensitivity of 0·5 pg/ml for plasma after extraction of peptides. The intra- and inter-assay coefficients of variation were 9·9 and 15·9%, respectively. Oxytocin was determined using the highly specific antiserum, THF-3, kindly donated by Dr Higuchi (Matsuoka, Japan). For details on cross-reactivity see Higuchi *et al.* (1985). The sensitivity of the assay was 0·5 pg/tube (0·5 pg/ml plasma). Intra- and inter-assay coefficients of variation were 7 and 10%, respectively.

The blood samples to be used for cortisol determination were drawn into NH4-heparin-containing tubes and stored at −20 °C prior to assay by high performance liquid chromatography (HPLC) with UV detection. After thawing and before assay, prednisolone was added as internal standard. The plasma was alkalinized and cortisol was extracted into dichloromethane; after evaporation of the organic solvent the sample was dissolved in the eluent then injected on an HPLC cartridge CP™ SPHER Si. The eluent consisted of a mixture of 335 ml dichloromethane, 150 ml dichloromethane saturated with water, 6 ml tetrahydrofuran, 12 ml methanol and 0·25 ml acetic acid. The lower limit of detection at the wavelength used (254 nm) was 10 nmol/l plasma; within-day variation was 4·6% and day-to-day variation was 8·7%. Clinical evaluations and laboratory tests were done by different people. Vasopressin and oxytocin were measured in the Rudolf Magnus Institute for Neurosciences (Utrecht); cortisol was determined in the laboratory of the Endegeest Psychiatric Hospital (Oegstgeest).

Neuropsychological assessment

The number of neuropsychological tests we could administer to these often very depressed in- and out-patients was restricted, due to the limited time span for which these patients could concentrate. In this study we wanted to focus on impairment in memory and the ability to learn new information, because vasopressin and oxytocin have been associated with these functions. The following tests were chosen.

1 The Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981).

2 The Wechsler Memory Scale, Form I (Wechsler, 1945).

3 Intellectual impairment was assessed from the difference between estimated pre-morbid intelligence quotient (EPIQ) and current IQ and memory quotient (MQ). The estimation of pre-morbid IQ was based on education, profession and intact abilities (Haan *et al.* 1990).

4 Two word learning lists of 10 nouns were presented. One for auditory (10-WLLA) and the other for visual (10-WLLV) presentation (Jennekens-Schinkel *et al.* 1984). The two lists were identical as to word frequencies and distribution of mono- and bi-syllabic words. Presentation rates were 10 words/17 s for auditory presentation and 1 word/s for visual presentation. Trials were followed by free recall. The items scored were: number of correct reproductions, number of errors (intrusions and preservations). Presentation was stopped when all words were reproduced or after five consecutive presentations. Delayed recall was tested after 30 min.

The blood samples were not taken on the same day as that on which the tests were

scheduled, to avoid the confounding effect of stress from visits to the laboratory on neuropsychological test results and vice versa. Blood was usually drawn 1 day before neuropsychological examination. No medication whatsoever was taken on the night preceding and in the morning of the neuropsychological testing day. All subjects were tested in the morning, at 10.00 h.

Data analysis

All calculations were performed using SPSS/PC+ V5.02 (SPSS INC, Chicago, IL). The comparability of melancholic and non-melancholic patients was examined for age, pre-morbid IQ and sex, using the t test or the χ^2 test. The significance of differences in neuropsychological performance between the two groups was examined by the t test. The responses to the repeated trials of the 10-WLLA and 10-WLLV were compared using Repeated Measures Analysis of Variance (ANOVA). Results at three timepoints were collected for plasma hormone levels. The means of these three concentrations were used for the analyses. Correlations between the plasma hormone levels of vasopressin, oxytocin and cortisol and the neuropsychological test scores for the entire sample and for the subgroups of melancholic and non-melancholic patients were assessed by measuring the Pearson correlation coefficient and Multiple ANOVA. Two-tailed probabilities were used throughout. Because sex, age, smoking, severity of depression and mean plasma cortisol may influence neuropsychological performance as well as plasma levels of vasopressin, covariance analysis using these variables as covariates was performed. The level of statistical significance was set at $P < 0{\cdot}05$. When multiple comparisons were made, the Bonferroni correction was used to avoid increasing the probability of Type I errors.

