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Shibata M, Ninomiya T, Jensen MP, Anno K, Yonemoto K, Makino S, Iwaki R, Yamashiro K, Yoshida T, Imada Y, Kubo C, Kiyohara Y, Sudo N, Hosoi M	Alexithymia is associated with greater risk of chronic pain and negative affect and with lower life satisfaction in a general population: the Hisayama Study	PLoS One	9	e90984	2014
Mitsui N, Asakura S, Shimizu Y, Fujii Y, Kako Y, Tanaka T, Oba K, Inoue T, Kusumi I	Temperament and character profiles of Japanese university students with depressive episodes and ideas of suicide or self-harm: a PHQ-9 screening study	Compr Psychiatry	54	1215-1221	2013

Naka T, Ide S, Nakako T, Hirata M, Majima Y, Deyama S, Takeda H, Yoshioka M, Minami M	Activation of β-adrenoceptors in the bed nucleus of the stria terminalis induces food intake reduction and anxiety-like behaviors.	Neuropharmacology	67	326-330	2013
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Tha KK, Terae S, Nakagawa S, Inoue T, Kitagawa N, Kako Y, Nakato Y, Popy KA, N, Zaitsu Y, Yoshida D, Ito YM, Miyamoto T, Koyama T, Shirato H	Impaired integrity of the brain parenchyma in non-geriatric patients with major depressive disorder revealed by diffusion tensor imaging.	Psychiatry Res	212(3)	208-215	2013
Takamura N, Masuda T, Inoue T, Nakagawa S, Koyama T	The effects of the co-administration of the α1-adrenoreceptor antagonist prazosin on the anxiolytic effect of citalopram in conditioned fear stress in the rat.	Prog Neuropsychopharmacol Biol Psychiatry	39(1)	107-111	2012
Inoue T, Tanaka T, Nakagawa S, Nakato Y, Kameyama R, Boku S, Toda H, Kurita T, Koyama T	Utility and limitations of PHQ-9 in a clinic specializing in psychiatric care.	BMC Psychiatry	12(1)	73	2012

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Research report

The influence of childhood abuse, adult stressful life events and temperaments on depressive symptoms in the nonclinical general adult population

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ABSTRACT

Background: Previous studies have shown the interaction between heredity and childhood stress or life events on the pathogenesis of major depression. We hypothesized that childhood abuse, affective temperaments, and adult stressful life events interact and influence depressive symptoms in the general adult population and tested this hypothesis in this study.
Methods: The 294 participants from the nonclinical general adult population were studied using the following self-administered questionnaire surveys: the Patient Health Questionnaire-9 (PHQ-9), Life Experiences Survey (LES), Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego auto-questionnaire (TEMPS-A), and Child Abuse and Trauma Scale (CATS). The data were analyzed with single and multiple regressions and structural equation modeling (Amos 20.0).
Results: Childhood abuse indirectly predicted the severity of the depressive symptoms through affective temperaments measured by TEMPS-A in the structural equation modeling. Four temperaments – depressive, cyclothymic, irritable, and anxious – directly predicted the severity of depressive symptoms and the negative appraisal of life events during the past year. The negative appraisal of life events during the past year mildly, but significantly, predicted the severity of depressive symptoms.
Limitations: The subjects of this study were nonclinical. The findings might not be generalized to patients with mood disorders.
Conclusions: This study suggests that childhood abuse, especially neglect, indirectly increased depressive symptoms through increased affective temperaments, which, in turn, increase the negative appraisal of stressful life events. An important role of affective temperaments in the effect of childhood abuse and stressful life events on depressive symptoms was suggested.

1. Introduction

Various factors, such as genetic factors, environmental factors, and personality traits, predispose individuals to depressive symptoms or the development of a major depressive disorder (Caspi et al., 2010; Mitsui et al., 2013). The heritability of major depressive disorders is low (37%) compared with schizophrenia (81%) and bipolar disorder (85%) (Bienvenu et al., 2011). Other environmental factors and personality traits likely contribute to the development of major depressive disorder. Adult stressful life events and child abuse are major environmental factors for major depressive disorder (Kendler et al., 1999; Kessler and Magee, 1993; Weich et al., 2009; Wise et al., 2001), and these two factors interact with genetic factors in Gene-by-Environment (G × E) interactions (Caspi et al., 2010, 2003). An epidemiological study showed that *s*-carriers in a repeat length polymorphism in the promoter region of the human serotonin transporter gene (5-*HTTLPR*) exhibited elevated depressive symptoms, diagnosable depression, and suicidality after experiencing adult stressful life events and childhood mistreatment (Caspi et al., 2003). To the best of our knowledge, no

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study has reported an interaction of adult stressful life events and childhood mistreatment with depressive symptoms or a major depressive disorder.

Personality traits, another predisposition factor for depressive symptoms or major depressive disorders, are known to be a risk factor for major depression (Kendler et al., 2004, 1993). Adult stressful life events interact with neuroticism and sex in the etiology of major depression, and the risk of neuroticism affecting illness is greater at high than at low levels of adult stressful life events (Kendler et al., 2004). Because neuroticism is related to the 5-*HTTLPR* polymorphism and *s*-carriers have high levels of neuroticism (Greenberg et al., 2000; Lesch et al., 1996), the interaction between neuroticism and adult stressful life events might be partly explained by the 5-*HTTLPR* G × E interaction (Caspi et al., 2003). Other personality traits shown on tests such as the Temperament and Character Inventory (TCI) and the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego auto-questionnaire version (TEMPS-A) are related to neuroticism and the 5-*HTTLPR* polymorphism (Gonda et al., 2009). The items on the TEMPS-A, formulated on the basis of the diagnostic criteria for affective temperaments, are divided into five groups as follows: the cyclothymic, depressive, irritable and hyperthymic groups based on the subscales representing the Kraepelinian temperaments, and the anxious group, based on the subscale developed secondarily by Akiskal and coworkers (Akiskal et al., 2005; Akiyama et al., 2003). The subscales of the TEMPS-A provided unique profiles of major depressive disorder and bipolar disorder (Matsumoto et al., 2005; Mendlowicz et al., 2005a) and are very useful for clinical practice, especially for bipolar spectrum diagnosis. An interaction of personality traits (temperaments) measured by the TEMPS-A with childhood abuse and adult stressful life events in influencing depressive symptoms has not been reported, however, identifying such an interaction is important for psychological and psychiatric evaluation of the general and clinical population.

We hypothesized that childhood abuse, adult stressful life events (stressful events within the last year) and affective temperaments interact with one another and influence depressive symptoms or the development of major depressive disorder (Fig. 1). Temperaments identified on the TEMPS-A are the putative 'fundamental states' that Kraepelin considered to be enduring subclinical states without or before the florid symptoms of manic-depressive illness (Kraepelin, 1913). For this reason, the factor 'temperaments' was located between two factors, childhood abuse and adult stressful life events, in this schema shown in Fig. 1. In this study, the effect and interaction of these three factors on depressive symptoms in the general adult population was examined, and we plan a further study that will examine these interactions in clinical subjects with mood disorder. The covariance structure analysis was used to analyze this sophisticated interaction model.

