Serum oxytocin correlated with later logical memory in older Japanese women: A 7-year follow-up study

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ABSTRACT

Objectives: This study aimed to investigate the longitudinal relationship between serum oxytocin and logical memory among older adults in rural Japan and clarify sex differences in this relationship.
Measurements: The first survey was conducted from October 2009 to March 2011 (Time 1) and the second from November 2016 to September 2017 (Time 2). The final analysis for Time 1 included 385 participants (median age 75 years, interquartile range [IQR] 70–81 years) and that for Time 2 included 76 participants (median age 80 years, IQR 76–83 years). We assessed cognition, logical memory, and living conditions, and measured serum oxytocin levels. Logical memory was evaluated using the Wechsler Memory Scale-Revised Logical Memory II delayed recall part A (LM II-DR). Serum oxytocin was measured using the enzyme immunoassay method.
Results: The median (IQR) oxytocin level among men (n = 20) was 34 (16–78) pg/mL at Time 1 and 53 (28–140) pg/mL at Time 2. The median (IQR) oxytocin level among women (n = 56) was 117 (35–412) pg/mL at Time 1 and 76 (32–145) pg/mL at Time 2. The median oxytocin level among women at Time 2 was significantly lower than that at Time 1 ($p = 0.004$). The multivariate analysis showed that for women, LM II-DR score at Time 2 was positively associated with oxytocin level at Time 1 ($p = 0.042$) and negatively associated with age ($p = 0.02$).
Conclusions: Our study suggests that maintaining high oxytocin levels in older women may prevent age-related decline in logical memory.

1. Introduction

Oxytocin (OT) is a nonapeptide hormone that is best known for its role in lactation and parturition. From description of the uterine-contracting properties of OT in 1906 until its sequence was elucidated 50 years later, research focused on the peripheral role of OT in reproduction [1]. OT is well known to influence social attachment, which includes social bonding in animals [2]. Over the past two decades, the effect of OT on human social behavior has become an active field of research, with OT reported to be associated with parental, romantic, and filial attachment in humans [3]. However, the robustness of conclusions in this field has been recently questioned because of problems with low statistical power in IN-OT studies [4], heterogeneity of IN-OT effects, poor reproducibility, and significance inconsistent with the sample size [5].

Despite questions being raised in this field, numerous studies have shown that peripheral OT levels were linked to affiliation-related cognition or emotional states [[6–8]]. Higher levels of the neuropeptide OT were found to benefit socioemotional functioning; however, little is known about the effects of OT on cognition or age-related changes in the OT system [9].

OT is involved in the hippocampus; therefore, we speculated there

was a relationship between OT and memory. The biological actions of OT are exerted via specific OT receptors (OTRs) that belong to the family of G protein-coupled receptors. OTRs are abundantly expressed in the hippocampus, and OTR signaling plays a vital role in the regulation of neural excitability, network oscillatory activity, synaptic plasticity, and social cognitive memory [10]. Therefore, we hypothesized that OT was involved in logical memory and that OT level would be correlated with performance on logical memory tests. We also hypothesized that there would be a sex difference in this correlation. Recent studies showed age-by-sex variations in the effects of OT on facial emotion recognition [11], meta-moods [12], and resting-state functional connectivity [13]. In addition, we recently reported that serum OT level was positively associated with logical memory among older adult women living in rural Japan [14]. However, because of the cross-sectional design of that study, we could not determine a causal relationship between memory dysfunction and OT level. In another study, we reported a positive correlation between baseline serum OT level and the brain volume of a region comprising the left hippocampus and amygdala 7 years later in 58 older adults in Japan [15]. These findings suggested that among older adults, OT levels were associated with age-related changes in hippocampal and amygdala volume. Therefore, the present study aimed to investigate the longitudinal relationship between serum OT level and logical memory in older adults living in rural Japan. We hypothesized that a high baseline OT level would be associated with a high level of logical memory 7 years later.