RESULTS

The entire sample had a mean pre-morbid IQ of 109·1 (S.D. = 12·2), a mean Full Scale IQ (FSIQ) of 96·4 (S.D. = 14·1) and a mean Memory Quotient (MQ) of 105·3 (S.D. = 17). The scores on the orientation subscale were not analysed as variance was insufficient. The results of both word learning lists (10-WLLA and 10-WLLV) are presented in Fig. 1. Only those word learning lists that were completed (i.e. consecutive trials followed by a delayed reproduction) were included ($N = 47$).

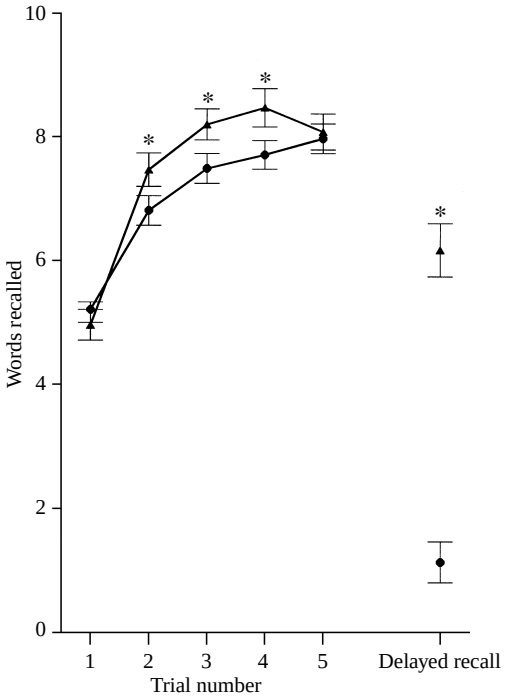

FIG. 1. The mean number of words recalled on successive trials of the Visual (▲) and Auditory (●) Word Learning Lists in 47 depressed patients. *$P < 0{\cdot}05$: Performance in the Visual Word Learning List (10-WLLV) averaged 0·43 words better than performance in the Auditory Word Learning List (10-WLLA) in the second, third and fourth trial ($F = 27{\cdot}7$ df = 1,147 $P < 0{\cdot}001$). The delayed recall after 30 min in the 10-WLLV was significantly higher than the delayed recall in the 10-WLLA ($t = 7{\cdot}76$ df = 46 $P = 0{\cdot}001$). Error bars indicate standard error of the mean (S.E.M.).

The patients made significantly more intrusion errors in the visual (mean = 0·65, S.D. = 0·9; range 0–3) than in the auditory (mean = 0·33, S.D. = 0·66; range 0–3) word learning list ($t = 2{\cdot}03$ df = 48 $P = 0{\cdot}05$). The number of intrusion errors made in the delayed recall of the visual list (mean = 0·53, S.D. = 1·44; range 0–9) was not significantly higher than those made in the delayed recall of the auditory list (mean = 0·11, S.D. = 0·48; range 0–3; $t = -1{\cdot}94$ df = 46 $P = 0{\cdot}06$). The number of perseverations was not significantly different between the two word learning lists ($t = 0{\cdot}57$ df = 48 $P = 0{\cdot}6$). The patients made more perseveration errors in the delayed recall of the visual list (mean = 0·30, S.D. = 0·59; range 0–2) than in the delayed recall

Table 1. *Clinical variables* (S.D.) *for non-melancholic and melancholic patients*