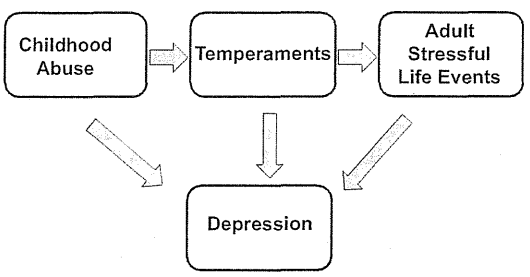

Fig. 1. Structural equation model of the hypothesis of this study. In this model, depressive symptoms are predicted by childhood abuse, temperament and stressful life events in adulthood.

2. Subjects and methods

2.1. Subjects

This research was conducted during July 2011 and December 2011 on 500 Japanese volunteers from the general adult population, who had no history of psychiatric disease. Of 500 volunteers, 294 subjects (58.8%) provided a complete response to the questionnaires. Five questionnaires, which are shown below (Section 2.2), and a questionnaire on demographic data (gender, age, education, marital status, family members, employment status, past history of physical and psychiatric diseases, and family history) were distributed. The completed questionnaires were returned anonymously to the research group by mail for complete confidentiality. Of the 294 subjects, 170 subjects (103 male, 67 female), who did not fulfill the criteria of the Mini-International Neuropsychiatric Interview screen (M.I.N.I screen) or did not fulfill the criteria of major or other depressive episode as screened by the Patient Health Questionnaire-9 (PHQ-9), were classified as 'healthy controls'. Written informed consent was obtained from all of the subjects. This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Hokkaido University Hospital.

2.2. Questionnaires

2.2.1. Patient health questionnaire-9 (PHQ-9)

The Japanese version of the PHQ-9 was self-completed by the patient in written form (Muramatsu et al., 2007). Major depressive episodes were diagnosed in two ways using the PHQ-9: diagnostic algorithm and a summary score. This study employed the diagnostic algorithmic threshold for diagnosing a major depressive episode that was regarded as fulfilled if the answer to question #1a or question #1b and five or more questions from #1a to #1i was at least "more than half the days" (question #1i was counted if present at all) (Spitzer et al., 1999). The diagnostic algorithmic threshold for diagnosing other depressive episodes was regarded as fulfilled if the answer to question #1a or question #1b and two, three or four of the questions from #1a–#1i was at least "more than half the days" (question #1i was counted if present at all). This study employed a summary score for assessing the severity of depressive symptoms.

2.2.2. Life experiences survey (LES)

The LES is a 57-item self-report measure that allows respondents to indicate events that they have experienced during the past year (Sarason et al., 1978). The format of the LES calls for subjects to rate separately the desirability and effect of the events that they have experienced. They are asked to indicate those events experienced during the past year (0–6 months or 7 months–1 year) as well as (a) whether they viewed the event as being positive or negative and (b) the perceived impact of the particular event on their life at the time of occurrence. Ratings are on a 7-point scale ranging from extremely negative (−3) to extremely positive (+3). Summing the impact ratings of those events designated as positive by the subject provides a *positive change score*. A *negative change score* is derived by summing the impact ratings of those events experienced as negative by the subject.

In this study, the LES was translated from English to Japanese, and Dr. J. H. Johnson, one of the developers of the LES, confirmed the accuracy of this Japanese translation of the LES through back translation. Our previous study confirmed the validity and reliability of the Japanese version of the LES (Nakai et al., 2012) as follows: the negative change score was significantly and positively correlated with depressive symptoms measured by the PHQ-9

scores (Pearson $r=0.21$), state anxiety measured by the State-Trait Anxiety Inventory X (STAI-X) (Pearson $r=0.22$) and trait anxiety measured by the STAI-X (Pearson $r=0.28$). The positive change score was not correlated with depressive symptoms, state anxiety or trait anxiety. These results were consistent with the results of the English version of the LES (Sarason et al., 1978). The test–retest reliability of the LES was confirmed with a moderate intraclass correlation coefficient (ICC) of 0.47 for the positive change score and 0.45 for the negative change score when administered twice within an 8-week period.

2.2.3. *Temperament evaluation of the Memphis, Pisa, Paris, and San Diego auto-questionnaire (TEMPS-A)*

The TEMPS-A is a self-rating questionnaire consisting of 109 items for men and 110 for women (Akiskal et al., 2005). The subjects completed the Japanese standardized version of the TEMPS-A, which is a true (=2) – false (=1) questionnaire measuring the following temperament dimensions: depressive, cyclothymic, hyperthymic, irritable and anxious (Matsumoto et al., 2005).

2.2.4. *Child abuse and trauma scale (CATS)*

The CATS is a 38-item scale. Initial findings have demonstrated that this measure has strong internal consistency (Cronbach's *alpha*=0.63–0.90) and test–retest reliability ($r=0.71$–0.91) (Sanders and Becker-Lausen, 1995). The CATS has been shown to correlate significantly with outcome measures such as dissociation, depression, stressful life events and interpersonal difficulties. On each item, participants rate how frequently a particular abusive experience occurred to them during their childhood and adolescence, using a scale of 0–4 (0=never; 4=always). The score for each subscale is the mean score on the items that make up that subscale. There are three subscales, measuring subjective reports of three aspects of adverse childhood experience—neglect/negative home atmosphere, punishment, and sexual abuse.

H. Tanabe, one of the authors, developed and validated the Japanese version of the CATS by the classic translation–back translation technique with the permission and confirmation of Dr. Sanders, the developer of the CATS (Tanabe et al., 2010).

2.2.5. *Mini-international neuropsychiatric interview (MINI) screen*

The MINI screen version was self-completed by the subjects in written form to screen for the 13 putative major psychiatric disorders (Sheehan et al., 1998).

2.3. *Data analysis*

According to the hypothesis presented in Fig. 1, we designed a structural equation model, in which depressive symptoms were predicted by childhood abuse, temperaments and adult stressful life events. Two latent variables, childhood abuse and temperaments were composed of three and four observed variables, respectively that were evinced from the original questionnaire subscales. We used AMOS 20.0 (SPSS, Chicago, IL) to perform this path analysis to obtain the direct and indirect effects among all of the variables, and we used maximum likelihood covariance estimation to analyze the model. For the inferential statistical evaluation of structural equation modeling (SEM), we calculated the indices of goodness of fit, such as the Goodness of Fit Index (GFI), Adjusted GFI (AGFI), Comparative Fit Index (CFI), and Root Mean Square Error of Approximation (RMSEA). According to the conventional criteria, GFI greater than 0.90, AGFI greater than 0.85, CFI greater than 0.95, and RMSEA less than 0.08 indicate an acceptable fit; GFI greater than 0.95, AGFI greater than 0.90, CFI greater than 0.97, and RMSEA less than 0.05 indicate a good fit (Schermelleh-Engel et al., 2003). We standardized and indicated

Table 1
Characteristics, PHQ-9, CATS, TEMPS-A, LES and correlation with PHQ-9 or effects on PHQ-9 in 294 general adult subjects.