2. Materials and methods

2.1. Participants

This longitudinal study was conducted as part of the Kurogawa study, which is a population-based prospective cohort study [[14–21]]. In this 7-year follow-up study, the first survey was conducted from October 2009 to March 2011 (Time 1), and the second from November 2016 to September 2017 (Time 2). The survey was conducted in Kurogawa, Imari, Saga Prefecture, Japan, and involved people aged ≥65 years. Kurogawa is a rural town that had a population of 3253 people in 2010, of whom 932 (28.7%) were aged over 65 years. At that time, the population density was 122.48 people/km^2.

At Time 1, the study was conducted alongside a national prevalence survey of dementia in Japan [22]. All older adults in Kurogawa were recruited for the study via information sessions held in each district. As previously reported [14], 596 older adults were registered in the study, which accounted for 63.9% of the population of Kurogawa aged over 65 years. Participants were assessed at either a community center or in their own homes. Their demographic data, living conditions, and medical history were recorded, including age, sex, height, weight, number of family members, years of education, social participation, whether they had lost their spouse, whether they consumed alcohol daily, and smoking history. Medical history included hypertension, diabetes mellitus, and cardiovascular disorders. Study exclusion criteria were current (or past history of) organic brain damage or any psychotic disorder at Time 1 (e.g., anxiety disorder, mood disorder, or alcohol or drug misuse), residing in a nursing home at Time 1, and taking medication at Time 1 (e.g., hypnotic or antianxiety drugs). Participants underwent psychological evaluation using psychological tests, and serum OT was measured from blood samples.

For Time 1, 385 participants (median age 75 years, interquartile range [IQR] 70–81 years) were included in the final analysis, as reported previously [14]. Of these, 144 were men (median age 75 years, IQR 69–79 years), and 241 were women (median age 75 years, IQR 71–81 years). All participants registered at Time 1 were recruited for Time 2, and 77 participants (20%) agreed to participate in the Time 2 survey. One participant with no logical memory test data was excluded from the final analysis. For Time 2, 76 participants (median age 80 years, IQR 76–83 years) were included in the final analysis. Of these, 20 were men

(median age 80 years, IQR 77.8–81.2 years), and 56 were women (median age 79.5, IQR 75–84 years). At Time 1, the median (IQR) age was 73 (69–76) years for all 76 participants, 72.5 (70.8–75) years for men, and 73 (69–77) years for women.

Written informed consent was obtained from all participants unless their cognitive function was insufficient to provide consent; in such cases, consent was obtained from their family. This study was carried out in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Faculty of Medicine of Saga University.

2.2. Measurements of cognitive function

At Time 1, participants underwent screening examinations for a prevalence survey of dementia [22]. At Time 2, participants underwent the same psychological tests as those administered at Time 1. These screening examinations comprised the Mini-Mental State Examination (MMSE) for cognitive screening [23], the Clinical Dementia Rating for global function assessment [24], and "logical memory A″ from the Wechsler Memory Scale-Revised (WMSR) for memory assessment [25]. We evaluated logical memory using the WMSR Logical Memory II delayed recall test (LM II-DR) for mild cognitive impairment because LM II-DR scores have been shown to be significantly associated with atrophy of the hippocampus [26]. LM II-DR Part A is a delayed recall test in which a short story is read orally by the examiner, recalled by the subject immediately and 30 min later, and scored at 30 min. LM II-DR Part A is scored on a 25-point scale, one point per word.