	Non-melancholic ($N = 22$)	Melancholic ($N = 27$)	F ratio, χ^2	P
Sex (M:F)	7:15	14:13	$\chi^2 = 1{\cdot}25$	0·26
Age (S.D.)	41·6 (12·3)	47·0 (14·5)	1·94	0·17
Age range (years)	24–70	22–77		
Smokers:Non-smokers	12:10	11:16	$\chi^2 = 0{\cdot}46$	0·50
Patients using benzodiazepines	2	6	$\chi^2 = 0{\cdot}72$	0·40
Severity of depression (MADRS)	28·9 (4·7)	34·4 (6·8)	10·27	0·002
Anxiety (BAS)	18·4 (6·3)	21·5 (5·3)	3·25	0·08
Psychomotor retardation (SRRS)	14·7 (6·2)	23·7 (8·8)	16·38	0·0002
CPRS total score	61·1 (10·2)	68·3 (12·8)	4·20	0·046
Estimated pre-morbid IQ (S.D.)	110·3 (12·8)	108·2 (11·8)	0·36	0·55
Deterioration IQ (S.D.)	9·1 (9·5)	14·7 (8·0)	4·96	0·03

Table 2. *Results of the WAIS-R for melancholic and non-melancholic patients presented as mean* (S.D.)

	Non-melancholic ($N = 22$)	Melancholic ($N = 27$)	F ratio	P†	P‡
Verbal tests					
Information	9·9 (2·5)	12·7 (19·7)	0·45	0·51	0·50
Digit span	7·4 (1·9)	6·8 (1·9)	1·06	0·31	0·85
Vocabulary	8·6 (2·0)	7·8 (2·2)	1·65	0·21	0·82
Arithmetic	10·2 (3·3)	9·2 (3·1)	0·98	0·33	0·83
Comprehension	10·2 (2·3)	9·2 (3·2)	1·65	0·21	0·50
Similarities	10·2 (2·1)	9·0 (2·9)	2·71	0·11	0·44
Performance tests					
Picture completion	9·2 (2·5)	7·0 (3·4)	6·26	0·02	0·07
Picture arrangement	9·1 (3·1)	9·1 (11·7)	0·0007	0·98	0·99
Block design	10·6 (3·4)	8·3 (2·8)	6·85	0·01	0·08
Object assembly	9·3 (2·7)	7·6 (2·9)	4·74	0·04	0·15
Verbal IQ	99·3 (11·3)	93·6 (12·1)	2·81	0·10	0·63
Performance IQ	104·0 (14·6)	91·7 (16·0)	7·66	0·01	0·07
Full scale IQ	101·2 (12·9)	92·5 (14·0)	5·03	0·03	0·26

† P value derived from t test.
‡ P value from covariance analysis corrected for scores on the MADRS, psychomotor retardation and CPRS.

of the auditory list (mean = 0·04, S.D. = 0·20; range 0–1; $t = -2{\cdot}73$ df = 46 $P = 0{\cdot}009$).

Neuropsychological performance and melancholic subtype

Melancholic patients were significantly more depressed, showed more psychomotor retardation and more deterioration of the estimated pre-morbid IQ (Table 1). They had significantly lower scores on three subscales of the WAIS-R (Table 2) and on three subtests of the Wechsler Memory Scale (Table 3). However, when adjusted for scores on the MADRS, psychomotor retardation and CPRS, none of these differences between neuropsychological performances of melancholic and of non-melancholic patients remained significant. There were no significant differences between melancholic and non-melancholic patients for the word learning lists.

Neuro-endocrinological data and neuropsychological performance

Cortisol

The mean concentrations of plasma cortisol were inversely correlated to scores of FSIQ ($r = -0{\cdot}45$ $P = 0{\cdot}001$; subscales Verbal IQ $r = -0{\cdot}48$ $P = 0{\cdot}001$ and Performance IQ $r = -0{\cdot}38$ $P = 0{\cdot}007$) and MQ $r = -0{\cdot}35$ $P = 0{\cdot}014$). The correlations were significant

Table 3. *Results of the Wechsler Memory Scale in melancholic and non-melancholic patients presented as mean (S.D.)*