Characteristics or measures		Value (number or mean ± SD)	Correlation with PHQ-9 (ρ) or effect on PHQ-9 (mean ± SD of PHQ-9 scores, *U*-test)
Age		42.4 ± 11.2	$\rho=-0.10$, n.s.
Gender (male:female)		171:123	male 2.7 ± 3.3 vs female 4.6 ± 4.5 *U*-test)
Education, years		14.9 ± 2.2	$\rho=-0.12$, n.s.
Employment status (employed:unemployed)		241 : 49	employed 3.4 ± 3.9 vs unemployed 3.8 ± 3.9
Homemakers of unemployed persons		43	n.s. (*U*-test)
Marital status	Never Married	45	Married 3.0 ± 3.6 vs Unmarried 5.3 ± 4.5 (*U*-test)
	Married	228	
	Divorce	16	
	Widowed	3	
Living-alone	(Yes:No)	222:62	Yes 4.0 ± 3.4 vs No 3.3 ± 4.1 (U-test)
Number of offspring		1.4 ± 1.0	$\rho=-0.11$, n.s.
Presence of offspring (Yes : No)		209:85	Yes 3.3 ± 3.9 vs No 4.1 ± 3.9, n.s.(*U*-test)
Comorbidity of physical disease (Yes:No)		63:229	Yes 3.5 ± 4.0 vs No 3.5 ± 3.9, n.s.(*U*-test)
1st-degree relative with psychiatric diseases (Yes:No)		40:254	Yes 3.8 ± 4.0 vs No 3.5 ± 3.9, n.s.(*U*-test)
PHQ-9 score		3.5 ± 3.9	
CATS (average score)	Sexual Abuse	0.03 ± 0.12	$\rho=0.03$, n.s.
	Neglect	0.58 ± 0.66	$\rho=0.32$
	Punishment	1.50 ± 0.64	$\rho=0.06$, n.s.
	Total	0.66 ± 0.47	$\rho=0.25$
TEMPS-A (average score)	Depressive	1.33 ± 0.17	$\rho=0.40$
	Cyclothymic	1.17 ± 0.20	$\rho=0.54$
	Hyperthymic	1.25 ± 0.21	$\rho=-0.04$, n.s.
	Anxious	1.18 ± 0.17	$\rho=0.47$
	Irritable	1.13 ± 0.16	$\rho=0.43$
LES (change score)	Negative	2.25 ± 4.28	$\rho=0.29$
	Positive	2.01 ± 3.39	$\rho=0.08$, n.s.

Data presented as means ± SD or numbers.
ρ=Spearman's rank correlation coefficient.
n.s. not significant.
* $P<0.05$.
** $P<0.01$.

all of the coefficients (with a maximum of 1 and a minimum of −1) for the covariance structure analysis.

We conducted the Mann-Whitney U-test for comparison of the demographic characteristics and the questionnaire data between the two groups. Spearman's rank correlation coefficient and multiple regression analysis were used for correlation between the parameters and the predictive factors.

The statistical analyses were conducted using IBM SPSS AMOS 20.0 (SPSS, Chicago, IL) for the covariance structure analysis, Excel Statistics for Macintosh (Esumi Co, Ltd., Tokyo, Japan) for the multiple regression analysis, Spearman's rank correlation coefficient, and GraphPad Prism 4 (GraphPad Software, La Jolla, CA, USA) for the Mann-Whitney *U*-test.

The differences were considered to be statistically significant at $p < 0.05$.

3. Results

3.1. Demographic characteristics, PHQ-9, CATS, TEMPS and LES of the subjects

The demographic characteristics, PHQ-9, CATS, TEMPS and LES of 294 subjects are presented in Table 1. Gender (female), marital status (unmarried), and living-alone were associated with high PHQ-9 summary scores as determined by the Mann-Whitney *U*-test. Neglect and the total scores of the CATS, the depressive, cyclothymic, anxious, and irritable temperament scores of TEMPS-A, and the negative change scores of LES were significantly correlated with the PHQ-9 summary scores as determined by Spearman's rank correlation coefficients.

3.2. Stepwise multiple regression analysis of the putative explanatory variables on the PHQ-9 suggested from Table 1

The putative explanatory variables that showed significant correlations with the PHQ-9 as determined by Spearman's rank correlation coefficients or had significant effects on the PHQ-9 summary scores as determined by the Mann-Whitney *U*-test in Table 1 were further analyzed by a stepwise multiple-regression analysis.

Table 2 shows the results of a stepwise multiple regression analysis where a PHQ-9 summary score was the dependent factor, and gender (female=2, male=1), marital status (married=2, unmarried=1), living alone (yes=2, no=1), a neglect score on the CATS, depressive, cyclothymic, anxious, and irritable temperament scores on the TEMPS-A, and a negative change score on the LES were independent factors. A total score on the CATS that had a significant correlation with PHQ-9 (Table 1) was excluded from the stepwise multiple regression analysis because it had a high correlation with a neglect score on the CATS (ρ=0.84). When entering these independent factors in a stepwise multiple regression analysis, a neglect score on the CATS, cyclothymic and anxious scores on the TEMPS-A, and a negative change score on the LES were significant predictors of PHQ-9 (F=43.7, $p < 0.0001$, adjusted R^2=0.38), whereas other factors were excluded from the model. Multicollinearity was denied in this multiple regression analysis.

Table 2
The results of a stepwise multiple regression analysis of PHQ-9.

Positive variables selected	Beta	*p*
Cyclothymic score of TEMPS-A	0.29	< 0.0001
Anxious score of TEMPS-A	0.18	0.0069
Neglect score of CATS	0.22	< 0.0001
Negative change score of LES	0.16	0.0016
Adjusted R^2	0.38	< 0.0001

Beta=standardized partial regression coefficient.
Dependent factor, PHQ-9 summary score.
Nine independent factors: gender (female=2, male=1), marital status (married=2, unmarried=1), living-alone (yes=2, no=1), neglect and total scores of CATS, depressive, cyclothymic, anxious, and irritable temperament scores of TEMPS-A, and a negative change score of LES. A total score of CATS, that had a significant correlation with PHQ-9 (Table 1), was excluded from the stepwise multiple regression analysis because it had a high correlation with a neglect score of CATS (ρ=0.84).

3.3. Correlation between the CATS subscale scores and the temperament scores on the TEMPS-A

As shown in Table 3, four temperament scores (excluding the hyperthymic temperament score) were significantly and positively correlated with the neglect and punishment subscale scores. The sexual abuse subscale score was significantly and positively correlated with the cyclothymic and anxious temperament scores.

Multiple regression analysis was performed to identify the independent predictors of the CATS subscales for each affective temperament on the TEMPS-A. Table 4 shows the results of the multiple regression analysis where each temperament score was the dependent factor, and the neglect, punishment, and sexual abuse subscale scores on the CATS were the independent factors. The hyperthymic temperament score was not analyzed because Spearman's rank correlation coefficients showed no correlation between the hyperthymic temperament score and the three subscale scores of the CATS. Only the neglect subscale score was a significant predictor of four temperament scores (Table 4).