2.3. Serum OT assay

At both Time 1 and Time 2, the collected blood samples were initially stored in vacuum-sealed blood collection tubes (Insepack II-D, Sekisui Medical Co., Ltd.) made from polyethylene terephthalate. The samples were taken during the day between 10:00 and 16:40, immediately chilled on ice and shipped to SRL (Fukuoka, Japan), where the serum was transferred to plastic tubes. The serum samples were stored at −80 °C in the freezer of our laboratory until the day of assay. The time from sampling to −80 °C storage was approximately 3–8 h. All samples were analyzed twice. Serum OT was assayed using a commercially available peptide enzyme immunoassay (EIA) kit (S-1355.0001; Peninsula Laboratories International, San Carlos, California) following the non-extraction protocol. The manufacturer claims the average half-maximal inhibitory capacity is 0.15 ng/mL. The intra- and inter-assay coefficients of variability (CV) were 13.0% and 9.8%, respectively. The inter-assay was determined using the following procedure. We ran the same high and low OT controls in duplicate on five different plates to monitor plate-to-plate variation. The plate means for high and low were calculated and then used to calculate the overall mean, standard deviation (SD), and % CV. Overall % CV = SD of plate means ÷ mean of plate means × 100. The average of the high and low % CV was reported as the inter-assay CV. The threshold for OT detection was <0.01 ng/mL.

Serum OT was assayed via EIA without an extraction step in this study. The debate on sample extraction before oxytocin assay and without extraction is important. Extraction is a process of removing potentially interfering molecules, reducing the influence of the sample matrix, and concentrating the analyte prior to analysis [[27,28]]. Some comprehensive reviews reported the issue of inconsistency in human oxytocin measurement, various debates, and proposed solutions [[29, 30]]. Previous studies have shown that without extraction, oxytocin measurements are 10–100 times higher than in extracted samples, and samples with and without extraction are unrelated [[27,31–34]]. Tabak et al. [30] pointed out that the non-extraction process has the following three problems. First, it is difficult to measure all forms of "bound" oxytocin with a single immunoassay. Second, high molecular weight plasma components with oxytocin immunoreactivity have not been conclusively identified by other biophysical techniques. And finally, it is currently unknown whether there are plasma proteins that interact

non-specifically with oxytocin antibodies that might contribute to total oxytocin immunoreactivity in unextracted samples. Therefore, Tabak et al. suggested that free oxytocin concentrations have been correlated to bioactivity assays [35] and thus reflect bioactive oxytocin levels [30].

Single measurements of baseline levels of endogenous oxytocin in plasma were not stable in typical laboratory conditions [36], therefore, it would be best practice to record multiple measures across a short time period to create an average for baseline samples [30]. However, this study had a single measurement of baseline levels as previously we reported [[14,15,21]].

2.4. Statistical analysis

Data were analyzed using PASW Statistics 18 software (SPSS, Chicago, IL, USA). A Shapiro-Wilk test was used to test the normality of the data. As the values for logical memory and OT were not normally distributed, the median value was used. Wilcoxon rank-sum tests were used to compare serum OT levels, MMSE scores, and LM II-DR scores between Times 1 and 2. Multivariate analysis was used to examine the relationship between LM II-DR score at Time 2 and OT level at Time 1, both for all participants and by sex. Age and years of education were included as independent variables because they were correlated with the LM II-DR score. The normal distribution of residuals in the multivariable regression analysis was confirmed using the Shapiro-Wilk test. The level of statistical significance was set at $p < 0.05$.

3. Results

The social and clinical characteristics of participants at Time 1 are presented in Table 1. Participants' serum OT levels and psychological test scores at Times 1 and 2 are presented in Table 2. LM II-DR scores at Time 2 were significantly lower than those at Time 1 ($p < 0.001$). The median OT level in women was significantly lower at Time 2 than at Time 1 ($p = 0.004$). Table 3 shows the multivariate analysis results for all participants, with LM II-DR scores at Time 2 as the dependent variable. OT level, age, and years of education at Time 1 were entered as independent variables. LM II-DR score at Time 2 was positively associated with years of education ($p = 0.048$). Table 4 shows the multivariate analysis results for women. LM II-DR score at Time 2 was the dependent variable, and OT, age, and years of education at Time 1 were entered as independent variables. LM II-DR score at Time 2 was positively associated with OT level at Time 1 ($p = 0.042$) and negatively associated with age ($p = 0.02$). Fig. 1 shows scatterplots illustrating the association between serum OT levels at Time 1 and LM II-DR part A scores at Time 2

Table 1
Participants' social and clinical characteristics (Time 1).

