



## Lithium in drinking water may be negatively associated with depressive temperament in the nonclinical population

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### ABSTRACT

**Purpose:** Recently, we reported that lithium levels in drinking water were significantly and positively associated with hyperthymic temperament scores, whereas latitude was significantly and negatively associated with the scores, suggesting that lithium in drinking water may positively maintain hyperthymic temperament and that latitude may negatively maintain it. In the present study, from the viewpoint of psychopharmacology, we investigated the other 4 affective temperaments in reference to lithium in drinking water with adjustment for latitude, temperature, and sunshine. **Methods:** We re-examined our previous dataset consisting of temperament data of 609 residents in Sapporo, Obihiro, Takaoka, Koshigaya, and Oita cities, in addition to the lithium levels in drinking water and climatic data of the five cities. Multiple regression analyses via the forced entry method were performed, whereby the individual temperament scores were dependent factors, and age, gender, the other four affective temperaments, lithium in drinking water, latitude, temperature, and sunshine were independent factors. **Results:** The multiple regression analysis revealed that lithium levels in drinking water were significantly and negatively associated with depressive temperament scores. The other three temperaments (i.e. irritable, cyclothymic and anxious temperaments) were not significantly associated with lithium levels in drinking water. **Discussion:** In conclusion, the present findings suggest that lithium in drinking water may be negatively associated with depressive temperament.

**Keywords:** *Lithium, Latitude, Temperature, Sunshine, Depressive temperament*

Received August 21, 2017 / Accepted August 30, 2017 / Published December 6, 2017.

### INTRODUCTION

In a series of our studies showing the effects of latitude on hyperthymic temperament, Kohno et al. [1] reported that latitude has a significant effect on hyperthymic temperament among residents living in two regions (Oita and Sapporo), and that lower and

higher latitudes are associated with higher and lower hyperthymic temperament scores, respectively. This “latitude effect” on hyperthymic temperament was confirmed by our subsequent extension study of three regions (Oita, Sapporo and Koshigaya) with different latitudes that indicated a dose-response relationship between hyperthymic

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temperament scores, sunshine and latitude [2]. These findings suggest that sunshine mediates the positive effect of latitude on hyperthymic temperament. Moreover, considering that temperature might mediate the effect of latitude on hyperthymic temperament, we investigated the association of hyperthymic temperament in residents in Sapporo, Obihiro, Takaoka, Koshigaya, and Oita cities (located at latitudes of 43° N, 42° N, 36° N, 36° N and 33° N ) in relation to sunshine, temperature, and latitude data [3]. Our findings showed that latitude predicted significant variance in hyperthymic temperament, and that ambient temperature, but not sunshine, significantly affected hyperthymic temperament scores [3].

On the other hand, several epidemiological studies have shown the inverse association between lithium levels drinking water and suicide rates [4-8], although a few studies failed to find this association [9] or reported an ambiguous association [10]. If lithium has an anti-suicidal effect, impulsivity and aggression may be decreased by lithium and thereby suicidality may be reduced [11-13]. Both impulsivity and aggression and hyperthymic temperament share a high energy level, although impulsivity and aggression appear suddenly, whereas hyperthymic temperament is a more enduring aspect of an individual. Therefore, it could be hypothesized that even very low levels of lithium may suppress not only impulsivity and aggression, but also hyperthymic temperament. In addition to the data previously reported [3], we measured lithium levels in the water of the five cities (Sapporo, Obihiro, Takaoka, Koshigaya, and Oita cities) and the effect of temperature, sunshine, and lithium levels on hyperthymic temperament was analyzed. As a result, we found that lithium levels in drinking water were significantly and positively associated with hyperthymic temperament scores whereas latitude was significantly and negatively associated with the scores, suggesting that lithium in drinking water may positively maintain hyperthymic temperament, and that latitude may negatively maintain it [14].

In the study [14], however, we did not investigate the associations between the other four temperaments (i.e. depressive, cyclothymic, irritable and anxious temperaments) and lithium levels in drinking water, latitude, temperature, and sunshine. In the present study, from the viewpoint of psychopharmacology, the association between lithium levels in drinking water and the four temperaments

were examined.