Table 3
Correlation (ρ) between CATS subscales and temperament scores of TEMPS-A.

	neg	pun	sex	dep	cyc	hyp	anx	irr
neg	1.00	0.34**	0.23**	0.30**	0.32**	−0.01	0.38**	0.39**
pun		1.00	0.14*	0.17**	0.17**	−0.09	0.16**	0.20**
sex			1.00	0.08	0.12*	−0.09	0.15*	0.09
dep				1.00	0.47**	−0.22**	0.56**	0.37**
cyc					1.00	0.19**	0.61**	0.60**
hyp						1.00	0.01	0.26**
anx							1.00	0.53**
irr								1.00

ρ=Spearman's rank correlation coefficient,
neg, neglect subscale; pun, punishment subscale; sex, sexual abuse subscale; dep, depressive temperament; cyc, cyclothymic temperament; hyp, hyperthymic temperament; anx, anxious temperament; irr, irritable temperament.
* $P < 0.05$.
** $P < 0.01$.

Table 4
Multiple regression analysis of each temperament score of TEMPS-A.

Independent factor	Dependent factor			
	Depressive	Cyclothymic	Anxious	Irritable
Neglect subscale	0.31**	0.33**	0.43**	0.37**
Punishment subscale	0.06	0.03	−0.003	0.03
Sexual abuse subscale	0.03	0.003	0.06	−0.05
ANOVA	F=14.2**	F=13.0**	F=24.3**	F=15.3**
adjusted R^2	0.12	0.11	0.19	0.13

Figures except for F values and adjusted R^2 present beta values (standardized partial regression coefficients).
Hyperthymic temperament was not analyzed because it was not correlated with any CATS subscale score (Table 3).
** $p < 0.01$.

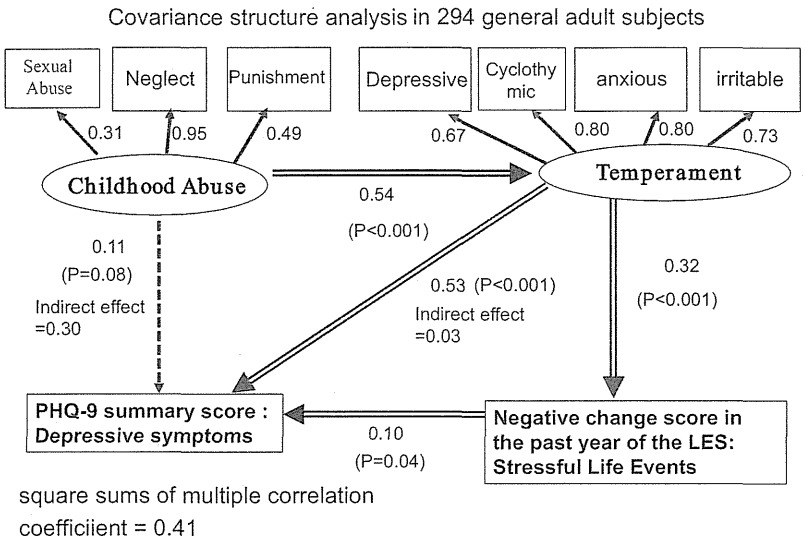

Fig. 2. The results of the covariance structure analysis in the structural equation model with childhood abuse (CATS), affective temperaments (TEMPS-A), adult stressful life events (LES), and depressive symptoms (PHQ-9): Results of 294 subjects from the nonclinical general adult population. Rectangles indicate the observed variables associated with the latent variables, which are shown as ovals. The arrows with double lines represent the statistically significant paths, and the broken lines show the non-significant paths. The numbers beside the arrows show the standardized path coefficients (minimum −1, maximum 1). The *P* values reveal the levels of statistical significance. Indirect effects indicate the effect mediated by the other variables.

3.4. Analysis of the structural equation modeling

To examine the causality of all of the variables, we built a structure equation model based on the results of the above correlation analysis and multiple regression analysis (Fig. 2). The results of the path coefficients calculated by AMOS are shown in Fig. 2.

A good fit of the model was obtained as follows: RMSEA= 0.078, GFI=0.951, AGFI=0.904, CFI=0.950. Only the path coefficient (0.11) of childhood abuse to the PHQ-9 summary score (depressive symptoms) was not significant ($p=0.08$). The other path coefficients were substantially significant ($p < 0.001$) except for that relating the LES to the PHQ-9 summary score (depressive symptoms) ($p < 0.05$). According to the structural equation modeling and consistent with the results of the multiple regression analysis (Table 4), four temperament scores on the TEMPS-A were significantly predicted by the subscales of the CATS. Hyperthymic temperament was excluded from the observed variables of the latent variable "temperament" because hyperthymic temperament was not correlated with the PHQ-9 summary score (Table 1) nor correlated with any subscales of the CATS (Table 3). A neglect subscale score showed a very high-standardized coefficient with the latent variable "childhood abuse". The PHQ-9 summary score was significantly predicted by four temperament scores on the TEMPS-A and a negative change score on the LES. The effect of the CATS subscales on the PHQ-9 summary score was indirect and mediated by the effect of the CATS subscales on four temperament scores on the TEMPS-A (indirect path coefficient=0.30). Four temperament scores on the TEMPS-A significantly predicted a negative change score on the LES, which, in turn, predicted the PHQ-9 summary score.

3.5. Comparison between the subjects with a major depressive episode and healthy subjects

The 294 subjects in this study did not have a history of psychiatric diseases, as indicated in the Subjects and methods section. The results of this study are associated with depressive symptoms in the general adult population, not with depressive symptoms of a major depressive episode. The PHQ-9, which could screen a major depressive episode, as mentioned in the Subjects and methods section (Furukawa, 2010), enables comparison between the subjects with a major depressive episode and the healthy subjects in terms of childhood abuse, negative stressful life events and temperaments. The diagnostic algorithmic threshold of the PHQ-9 for diagnosing a major depressive episode found 7 subjects (1 male, 6 female) with a major depressive episode, although these diagnoses were tentative because these subjects did not have psychiatric interviews. Because of the large gender imbalance, six female subjects with a major depressive episode were compared with 67 healthy female subjects (Table 5).

As shown in Table 5, the female subjects with a major depressive episode showed significantly higher scores on the PHQ-9, the neglect and total scores on the CATS, depressive, cyclothymic, anxious, and irritable temperaments, and a negative change score on the LES than the healthy female subjects, consistent with the model shown in Fig. 2.

4. Discussion

This study is the first report showing that childhood abuse indirectly predicted the severity of depressive symptoms through the affective temperaments measured by the TEMPS-A in the structural equation modeling of nonclinical general adult population. Four temperaments – depressive, cyclothymic, irritable, and anxious – directly predicted the severity of depressive symptoms and the negative change score on the LES during the past year. The negative change score of the LES during the past year mildly, but significantly, predicted the severity of depressive symptoms. Compared with the effect of the negative change score on the LES, the direct effect of temperament and the indirect effect of childhood abuse were more marked. The validity of this result of the structural equation modeling was supported by the results of the multiple regression analysis based on the clinical demographic characteristics and the questionnaire data that were correlated with the severity of depressive symptoms as follows: a stepwise multiple regression analysis showed that four factors - neglect,

Table 5
Comparison of PHQ-9, CATS, and LES of 67 healthy female subjects and 6 female subjects with a major depressive episode.