Clinical characteristics	Overall	Men	Women
N	76	20	56
Age, years (median, IQR[†])	73 (69–76)	72.5 (70.8–75)	73 (69–77)
Education, years (median, IQR)	9 (9–12)	10.5 (9–12)	9 (9–10.25)
BMI[‡], kg/m^2 (median, IQR)	24.0 (21.3–26.0)	24.6 (21.7–26.3)	23.7 (21.3–25.8)
Living with family, n (%)	70 (92.1)	20 (100)	50 (89.3)
Loss of spouse, n (%)	12 (15.8)	0 (0)	12 (21.4)
Current smoking, n (%)	1 (1.3)	1 (5)	0
Alcohol consumed daily, n (%)	9 (11.8)	9 (45)	0
Diabetes mellitus, n (%)	14 (18.7) (1 subject data missing)	3 (15)	11 (20) (1 subject data missing)
Hypertension, n (%)	42 (56) (1 subject data missing)	8 (40)	34 (61.8) (1 subject data missing)

Abbreviations: [†]IQR, interquartile range; [‡]BMI, body mass index.

Table 2
Participants' serum oxytocin levels and psychological test scores.

		Time 1	Time 2	P
Oxytocin, pg/mL (median, IQR[†])	Overall (n = 76)	80 (28–371)	63 (30–145)	.015*
	Men (n = 20)	34 (16–78)	53 (28–140)	.654
	Women (n = 56)	117 (35–412)	76 (32–145)	.004*
MMSE[‡] (median, IQR)	Overall (n = 76)	29 (28–30)	28 (25–29)	<.001*
	Men (n = 20)	28 (27–30)	27 (25–28.75)	<.001*
	Women (n = 56)	29 (28–29.75)	28 (25–29)	<.001*
LM II-DR[§] (part A) (median, IQR)	Overall (n = 76)	10 (7–12)	4 (2–8)	<.001*
	Men (n = 20)	10.5 (8.5–11.3)	3 (0–6)	<.001*
	Women (n = 56)	9.5 (7–12.25)	5 (2.75–8.25)	<.001*
CDR				
0, n (%)	Overall	73 (96.1)	68 (89.5)	
	Men	19 (95)	18 (90)	
	Women	54 (96.4)	50 (89.2)	
0.5, n (%)	Overall	3 (3.9)	8 (10.5)	
	Men	1 (5)	2 (10)	
	Women	2 (3.6)	6 (11.5)	
1, n (%)		0	0	
2, n (%)		0	0	
3, n (%)		0	0	

Abbreviations: [†]IQR, interquartile range; [‡]MMSE, Mini-mental State Examination; [§]LM II-DR, Wechsler Logical Memory II-delayed recall part A; [¶]CDR, Clinical Dementia Rating.
*Significance ($p < 0.05$).

Table 3
Multivariate analysis for all participants with Time 2 LM II-DR[†] score as the dependent variable.

	B	SE[‡]	β	P
Oxytocin	.539	.837	.072	.522
Age	−.214	.113	−.213	.063
Education	.525	.261	.226	.048*
R^2	.118			

All independent variables were for Time 1.
Abbreviations: [†]LM II-DR, Wechsler Logical Memory II-delayed recall part A; [‡]SE, Standard error.
*Significance ($p < 0.05$).

Table 4
Multiple linear regression analysis for women with Time 2 LM II-DR[†] score as the dependent variable.

	B	SE[‡]	β	P
Oxytocin	2.241	1.076	.255	.042*
Age	−.287	.120	−.303	.02*
Education	.469	.356	.167	.194
R^2	.234			