## SUBJECTS AND METHODS

### *Subjects*

We re-examined the previous dataset consisting of the temperament data of 609 residents in Sapporo, Obihiro, Takaoka, Koshigaya, and Oita cities, as well as lithium levels in the drinking water and climatic data of the five cities [14]. The participants' mean age was 33.4 years  $\pm$  9.1 (SD). There were 270 males and 339 females. All participants were screened for present and past psychiatric disorders. None demonstrated psychiatric history or disorder. Written informed consent was obtained from all participants, and the 3 universities and 2 hospital ethical committees approved the studies.

### *Temperament assessment*

The participants completed the Japanese version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-auto questionnaire (TEMPS-A). This 110-item true-false questionnaire measures the following temperament dimensions: depressive, cyclothymic, hyperthymic, irritable and anxious [15, 16]. TEMPS-A was translated into Japanese, and the reliability and validity of the Japanese version have been established [16-18].

### *Sunshine and temperature*

The mean annual total sunshine hours were denoted "sunshine" for Sapporo, Obihiro, Koshigaya, Takaoka, and Oita. The mean annual ambient temperatures (°C) of the 5 regions from 1993 to 2012 were denoted "temperature".

### *Lithium levels in drinking water*

Tap water samples (chiefly from the main rail station, the city office, or water purification plant) of each city were taken and their lithium levels were measured by using mass spectroscopy analyzed by a third party. This method can measure very small amounts of lithium; the minimal amount of lithium that can be measured is 0.1 ppb (0.1  $\mu$ g/l). If lithium levels of drinking water were measured at multiple points in the same city, the mean value was calculated. We previously confirmed only a very small fluctuation in levels over time because the correlation coefficient between the lithium levels and those re-measured after 1 year in the same places was 0.998 [5].

**Table 1.** Participant demographics, TEMPS-A scores, latitude, sunshine, temperature, and lithium levels of drinking water in 5 cities: Sapporo, Obihiro, Koshigaya, Takaoka, and Oita.

Variables	Sapporo	Obihiro	Koshigaya	Takaoka	Oita
N	94	106	125	189	95
Age	29.4±4.9	32.6±7.4	36.6±9.4	37.1±9.9	26.8±5.8
Gender (M/F)	66/28	48/58	42/83	47/142	67/28
TEMPS-A scores					
Depressive	5.8±3.4	7.3±3.2	7.3±3.1	7.9±3.8	6.8±3.2
Cyclothymic	3.3±3.8	3.9±3.6	3.8±3.1	5.0±3.9	4.4±3.5
Hyperthymic	3.8±3.2	3.5±2.8	3.8±2.9	4.3±3.5	5.0±3.9
Irritable	2.7±3.7	2.7±2.9	2.3±2.4	3.1±3.3	3.0±3.0
Anxious	3.9±4.2	4.7±4.4	4.8±3.8	5.2±4.6	4.5±3.7
Latitude	43°N	42°N	36°N	36°N	33°N
Sunshine (h)	1684.6±98.4	2008.4±104.5	1862.9±189.9	1631.3±121.3	2002.9±127.9
Temperature (°C)	9.1±0.4	7.0±0.5	15.3±0.5	14.1±0.5	16.7±0.5
Lithium (µg/L)	29.0±17.3	0.1±0.1	2.6	1.5	43.0±5.0

Mean±SD

### Data analysis

Multiple regression analyses via the forced entry procedure were performed whereby individual temperament (i.e. depressive, cyclothymic, irritable and anxious temperaments) scores were dependent factors and age, gender, the other four affective temperaments, lithium in drinking water, latitude, temperature, and sunshine were independent factors. Multicollinearity was checked using the Variance Inflation Factor (VIF), and if the VIF was more than 10, the relevant independent factor was deleted.

## RESULTS

Table 1 shows demographics of 609 participant, the mean and SD of their TEMPS-A scores, latitude, sunshine, temperature, and lithium levels of drinking water in their residential cities. Oita and Sapporo cities had relatively larger amounts of lithium in the drinking water than Obihiro, Takaoka, and Koshigaya cities.