Characteristics or measures		Healthy female subjects $n=67$	Female subjects with a major depressive episode ($n=6$)
Age		44.6 ± 11.4	50.0 ± 16.5
PHQ-9		2.2 ± 2.5	16.5 ± 3.2**
CATS (average score)	Sexual abuse	0.03 ± 0.12	0.06 ± 0.12
	Neglect	0.50 ± 0.52	1.64 ± 0.80*
	Punishment	1.57 ± 0.56	2.03 ± 0.42
	Total	0.61 ± 0.35	1.40 ± 0.60**
TEMPS-A (average score)	Depressive	1.34 ± 0.14	1.50 ± 0.16*
	Cyclothymic	1.10 ± 0.10	1.27 ± 0.11**
	Hyperthymic	1.19 ± 0.15	1.17 ± 0.09
	Anxious	1.13 ± 0.13	1.46 ± 0.18**
	Irritable	1.07 ± 0.10	1.29 ± 0.14**
LES (change score)	Negative	1.6 ± 4.0	8.6 ± 7.7**
	Positive	1.5 ± 2.9	1.3 ± 1.3

Data presented as means ± SD.
Two groups were compared by Mann-Whitney *U*-test.
* $P<0.05$.
** $P<0.01$.

cyclothymic and anxious temperaments, and a negative change score on the LES – predicted the severity of depressive symptoms. These factors were statistically significant predictors or factors with high path coefficients in the structural equation modeling.

There has been no study that examined the effect of childhood abuse on the TEMPS-A. Pompili et al. (2009) reported that psychiatric inpatients with a history of childhood abuse showed a higher incidence of the irritable temperament trait than did the non-abused patients. In the multiple regression analysis of this study, only neglect among the childhood abuse subscales significantly predicted high scores of depressive, cyclothymic, irritable, and anxious temperaments in the nonclinical general adult population. The affective temperaments measured by the TEMPS-A are considered antecedents or subsyndromal manifestations of mood disorders. The depressive, cyclothymic, and anxious temperaments scores of mood disorder patients are reportedly higher than those of healthy controls (Matsumoto et al., 2005). In particular, cyclothymic temperament is more evident in bipolar disorders (Mendlowicz et al., 2005a, 2005b) and is the major and important factor in the soft bipolar spectrum (Akiskal and Pinto, 1999; Goto et al., 2011; Takeshima and Oka, 2013). This study suggests the possibility that childhood abuse might increase soft bipolarity in the general adult population, which, in turn, might affect the pathogenesis or clinical outcomes of mood disorders. Several studies have reported that the history of childhood abuse is closely related to the onset, course, and treatment response of mood disorders (Alloy et al., 2006; Caspi et al., 2003; Daruy-Filho et al., 2011; Levitan et al., 1998; Nanni et al., 2012). The results of this study link childhood abuse to affective temperaments in aspects of depressive symptoms. Because this study examined the nonclinical general adult population, which constitutes a limitation of this study, the linkage between childhood abuse and affective temperaments should be studied further in a large sample size of mood disorder patients. Although this study shows the relative importance of neglect compared with sexual abuse and punishment, the results with a different population such as psychiatric patients might show a different contribution from each abuse.

Among the five temperaments of the TEMPS-A, depressive, cyclothymic, irritable, and anxious, but not hyperthymic, temperaments, were significantly and positively correlated with depressive symptoms in single regression analyses. Similar findings have been reported in nonclinical subjects by earlier studies (Iliceto et al., 2011; Rozsa et al., 2008). The multiple regression analyses of this study clarified that only cyclothymic and anxious temperaments significantly predicted depressive symptoms. This finding was supported by higher path coefficients from the latent variable "temperament" to cyclothymic and anxious temperaments in the structural equation modeling. The earlier studies reported only correlations between temperaments and depressive symptoms, and they did not investigate the other factors that influenced temperaments (Iliceto et al., 2011; Rozsa et al., 2008). Our study revealed the direct effects of childhood abuse on temperaments, resulting in increased depressive symptoms.

In the LES, each subject rates separately the desirability and effect of events that they have experienced on a 7-point scale ranging from extremely negative (−3) to extremely positive (+3) (Sarason et al., 1978). A negative change score indicates the subjective severity of stressful life events rather than objective severity; i.e., it indicates a negative appraisal of life events. In the structural equation modeling of this study, four temperaments predicted negative scores on the LES, suggesting that these temperaments (depressive, cyclothymic, irritable, and anxious) might increase vulnerability to stressful life events. There has been only one report that studied the relationship between affective temperaments and stress. Sakai et al. (2005) showed that affective temperament measured by the TEMPS-A influenced interpersonal relationship stressors, i.e., conflicts, more than workload-related stressors and that irritable temperament was associated with the most prominent vulnerability, followed by cyclothymic and anxious temperaments. Their results are consistent with ours.

A positive correlation ($r=0.24$) between depressive symptoms and negative change scores on the LES in nonclinical university students was reported in the original manuscript of the LES (Sarason et al., 1978). In our study, this correlation coefficient between depressive symptoms and negative change scores on the LES showed a similar value ($\rho=0.29$); however, it was unexpectedly much lower than those between depressive symptoms and temperaments in the single regression analyses (Table 1) and obviously lower than those between depressive symptoms and childhood abuse (indirect) or temperament (direct) in the structural equation modeling (Fig. 2). This finding indicates that baseline depressive symptoms in nonclinical adults are influenced more strongly by childhood abuse (indirect effect) and temperament (direct effect) than by negative life events. Because there has been no study that examined the complex interaction between childhood abuse, temperament, and negative life events, our results could not be compared with earlier studies.

This study, using the structural equation model, showed that childhood abuse, especially neglect, increases affective temperament, which, in turn, increases the negative appraisal of stressful life events and increases depressive symptoms. The important role of affective temperament in the effect of childhood abuse and stressful life events on depressive symptoms was suggested. Further studies to investigate the effect of childhood abuse, affective temperaments, and adult stressful life events in mood disorder patients are necessary for further understanding.

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Conflict of interest

The authors report no financial or other relationship that is relevant to the subject of this article.

TI has received honoraria from GlaxoSmithKline, Pfeizer, Astellas, Eli Lilly, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Asahi Kasei Pharma, Shionogi, Janssen Pharmaceutical, Takeda Pharmaceutical and Yoshitomi Pharmaceutical, has received research/grant support from Otsuka Pharmaceutical, and is a member of the advisory boards of GlaxoSmithKline, Eli Lilly, Mochida Pharmaceutical and Mitsubishi Tanabe Pharma.