All independent variables were for Time 1.
Abbreviations: [†]LM II-DR, Wechsler Logical Memory II-delayed recall part A; [‡]SE, standard error.
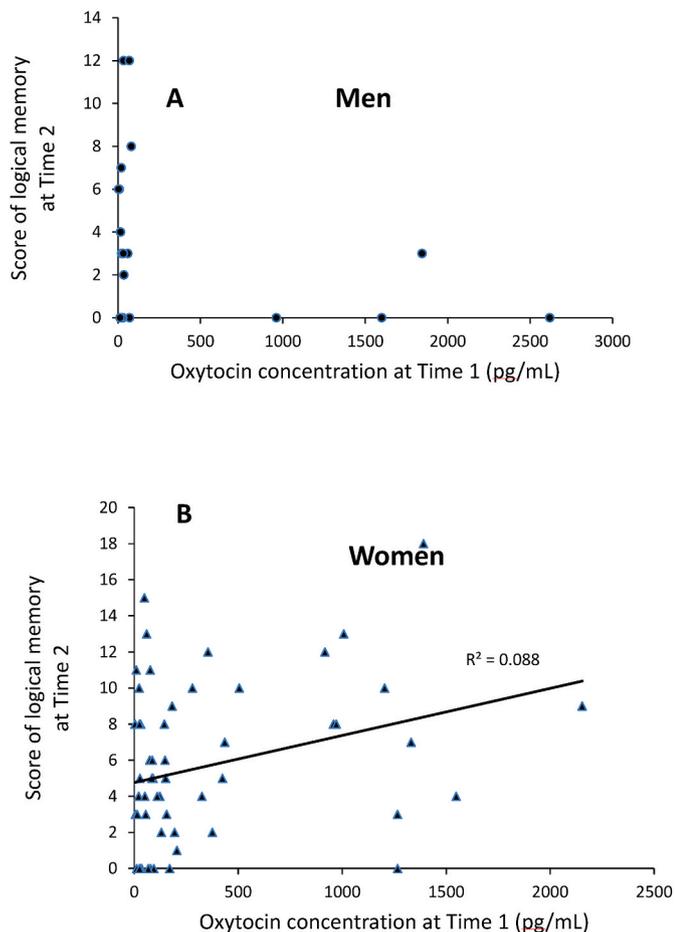*Significance ($p < 0.05$).

Fig. 1. Scatterplots illustrating the association between serum oxytocin levels at Time 1 and Wechsler Memory Scale-Revised Logical Memory delayed recall part A scores at Time 2 in men **(A)**, and in women **(B)**. The regression line for each relationship is shown.

in men **(A)** and in women **(B)**.

4. Discussion

4.1. Principal findings

In this study, we hypothesized that a high baseline OT level would be associated with high logical memory performance 7 years later. Furthermore, we hypothesized that there would be a sex difference in this relationship. Our findings were consistent with our hypothesis, with baseline OT level positively correlated with logical memory 7 years later in older women living in rural areas. We previously reported a positive correlation between baseline serum OT level and left hippocampal and amygdala volume 7 years later in 58 older adults (14 men, mean age 72.36 ± 63.41 years) living in rural Japan [15]. Although that study did not analyze this relationship by sex, 75.9% of those subjects were women.

4.2. OT and hippocampus and amygdala and memory

OT is involved in emotion-mediated memory processes through the hippocampus and amygdala. OT is also involved in hippocampal function via OTR, genes, neurogenesis, and synaptic plasticity. OTRs are abundantly expressed in the hippocampus [10], as well as widely expressed in peripheral tissues [37]. Furthermore, genes related to OT are highly expressed in subcortical and temporal brain structures, including the hippocampus and amygdala [38]. OT contributes to

neurogenesis and synaptic plasticity in the hippocampus. For example, OT has been shown to stimulate hippocampal neurogenesis [39], and conditional deletion of hippocampal CA2/CA3a OTRs impaired the persistence of long-term social recognition memory in adult mice [40]. Moreover, the effects of stress on hippocampal synaptic plasticity and memory were reduced by intranasal administration of OT in male rats [41].

OT is also involved in amygdala function, and intranasal administration of OT altered amygdala activity in response to social and emotional contexts. Specifically, OT-induced increases in amygdala activity were only found in negative social-affective processes, whereas the main contributor to OT-induced decreases in amygdala activity in humans were contrasts on negative-valenced processes [42]. We speculated that OT was involved in emotion-mediated memory processes through the hippocampus and amygdala, because the hippocampus and amygdala are involved in memory processes via emotions [43].