	Non-melancholic ($N = 22$)	Melancholic ($N = 27$)	F ratio	P†	P‡
Information	5·9 (0·29)	5·5 (0·75)	5·25	0·03	0·06
Orientation‖	5·0 (0)	4·6 (0·5)	—	—	—
Mental control	7·8 (0·92)	7·0 (1·8)	3·21	0·08	0·38
Logical memory	9·0 (3·4)	7·0 (3·0)	4·59	0·04	0·35
Digits total	9·6 (1·4)	9·3 (1·7)	0·22	0·64	0·98
Visual reproduction	9·5 (3·2)	7·7 (4·1)	2·75	0·10	0·53
Associate learning	16·6 (3·1)	14·7 (4·3)	2·87	0·10	0·49
Memory IQ	110·5 (16·4)	101·1 (16·5)	3·93	0·05	0·53

† P value derived from t test.
‡ P value from covariance analysis corrected for scores on the MADRS, psychomotor retardation and CPRS.
‖ Orientation was not analysed due to insufficient variance.

Table 4. *Number of consecutive trials presented in the Visual and Auditory Word Learning Lists and the number of correct words reproduced in the delayed recall*

	Visual Word Learning List		Auditory Word Learning List	
Number of trials presented	Patients	Number of words in the delayed recall	Patients	Number of words in the delayed recall
2	6	7·2 ± 3·1	4	1·2 ± 2·3
3	7	6·0 ± 3·4	2	4·0 ± 5·7
4	8	7·8 ± 1·7	3	0
5	26	5·4 ± 3	38	1·0 ± 2·0

after a Bonferroni correction of $P < 0{\cdot}025$. No correlations were found between plasma cortisol levels and performances on the word learning lists.

Oxytocin

No significant associations were found between any of the neuropsychological test results and plasma concentrations of oxytocin.

Vasopressin

Mean plasma vasopressin concentrations were significantly positively correlated to the delayed recall of auditory presented words ($r = 0{\cdot}51$ $P < 0{\cdot}001$ $N = 47$) on the 10-WLLA. When the patient group was subtyped according to melancholia, this correlation remained significant for melancholic ($r = 0{\cdot}73$ $P < 0{\cdot}001$ $N = 25$), but not for non-melancholic patients ($r = -0{\cdot}038$ $P = 0{\cdot}87$ $N = 22$). The number of auditory and visual presentations was not equal for all patients (Table 4), but the relationship between mean plasma vasopressin concentrations and the delayed recall remained significant in the group of patients that needed five consecutive trials ($r = 0{\cdot}42$ $P = 0{\cdot}04$ $N = 24$) as well as in the group of patients that reproduced the 10 words presented in 2, 3 or 4 consecutive trials ($r = 0{\cdot}65$ $P = 0{\cdot}001$ $N = 23$). For melancholic patients, the mean vasopressin plasma concentration was significantly negatively related to the number of words reproduced in the delayed recall of the 10-WLLV ($r = -0{\cdot}46$ $P = 0{\cdot}02$ $N = 25$). This correlation was not significant for non-melancholic patients ($r = 0{\cdot}14$ $P = 0{\cdot}55$ $N = 22$).

Mean plasma vasopressin concentrations were significantly correlated to the number of intrusions (i.e. self-generated not correctly reproduced words) in the 10-WLLV ($r = 0{\cdot}44$ $P = 0{\cdot}002$ $N = 47$), but not significantly so, to the number of intrusions in the 10-WLLA ($r = -0{\cdot}04$ $P = 0{\cdot}82$ $N = 47$). These correlations were not significantly different for melancholic and for non-melancholic patients.

Confounding effects

We investigated the possibility that covariates related to plasma vasopressin concentrations could have influenced the apparent relationship between mean plasma concentrations vaso-

pressin and the delayed recall of words in the 10-WLLA and 10-WLLV, and the number of intrusions in the 10-WLLV. Correction for the suspected confounding effects of sex, age, smoking status, mean plasma cortisol concentrations, severity of depression (MADRS), psychomotor retardation (Widlöcher scale) and general psychopathology (CPRS) did not alter the results: the adjusted correlation between mean plasma vasopressin concentration and the delayed recall of auditory presented words in melancholic patients was $r = 0{\cdot}76$ $P < 0{\cdot}001$ ('raw' correlation was $r = 0{\cdot}51$ $P < 0{\cdot}001$); the adjusted correlation between mean plasma vasopressin concentration and the delayed recall of visually presented words in melancholic patients was $r = -0{\cdot}52$ $P = 0{\cdot}024$ ('raw' correlation was $r = -0{\cdot}46$ $P = 0{\cdot}02$); the adjusted correlation between mean plasma vasopressin concentration and number of intrusions in the 10-WLLV was $r = 0{\cdot}46$ $P = 0{\cdot}003$ ('raw' correlation was $r = 0{\cdot}44$ $P = 0{\cdot}002$).