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Alexithymia Is Associated with Greater Risk of Chronic Pain and Negative Affect and with Lower Life Satisfaction in a General Population: The Hisayama Study

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Abstract

Introduction: Chronic pain is a significant health problem worldwide, with a prevalence in the general population of approximately 40%. Alexithymia — the personality trait of having difficulties with emotional awareness and self-regulation — has been reported to contribute to an increased risk of several chronic diseases and health conditions, and limited research indicates a potential role for alexithymia in the development and maintenance of chronic pain. However, no study has yet examined the associations between alexithymia and chronic pain in the general population.

Methods: We administered measures assessing alexithymia, pain, disability, anxiety, depression, and life satisfaction to 927 adults in Hisayama, Japan. We classified the participants into four groups (low-normal alexithymia, middle-normal alexithymia, high-normal alexithymia, and alexithymic) based on their responses to the alexithymia measure. We calculated the risk estimates for the criterion measures by a logistic regression analysis.

Results: Controlling for demographic variables, the odds ratio (OR) for having chronic pain was significantly higher in the high-normal (OR: 1.49, 95% CI: 1.07–2.09) and alexithymic groups (OR: 2.56, 95% CI: 1.47–4.45) compared to the low-normal group. Approximately 40% of the participants belonged to these two high-risk groups. In the subanalyses of the 439 participants with chronic pain, the levels of pain intensity, disability, depression, and anxiety were significantly increased and the degree of life satisfaction was decreased with elevating alexithymia categories.

Conclusions: The findings demonstrate that, in the general population, higher levels of alexithymia are associated with a higher risk of having chronic pain. The early identification and treatment of alexithymia and negative affect may be beneficial in preventing chronic pain and reducing the clinical and economic burdens of chronic pain. Further research is needed to determine if this association is due to a causal effect of alexithymia on the prevalence and severity of chronic pain.

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Introduction

Chronic pain is a common problem, with prevalence estimates at approximately 40% of the general population [1,2]. The impact of pain on economies is enormous. For example, the cost of back pain alone is equivalent to more than one-fifth of one country's total health expenditure and to 1.5% of the annual gross domestic product of the UK [3]. In addition to its economic impact, chronic pain is arguably one of the health care issues with the greatest negative impact on quality of life.

Chronic pain is known to have significant biological, psychological, and social causes and consequences [4–6], and thus adequate pain assessments and treatments should address all of these factors. In order to expand the potential targets of pain treatment and therefore help minimize the prevalence of the

negative impacts of chronic pain, research is needed to identify the biopsychosocial factors that are most consistently associated with pain and pain-related outcomes.

A potential factor that may contribute to the development and maintenance of chronic pain is alexithymia [7,8]. Alexithymia is the label used to describe a personality trait associated with an inability to regulate negative affect [9]. The term is derived from Greek, and literally means "a lack of words for feelings" [10]. Alexithymia is a disturbance of both cognitive and affective functioning characterized by difficulty in recognizing or describing one's emotions. The most common measure of alexithymia is the 20-item Toronto Alexithymia Scale (TAS-20) [11]. The TAS-20 assesses three components of alexithymia: (1) difficulty identifying feelings (DIF); (2) difficulty describing feelings (DDF); and (3) externally-oriented thinking (EOT).

In our previous research, we found a measure of alexithymia to be positively associated with pain intensity and interference, and negatively associated with vitality in a sample of individuals with neuromuscular disease and chronic pain [12]. We also found evidence that the effects of alexithymia on pain may be mediated by negative affect [13]. Additionally, research in pain populations by our group and others has identified the TAS-20 DIF scale as the most consistent factor associated with chronic pain and pain-related dysfunction [7,14,15]. However, the studies addressing the relationship between alexithymia and chronic pain to date have used participants who are not necessarily representative of the population (e.g., patients, transit workers, and students), which limits the generalizability of extant findings. To our knowledge, there are no studies examining the role that alexithymia might play in comprehensive chronic pain in a general population.

To elucidate this association, we performed a population-based cross-sectional survey in a Japanese community. We hypothesized that (1) the measure of alexithymia is associated with chronic pain, (2) this association is mediated by negative affect, and (3) the DIF domain of alexithymia is associated with criterion measures stronger than the other components of alexithymia. Our planned analyses regarding the associations between alexithymia and measures of additional pain-related outcomes (specifically, pain intensity, depression, anxiety, disability, and life satisfaction) were considered exploratory, as these associations have not yet been tested in prior research.

Methods

1. Study participants

The Hisayama Study is an ongoing, long-term cohort study examining cardiovascular disease and its risk factors in Hisayama, a suburban town adjoining Fukuoka City, a metropolitan area in southern Japan. Full community surveys of the health status of residents aged 40 and older have been repeated every five years since 1961 [16]. Data for the present study were taken from responses to questions regarding pain and psychological functioning included in the whole survey administered in 2010.

Among 2,223 residents aged 40 and older who participated in the health survey, a total of 1,027 residents (participation rate: 46%) consented to participate in these questions of the 2010 whole survey. Of these, 66 had missing data and 34 did not complete the questionnaires, leaving a final sample of 927 participants (326 men and 601 women) (Fig. S1). This study was approved by the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

2. Measures

2.1. Alexithymia. Alexithymia was assessed for each participant using the 20-item Toronto Alexithymia Scale (TAS-20), which is the most psychometrically valid measurement of alexithymia [11]. As mentioned above, the TAS-20 consists of 20 statements that reflect three domains of alexithymia: (1) DIF; (2) DDF; and (3) EOT. Each item is rated on a 5-point Likert scale, with 1 = "strongly disagree" and 5 = "strongly agree."

We classified the participants as alexithymic (TAS-20 score >60) or non-alexithymic (TAS-20 score ≤ 60) based on their total TAS-20 scores according to previous studies [9], and subsequently classified the non-alexithymic group into three subgroups: low-normal alexithymia (score <44), middle-normal alexithymia (score 44–50) and high-normal alexithymia (score 51–60) based on their tertile values. In addition to the tertile values in this study, a total score of 51–60 has been defined as "borderline alexithymia" or "possible alexithymia" in some studies [17]. We also divided the TAS-20 subscale scores of the three domains into quartiles, as there are no published cutoffs for classifying individuals into alexithymic groups for the TAS-20 subscales. The Japanese version of the TAS-20 has been shown to be both reliable and valid [18].

2.2. Assessment of presence of acute and chronic pain. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and also explains that "Pain is always subjective." The definition of 'chronic' pain based on duration has not been clearly established, but 3 or 6 months or more is generally used [19,20]. According to this definition, we defined chronic pain as having any subjective pain for more than 6 months.

As part of the Hisayama Study health survey, the participants were asked to indicate whether they experienced any pain and how long the pain has lasted. Those who reported <6 months of pain and those with pain that had been experienced for 6 months or longer were classified as having acute (i.e., recent onset) and chronic pain, respectively. For complementary information, the participants with pain were asked to select their primary pain site using the IASP site categories [19]: 1 = head and face, 2 = neck, 3 = shoulder and arms, 4 = chest, 5 = back, 6 = stomach, 7 = low back, 8 = legs, 9 = pelvic and genital area, 10 = pain at more than one site.