4.3. OT and sex differences

Our study showed that baseline OT level was positively correlated with logical memory 7 years later only in older women. Numerous studies have reported sex differences in memory and hippocampal function. For example, a meta-analysis showed that women had an overall advantage over men in episodic memory, especially verbal tasks. This advantage was also present in older adults, but less so than in adolescents and middle-aged people [44]. In cognitively normal older women (but not men), bilateral hippocampus volume was positively correlated with associative memory performance [45]. Moreover, greater relative cerebral blood flow in the left temporal pole was associated with better performance on the WMSR immediate and delayed recall tests exclusively in women [46]. Various brain regions that are responsible for cognitive processes, such as the hippocampus, amygdala, and neocortex, are sexually dimorphic [47]. However, reports on sex differences in plasma OT levels are inconsistent. These discrepancies may be because of differences in the commercially available methods for quantifying plasma OT concentrations used between studies [48]. Another meta-analysis reported that OT concentrations were higher in women than in men and that they increased with age [49]. Furthermore, a meta-analysis of functional magnetic resonance imaging studies of intranasal OT administration reported sex differences in amygdala activity [50].

4.4. Peripheral and central OT

There is much debate about the relationship between peripheral and central OT levels. A meta-analysis reported a positive correlation between central and peripheral concentrations of OT; however, this association was moderated by the experimental context. For example, although there was no association under basic conditions, significant associations were observed following intranasal OT administration and exposure to stressors [51].

5. Limitations

The study had three limitations: the non-extraction protocol in the OT assay; the small number of participants; and the low rate of continued participation.

First, a non-extraction protocol was used to analyze serum OT using a commercial peptide EIA kit. There is the large controversy in analysing OT via EIA without an extraction step. Previous studies have shown that without extraction, oxytocin measurements are 10–100 times higher than in extracted samples, and samples with and without extraction are unrelated [[27,31–34]]. Tabak et al. [30] pointed out that the non-extraction process has the following three problems. First, it is difficult to measure all forms of "bound" oxytocin with a single immunoassay. Second, high molecular weight plasma components with

oxytocin immunoreactivity have not been conclusively identified by other biophysical techniques. And finally, it is currently unknown whether there are plasma proteins that interact non-specifically with oxytocin antibodies that might contribute to total oxytocin immunoreactivity in unextracted samples. Therefore, Tabak et al. suggested that free oxytocin concentrations have been correlated to bioactivity assays [35] and thus reflect bioactive oxytocin levels [30].

Second, the number of participants in this study was small. Therefore, it was difficult to find significant differences in the statistical analyses, especially men.

Third, the rate of continued participation was as low as 20%. Therefore, there could have been some bias in the Time 2 participants.

6. Conclusions

The present study found that baseline OT level was positively correlated with logical memory 7 years later in older women living in rural Japan. This result suggests that maintaining high OT levels in older women may help prevent age-related decline in the logical memory.

Authors' contributions

Yutaka Kunitake: Writing (original draft), investigation, and formal analysis. **Yoshito Mizoguchi:** Supervision. **Yoshiomi Imamura:** Investigation, validation, and formal analysis. **Hiroko Kunitake:** Investigation and validation. **Ryuzo Orihashi:** Investigation. **Jun Matsushima:** Investigation. **Hiroshi Tateishi:** Investigation. **Toru Murakawa-Hirachi:** Investigation. **Shigeto Yamada:** Funding acquisition. **Akira Monji:** Conceptualization and supervision.

Data availability statement

The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Funding statement

Ethics approval statement

The study was approved by the Ethical Committee of the Faculty of Medicine of Saga University.

Patient consent statement

Written informed consent was obtained from all participants unless their cognitive function was insufficient to provide consent, in which case consent was obtained from their family.

Permission to reproduce material from other sources

We did not use any materials from other sources in this research.

Clinical trial registration

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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