DISCUSSION

The neuropsychological performance of 49 depressed patients was measured and its correlation to baseline plasma concentrations of cortisol, vasopressin and oxytocin was tested. Correct interpretation of our data demands that several issues be taken into account. (1) We used mean levels of baseline plasma cortisol, based on three samplings (8.00, 16.00 and 23.00 h) in medication-free depressed patients. Possible non-suppression of cortisol in response to dexamethasone was not tested. Hypercortisolaemia may be associated with increased levels of ACTH, which itself has cognition enhancing properties. We did not measure ACTH concentrations in our samples. (2) We measured baseline endogenous plasma vasopressin concentrations under naturalistic circumstances. We are aware of the fact that this design introduced a methodological weakness. However, the elevated plasma vasopressin concentrations we found could not be accounted for by sex, age, smoking, blood pressure instability, hypovolaemia, hyperosmolality or dehydration (Van Londen *et al.* 1997). Plasma vasopressin and oxytocin are produced centrally in the paraventricular (PVN), supraoptic and accessory nuclei of the hypothalamus. Recently, evidence of a higher activation of vasopressin-immunoreactive and oxytocin-immunoreactive neurons in the PVN of the hypothalamus of depressed patients was found (Purba *et al.* 1996). It may well be that the high plasma concentrations of vasopressin we found in depressed patients (up to 33·7 pg/ml) is a reflection of central release of vasopressin in the brain. Though vasopressin and oxytocin may have difficulty in crossing the blood–brain barrier, they do enter the circulation to some extent (Pardridge, 1983). (3) Although exogenously administered vasopressin analogs as well as high endogenous release seem to be related to similar memory enhancing effects (delayed recall of auditory presented words), exogenous vasopressin may have CNS effects different from those of endogenous vasopressin. (4) The cross-sectional nature of this study does not allow the inference of cause and effect. (5) We measured plasma vasopressin in patients and in healthy controls, but unfortunately, in retrospect, neuropsychological testing was done only in patients. Therefore, the correlational findings between plasma vasopressin levels and the neuropsychological data cannot be compared with the situation in normal controls.

Do melancholic patients differ from non-melancholic patients with respect to neuropsychological performance?

The melancholic patients performed less well on the neuropsychological battery than did the non-melancholic patients, but these differences could be accounted for by the severity of the illness. We had found earlier that mean plasma vasopressin concentrations were higher in melancholic patients than in non-melancholic patients (Van Londen *et al.* 1997). The mean plasma vasopressin concentrations were not correlated to scores on the MADRS (illness severity) or to those of the BAS (anxiety), but were correlated significantly to the extent of psychomotor retardation in these patients (Van Londen *et al.* 1998). In melancholic patients, the plasma vasopressin concentrations were significantly positively related to the number of reproduced words in the auditory test and significantly negatively related to the number of reproduced words of the visual word learning test. These correlations were not significant in non-melancholic patients. Does this mean that

melancholic patients have a subtype of depression that is different from that of non-melancholic patients in terms of pathophysiology? We are inclined not to believe so: had the patient groups been larger, statistically significant relationships could probably have been shown for non-melancholic patients as well.

Are high cortisol and oxytocin levels in plasma associated with neuropsychological impairment?

As we expected, high baseline plasma concentrations of cortisol were related to a lower degree of global intellectual functioning. Mitchell (1995), in a careful review of 17 studies in which cognitive impairment was examined in relation to measures of hypothalamic–pituitary–adrenocortical (HPA) axis activity, concluded that a significant correlation between these two variables was found consistently. Prospective studies in this area have shown that when depression is successfully treated, hypercortisolaemia tends to normalize and cognitive function improves (Mitchell, 1995). Our findings are consistent with the hypothesis that HPA overactivity, resulting in elevated baseline plasma cortisol concentrations, may be related to or even cause cognitive impairment (Wauthy *et al.* 1991).