2.3. Pain intensity. The participants were asked to rate the average intensity of their pain in the past week on a 100-mm visual analogue scale (VAS). Anchors were "No pain" (0 mm) and "Pain as bad as it could be (100 mm)." A great deal of evidence supports the reliability and validity of the VAS as a measure of pain intensity [21].

2.4. Disability. Participants were asked to rate their average disability in the past week on a 100-mm VAS. Anchors were "No disability" (0 mm) and "Disability as bad as it could be (100 mm) [22]."

2.5. Life satisfaction. Participants were asked to rate their global life satisfaction on a 100-mm VAS. Anchors were "Feeling no life satisfaction at all" (0 mm) and "Feeling life satisfaction as good as it could be (100 mm) [23]."

2.6. Negative affect. Negative affect was measured with the depression and anxiety scales of a Japanese version of the Symptom Checklist 90-revised (SCL-90-R). SCL-90-R scales have established validity and reliability [24].

2.7. Demographic/descriptive variables and covariates. Age, sex, marital status, educational level, and economic status are factors that could potentially influence both

pain and alexithymia and were therefore assessed and controlled in all analyses. Marital status was classified as never married, divorced, separated, widowed, married, or cohabiting. Educational level was classified as one of three education duration categories: under 9 years, 9–12 years, or over 12 years. Economic status was assessed by a question asking, 'How difficult or easy is your current financial status?' Response options for this question were 'Very hard,' 'Hard,' 'Normal,' 'Easy,' and 'Very easy.' Based on the participant's response, economic status was divided into three classes: low (very hard or hard), average (normal), and high (easy and very easy). Similar one-item questions about economic status have demonstrated validity through their associations with psychological and physical health [25].

3. Statistical analysis

We first computed the means and standard deviations, medians and interquartile ranges (of continuous variables), and rates (of categorical variables) of the study variables for descriptive purposes. To better understand the association between alexithymia and potential confounding factors (i.e., age, sex, marital status, educational level, and economic status), we examined their trend tests using a linear regression analysis, logistic regression analysis, or the Jonckheere-Terpstra test, as appropriate. Logistic regression analysis was used to examine the unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and p for trend of chronic pain according to the TAS-20 score levels taken as categorical variables. In the multivariable-adjusted model, adjustments were made for age, sex, marital status, years of education, and economic status. We estimated the ORs per 1-point increment in the TAS-20 score using the relevant logistic model including the TAS-20 score taken as a continuous variable. The heterogeneity in the association between sexes was tested by adding the interaction term to the relevant logistic model. We also estimated the association (ORs and p for trend) between the quartiles of the TAS-20 subscales and the presence of chronic pain using logistic regression analysis. The trends in the dose-response associations between TAS-20 score levels and the pain intensity, disability, anxiety, depression, and life satisfaction were tested using the Jonckheere-Terpstra trend test for the participants with chronic pain. The SAS software package version 9.2 (SAS Institute, Cary, NC, USA) was used for all analyses. Two-sided values of $p<0.05$ were considered significant in all analyses.

Results

The characteristics of the study sample are summarized in Table 1 as a function of the TAS-20 categories. The prevalence of alexithymic (TAS-20>60) in all participants was 7.8% (n = 72; 35 men, 37 women). There were significant associations between the TAS-20 categories and both education level and economic status, with lower education level and lower economic status associated with higher levels of the TAS-20 categories relative to those with higher education level or economic status. The scores for negative affect, such as depression and anxiety symptoms, were significantly increased with elevating TAS-20 categories. No significant associations were found between the TAS-20 categories and age, sex, or marital status.

Approximately 47% of the participants (n = 439; 152 men, 287 women) were classified as having chronic pain, and 17.9% (n = 166; 41 men, 125 women) were classified as having acute pain. For those with pain, the primary pain sites were the low back (30.1%), shoulders and arms (30.1%), legs (19.6%), head, face, or neck (13.2%), and other sites (7.2%) in the chronic pain group, and shoulders and arms (34.9%), low back (22.9%), legs (16.9%), head, face, or neck (15.0%), back (6.0%), and other sites (4.2%) in the acute pain group. The prevalence of alexithymic turned out to be 4.0% in the painless group, 6.6% in the acute pain group, and 10.9% in the chronic pain group.

The prevalence of pain as a function of the TAS-20 categories is shown in Figure 1. As the scores of the TAS-20 categories increased, the prevalence of chronic pain increased and that of 'no pain' decreased.

Table 2 shows the unadjusted and multivariable-adjusted ORs for the presence of chronic pain according to the TAS-20 categories. Compared with the low-normal alexithymia group, the unadjusted ORs for the presence of chronic pain were significantly higher, around twofold higher, in the high-normal alexithymia and alexithymic groups. After adjusting for age, sex, marital status, years of education, and economic status, this association remained substantially unchanged. Approximately 40% of the participants belonged to these two (high-normal alexithymia and alexithymic) high-risk groups.

As a continuous variable, every 1-point increment in the TAS-20 score was associated with a 1.04-times (95%CI: 1.02–1.06) higher likelihood of the presence of chronic pain after the adjustment for the aforementioned confounding factors. The subgroup analysis stratified by sex showed that the odds ratios in the high-normal alexithymia and alexithymic groups were significant for both sexes, without any evidence of significant heterogeneity in the association between sexes (p for heterogeneity = 0.54).

Because including the participants with acute pain in the group without chronic pain in the present analysis may have underestimated the association, we examined the difference between the chronic pain and no-pain groups only. In these analyses, the odds ratios were even higher in the high-normal alexithymia group (OR: 2.05, 95% CI: 1.40–3.00) and alexithymic group (OR: 3.60, 95% CI: 1.83–7.08). The relationships between TAS-20 categories and chronic pain became nonsignificant after adjusting for depression symptoms (p for trend = 0.57) or for anxiety symptoms (p for trend = 0.57).

Figure 2 presents the odds ratios for chronic pain as a function of quartiles of the TAS-20 subscales score, controlled for demographic factors. There were significant differences between the first quartile and both the third and the fourth quartiles in DIF subscale score. There was also a significant difference between the first quartile and the fourth quartile in DDF subscale score. However, there was no significant association between the EOT subscale score quartiles and the presence of chronic pain. Thus, the TAS-20 DIF subscale demonstrated the strongest association with the presence of chronic pain, although in this sample the TAS-20 DDF subscale may also play a role.

Table 3 shows the association between the TAS-20 categories and pain-related outcomes of the 439 participants with chronic pain. As the level of the TAS-20 categories increased, so did the levels of pain intensity, disability, and depression and anxiety symptoms. The TAS-20 categories were negatively associated with life satisfaction.

Discussion

To our knowledge, this is the first study to examine the association between alexithymia and chronic pain in a sample that is representative of the general population. As hypothesized, we found that alexithymia is significantly associated with a higher prevalence of chronic pain and that this association is mediated by negative affect, such as depression and anxiety symptoms. Also as hypothesized, the TAS-20 subscale assessing difficulty identifying

Table 1. Characteristics of the study population according to the TAS-20 score level.