A multiple regression analysis showed that depressive temperament scores were not significantly associated with lithium levels in drinking water ( $\beta=-0.066$ ,  $p=0.124$ ), sunshine, temperature, or latitude. However, multicollinearity occurred between temperature (VIF=18.039) and latitude (VIF=17.265). When only latitude was deleted, multicollinearity disappeared and depressive temperament scores was significantly and negatively associated with lithium levels in drinking water ( $\beta=-0.088$ ,  $p=0.031$ ). Also when only temperature was deleted,

multicollinearity disappeared and depressive temperament scores were significantly and negatively associated with lithium levels in drinking water ( $\beta=-0.085$ ,  $p=0.033$ ) and latitude as shown in Table 2.

Another multiple regression analysis showed that irritable temperament scores were significantly and positively associated with lithium levels in drinking water ( $\beta=0.080$ ,  $p=0.037$ ), but not with sunshine, temperature, or latitude. However, multicollinearity occurred between temperature (VIF=17.346) and latitude (VIF=18.059). When only latitude was deleted, multicollinearity disappeared and irritable temperament scores were significantly and positively associated with lithium levels in drinking water ( $\beta=0.075$ ,  $p=0.040$ ). Also when only temperature was deleted, multicollinearity disappeared but irritable temperament scores were not significantly and positively associated with lithium levels in drinking water ( $\beta=0.067$ ,  $p=0.059$ ). Therefore, the association of lithium with irritable temperament was not reliable.

Other multiple regression analyses and the subsequent deletion of a factor of which the VIF was more than 10 showed that cyclothymic temperament scores were significantly and negatively associated with latitude, but not with lithium levels in drinking water or sunshine, and that anxious temperament scores were not associated with lithium levels in drinking water, sunshine, temperature or latitude.

**Table 2.**

Independent variable	Beta	p	VIF
Age	0.075	0.046	1.301
Gender (F=1, M=2)	-0.021	0.552	1.189
Cyclothymic temperament	0.184	<0.0001	2.044
Hyperthymic temperament	-0.158	<0.0001	1.154
Irritable temperament	0.104	0.023	1.927
Anxious temperament	0.365	<0.0001	1.744
Sunshine	0.020	0.561	1.107
Latitude	-0.077	0.026	1.103
Lithium	-0.085	0.033	1.469
ANOVA	F=32.9	<0.0001	
R <sup>2</sup> (adjusted R <sup>2</sup> )	0.355 (0.344)		

Depressive temperament scores were significantly and negatively associated with lithium levels in drinking water and latitude.

## DISCUSSION

The present findings show that lithium levels in drinking water were significantly and negatively associated with depressive temperament scores robustly whereas lithium levels were not significantly and positively associated with irritable temperament scores after the deletion of temperature from the multiple regression analysis. Therefore, we identified only depressive temperament as a temperament significantly associated with lithium. With regard to the negative association between depressive temperament and lithium, similar to the positive association between hyperthymic temperament scores and lithium levels in drinking water [14] despite very small doses, the antidepressant effect of lithium [19, 20] may be involved in attenuating depressive temperament (i.e. alleviation of depressive temperament by even very low levels of lithium).

The “Latitude effect” [3] has been also demonstrated to be significantly and negatively associated with depressive and cyclothymic temperament scores, which is similar to the negative association between latitude and hyperthymic temperament [14]. Further studies are also required to determine which factors (e.g., food, culture, economy, and so on) associated with specific latitudes, also affect depressive, cyclothymic, and hyperthymic temperaments.

One of the limitations of this study is that the light, temperature and lithium exposure that residents actually received was not measured. Another limitation is the small number of regions studied. Moreover, it is unknown why cyclothymic and anxious

temperaments were not associated with lithium levels in drinking water. Additionally, residents’ history of house-moving and daily intake of tap water were not investigated. Moreover, their demographic data such as employment status, food and economic factors could not be investigated to be adjusted for the analysis. Finally, the findings might not be generalized to residents across Japan or other countries.

In conclusion, the present findings suggest that lithium in drinking water may be negatively associated with depressive temperament.

## CONFLICTS OF INTEREST

All authors declare no competing interests.

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