Because it is suggested that vasopressin and oxytocin exert opposite effects on memory storage and retrieval processes, we hypothesized that the depressed patients with elevated baseline oxytocin concentrations would perform less well in the neuropsychological tasks. We found no such association. However, because the range of the plasma values of oxytocin was fairly narrow and differences between patients thus very small, these results should be interpreted with caution. It may well be, that oxytocin has more difficulty escaping the blood–brain barrier than vasopressin. On the other hand, as far as we know, no direct significant relations have so far been found between temporary memory impairment and oxytocin plasma concentrations in human studies (Silber *et al.* 1987, 1990).

Are high plasma concentrations of vasopressin related to better neuropsychological performance?

We found two vasopressin-related changes in the neuropsychological performances of the depressed patients: first, plasma vasopressin concentrations were related significantly to the number of recalled auditory presented words after 30 min, and secondly plasma vasopressin concentrations were related significantly to the number of intrusions in the visual list and related, but not significantly so, to the number of intrusions in the auditory word learning list.

With regard to the first observation others have found that peripheral administration of vasopressin to depressed patients results in an increase in overall recall of learned auditory presented information (Gold *et al.* 1981; Weingartner *et al.* 1981). Whether this can be interpreted as an enhanced speed of encoding information, or modulation of a retrieval strategy, or improved quality of consolidation is unknown. Animal research supports the idea that vasopressin may act as a neuromodulator in an extrinsic neuronal system, i.e. limbic structures, which facilitates the encoding of information (Hijman, 1992). When low doses of vasopressin were administered as a nasal spray to healthy young subjects, no effects on memorizing word lists or long-term recall were seen, but marked changes in the auditory evoked brain potentials (AEP) to tone pips appeared, no matter whether attention was paid to the stimuli or not (Fehm-Wolfsdorf *et al.* 1988). The authors conclude that vasopressin has a primary excitatory role in cortical processing, rather than a direct beneficial effect on learning and memory. Our findings do not allow speculation in favour of either of the two interpretations of the hypothesized cognitive effects of vasopressin.

The second finding, with the visual list, and the observation that exogenously administered vasopressin produced marked changes in the evoked auditory potentials, suggests that elevated vasopressin may influence cognitive performance by shifting the focus to an auditory input, possibly at the expense of the attention that is directed towards a visually presented input. Another possibility is that an elevated vasopressin concentration increases the general cortical arousal to a supraoptimal level, leading to distractibility and increased number of intrusion errors. Our neuropsychological data showed that these patients with high endogenous plasma concentrations of vasopressin made most of their intrusion errors in the first five words of the visual word learning list. They persisted in making these mistakes in the subsequent trials, although the assistant repeatedly presented the

correct words. The intrusions were phonologically and semantically associated with the visually presented words. An interpretation of this is that these patients were aroused, and could not concentrate sufficiently to memorize correctly. Furthermore, the approach of these patients was too rigid to allow them to correct themselves. The fact that significantly less intrusion errors were made in the auditory than in the visual word learning list could suggest that auditory input is processed more directly than visual input and thus less vulnerable to errors of interpretation.

In summary, we found that, in our sample of depressed patients, global intellectual functioning was negatively related to baseline concentrations of cortisol. No significant relationships were found between neuropsychological performance and oxytocin plasma concentrations. The patients with high baseline plasma vasopressin concentrations remembered more words in the delayed recall of auditory presented material and produced more intrusions in the visual presented material than did the patients with plasma vasopressin in the normal range. Assuming that major depression and neuropsychological performance are somehow linked at a physiological level, we hypothesize on the basis of our results and earlier results that not only the catecholamines and the activation of the HPA axis are involved, but that the neuropeptide, vasopressin, also has a role, directly or indirectly through increasing arousal and attention, in the modulation of memory processes.

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REFERENCES

Argiolas, A. & Gessa, G. L. (1991). Central functions of oxytocin. *Neuroscience and Biobehavioral Reviews* **15**, 217–231.

Åsberg, M., Montgomery, S., Perris, C., Schalling, D. & Sedvall, G. (1978). A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica* **271** (suppl.), 5–27.

Beckwith, B. E., Till, R. E., Reno, C. R. & Poland, R. E. (1990*a*). Dose-dependent effects of DDAVP on memory in healthy young adult males: a preliminary study. *Peptides* **11**, 473–476.

Beckwith, B. E., Petros, T. V. & Knutson, K. K. (1990*b*). Effects of DDAVP on gender-specific verbal and visuospatial tasks in healthy young adults. *Peptides* **11**, 1313–1315.

Bruins, J., Hijman, R. & Van Ree, J. M. (1992). Effect of a single dose of Des-Glycinamide [Arg^8]Vasopressin or oxytocin on cognitive processes in young healthy subjects. *Peptides* **13**, 461–468.

Bruins, J., Kumar, A. & Schneider-Helmert, D. (1990). Influence of desglycinamide-(Arg^8) vasopressin on memory in healthy subjects. *Neuropsychobiology* **23**, 82–88.

Caine, E. D., Yerevanian, B. I. & Bamford, K. A. (1984). Cognitive function and the dexamethasone suppression test in depression. *American Journal of Psychiatry* **141**, 116–118.

De Wied, D., Joëls, M., Burbach, P. H., De Jong, W., De Kloet, E. R., Gaffori, O. W. J., Urban, I. J. A., Van Ree, J. M., Van Wimersma Greidanus, Tj. B., Veldhuis, H. D., Versteeg, D. H. G. & Wiegant, V. M. (1988). Vasopressin effects on the central nervous system. In *Peptide Hormones: Effects and Mechanisms of Action* (ed. A. Negro-Vilar and P. M. Conn), Vol. I, pp. 97–140. CRC Press Inc: Boca Raton, Florida.

De Wied, D., Diamant, M. & Fodor, M. (1993). Central nervous system effects of the neurohypophyseal hormones and related peptides. *Frontiers of Neuroendocrinology* **14**, 251–302.

Ettenberg, A., Van der Kooy, D., Le Moal, M., Koob, G. F. & Bloom, F. E. (1983). Can aversive properties of (peripherally-injected) vasopressin account for its putative role in memory? *Behavioural Brain Research* **7**, 331–350.

Fehm-Wolfsdorf, G., Born, J., Voigt, K. & Fehm, H. L. (1984). Human memory and neurohypophyseal hormones: opposite effects of vasopressin and oxytocin. *Psychoneuroendocrinology* **9**, 285–292.

Fehm-Wolfsdorf, G., Bachholz, G., Born, J., Voigt, K. & Fehm, H. L. (1988). Vasopressin but not oxytocin enhances cortical arousal: an integrative hypothesis on behavioral effects of neurohypophyseal hormones. *Psychopharmacology* **94**, 496–500.

Ferrier, B. M., Kennett, D. J., Devlin, M. C. (1980): Influence of oxytocin on human memory processes. *Life Sciences* **27**, 2311–2317.

Gold, P. W., Goodwin, F. K., Ballenger, J. C., Post, R. M., Weingartner, H. & Robertson, G. L. (1981). Central vasopressin function in affective illness. *International Journal of Mental Health* **9**, 91–107.

Haan, J., Lanser, J. B. K., Zijderveld, I., Van der Does, I. G. & Roos, R. A. C. (1990). Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type. *Archives of Neurology* **47**, 965–967.

Hartlage, S., Alloy, L. B., Vázquez, C. & Dykman, B. (1993). Automatic and effortful processing in depression. *Psychological Bulletin* **113**, 247–278.

Higuchi, T., Honda, K., Fukuoka, T., Negoro, H. & Wakabayashi, K. (1985). Release of oxytocin during suckling and parturition in the rat. *Journal of Endocrinology* **105**, 339–346.

Hijman, R. (1992). Desglycinamide-[Arg^8]-vasopressin in patients with memory disturbances. Ph.D. thesis, University of Utrecht, The Netherlands.

Jennekens-Schinkel, A., Wintzen, A. R. & Lanser, J. B. K. (1984). A clinical trial with desglycinamide arginine vasopressin for the treatment of memory disorders in man. *Progress in Neuropsychopharmacology and Biological Psychiatry* **9**, 273–284.

Kennett, D. J., Devlin, M. C. & Ferrier, B. M. (1982). Influence on oxytocin on human memory processes: validation by a control study. *Life Sciences* **31**, 273–275.

Mitchell, A. J. (1995). The contribution of hypercortisolaemia to the cognitive decline of geriatric depression. *International Journal of Geriatric Psychiatry* **10**, 401–409.

Montgomery, S. A. & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Pardridge, W. M. (1983). Neuropeptides and the blood–brain barrier. *Annual Review of Physiology* **45**, 73–82.

Purba, J. S., Hoogendijk, W. J. G., Hofman, M. A. & Swaab, D. F. (1996). Increased numbers of vasopressin and oxytocin expressing

neurons in the paraventricular nucleus of the human hypothalamus in depression. *Archives of General Psychiatry* **53**, 137–143.

Reus, V. I. (1984). Hormonal mediation of the memory disorder in depression. *Drug Development Research* **4**, 489–500.

Silber, M., Almkvist, O., Larsson, B., Stock, S. & Uvnäs-Moberg, K. (1987). The effect of oral contraceptive pills on levels of oxytocin in plasma and on cognitive functions. *Contraception* **36**, 641–650.

Silber, M., Almkvist, O., Larsson, B. & Uvnäs-Moberg, K. (1990). Temporary peripartal impairment in memory and attention and its possible relation to oxytocin concentration. *Life Sciences* **47**, 57–65.

Tyrer, P., Owen, R. T. & Cichetti, D. V. (1984). The brief scale for anxiety: a subdivision of the Comprehensive Psychopathological Rating Scale. *Journal of Neurology Neurosurgery and Psychiatry* **47**, 970–975.

Van Londen, L., Goekoop, J. G., Van Kempen, G. M. J., Frankhuijzen-Sierevogel, J. C., Wiegant, V. M., Van der Velde, E. A. & De Wied, D. (1997). Plasma levels of arginine vasopressin elevated in patients with major depression. *Neuropsychopharmacology* **17**, 284–292.

Van Londen, L., Kerkhof, G. A., Van den Berg, F., Goekoop, J. G., Zwinderman, A. H., Frankhuijzen-Sierevogel, J. C., Wiegant, V. M. & De Wied, D. (1998). Plasma arginine vasopressin and motor activity in major depression. *Biological Psychiatry* **3**, 196–204.

Wauthy, J., Ansseau, M., von Frenckell, R., Mormont, C. & Legros, J.-J. (1991). Memory disturbances and dexamethason suppression test in major depression. *Biological Psychiatry* **30**, 736–738.

Wechsler, D. (1945). *The Wechsler Memory Scale*, *Form I*. The Psychological Corporation: New York.

Wechsler, D. (1981). *The Wechsler Adult Intelligence Scale-Revised*. The Psychological Corporation: New York.

Weingartner, H., Gold, P. W., Ballenger, J. C., Smallberg, S. A., Summers, R., Rubinow, D. R., Post, R. M. & Goodwin, F. K. (1981). Effects of vasopressin on human memory functions. *Science* **211**, 601–603.

Widlöcher, D. J. (1983). Psychomotor retardation: clinical, theoretical and psychometric aspects. *Psychiatric Clinics of North America* **6**, 27–40.

Winokur, G., Black, D. W. & Nasrallah, A. (1987). Nonsuppressor status: relationship to specific aspects of the depressive syndrome. *Biological Psychiatry* **22**, 360–368.

Wolkowitz, O. M., Reus, V. I., Weingartner, H., Thompson, K., Breier, A., Doran, A., Rubinow, D. & Pickar, D. (1990). Cognitive effects of corticosteroids. *American Journal of Psychiatry* **147**, 1297–1303.