	Total	TAS-20 score				p for trend
		Low-normal	Middle-normal	High-normal	Alexithymic	
		<44	44–50	51–60	>60	
	n=927	n=278	n=283	n=294	n=72	
Sociodemographic characteristics						
Age, year	61±11	60±11	61±11	61±11	63±13	0.10
Women, %	64.8	64.7	66.4	66.7	51.4	0.32
Marital status (married/cohabiting), %	81.8	86.0	78.1	80.6	84.7	0.33
Educational levels (under 9 years), %	17.0	11.2	15.9	21.4	26.4	<0.001
Economic status (low), %	19.6	17.3	16.3	22.8	29.2	0.01
Negative affect						
Depression symptom, score	0.69 (0.46–1.00)	0.54 (0.31–0.77)	0.62 (0.38–0.85)	0.85 (0.62–1.23)	1.31 (0.85–1.77)	<0.001
Anxiety symptom, score	0.40 (0.20–0.70)	0.20 (0.10–0.40)	0.30 (0.20–0.50)	0.60 (0.30–0.80)	1.00 (0.60–1.30)	<0.001

Values are means ± std. dev. or frequencies or median (interquartile range).
The TAS-20: the 20-item Toronto Alexithymia Scale.
doi:10.1371/journal.pone.0090984.t001

feelings is more closely associated with pain than the other two TAS-20 subscales. We also found that alexithymia was associated with measures of additional pain-related quality of life domains (depression, anxiety, disability, and satisfaction with life) in the subsample of individuals with chronic pain. These findings have important implications for understanding pain and promoting general health.

1. Comparison with previous reports

The prevalence of alexithymic was reported to be approximately 10% in studies based in Finland (age range: 30–97 years) and Germany (age range: 20–69 years) [26,27]. Our prevalence result, 7.8% (age range: 40–91 years), is probably lower because our participants did not include younger people (in their 20 s), who have been reported to have relatively high TAS-20 scores in Japan [18]. Although as far as we know there are no population-based studies on the relationship between alexithymia and chronic pain, there are some hospital-based cross-sectional studies for various patient populations. Most of these studies found a positive association between alexithymia and the presence of chronic pain [15,28–30].

For example, Mehling and Krause reported that scoring in the upper quartile of the alexithymia total score was associated with twofold (adjusted OR = 2.00, 95%CI: 1.31–3.00) higher odds of the 12-month prevalence of low back pain, which was assessed by the medical history taken during the drivers' relicensing exams of 1,180 San Francisco transit operators [8]. These results are consistent with our finding. However, several studies have shown negative [31–33] or mixed correlations [34]. The discrepancy in correlations may be due to differences in health status or study design (e.g., using healthy controls or patient controls).

A population-based prospective longitudinal study [35] was conducted with the same population as that in the aforementioned cross-sectional study by Mehling and Krause [8]. The longitudinal

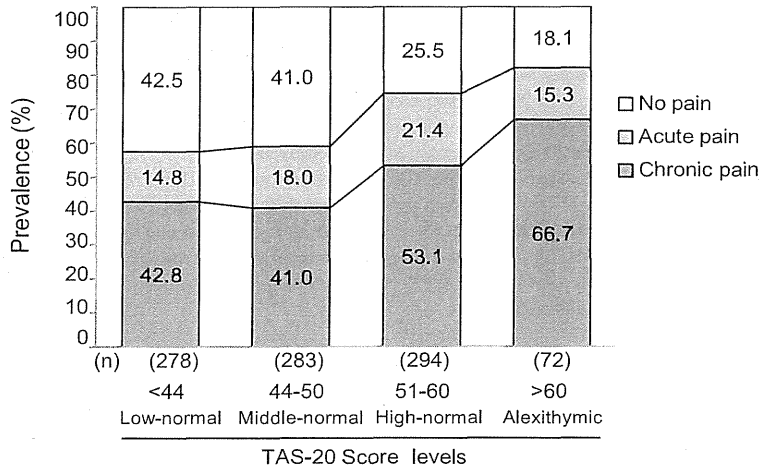

Figure 1. Self-reported pain prevalence according to the TAS-20 score levels in a general population from the Hisayama Study health survey. Acute pain: <6 months of pain. Chronic pain: pain that had been experienced for 6 months or longer.
doi:10.1371/journal.pone.0090984.g001

Table 2. Odds ratios for chronic pain according to the TAS-20 category score.

Alexithymia level	TAS-20 score	Number of participants	Number with Chronic pain	Unadjusted			Multivariable-adjusted		
				OR (95%CI)	p value	p for trend	OR (95%CI)	p value	p for trend
Total									
Low-normal	<44	278	119	1.00 (reference)			1.00 (reference)		
Middle-normal	44–50	283	116	0.93 (0.66–1.30)	0.66	<0.001	0.91 (0.65–1.28)	0.6	<0.001
High-normal	51–60	294	156	1.51 (1.09–2.10)	0.01		1.49 (1.07–2.09)	0.02	
Alexithymic	>60	72	48	2.67 (1.55–4.61)	<0.001		2.56 (1.47–4.45)	0.001	
Men									
Low-normal	<44	98	40	1.00 (reference)			1.00 (reference)		
Middle-normal	44–50	95	38	0.97 (0.54–1.72)	0.91	0.007	0.96 (0.54–1.72)	0.9	0.01
High-normal	51–60	98	51	1.57 (0.89–2.77)	0.12		1.56 (0.88–2.77)	0.13	
Alexithymic	>60	35	23	2.78 (1.24–6.22)	0.01		2.55 (1.12–5.82)	0.03	
Women									
Low-normal	<44	180	79	1.00 (reference)			1.00 (reference)		
Middle-normal	44–50	188	78	0.91 (0.60–1.37)	0.64	0.004	0.89 (0.58–1.35)	0.58	0.005
High-normal	51–60	196	105	1.48 (0.97–2.22)	0.06		1.48 (0.98–2.25)	0.06	
Alexithymic	>60	37	25	2.66 (1.26–5.63)	0.01		2.59 (1.21–5.53)	0.01	

OR: odds ratio; CI: confidence interval.
Multivariable adjustment was made for age, gender, marital status, years of education and economic status. In the stratified analyses of gender, ORs were not adjusted for gender.
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study revealed a negative association between alexithymia and the 7.5-year incidence of compensated claims for low back pain, which was assessed by physician-confirmed diagnoses from administrative workers' compensation data. As the authors mentioned, a possible interpretation of their results is that alexithymic patients with chronic pain were unlikely to complain by filing a workers' compensated claim for low back pain injury because of their fear of being shamed and self-devaluated and/or their shyness and anxiety concerning the verbal expression of their emotions. Further prospective longitudinal studies with an appropriate method for estimating chronic pain are warranted.

2. Alexithymia, negative affect, and pain

Alexithymia is a personality trait associated with poor emotional awareness and affect regulation [9]. Our present findings confirm that this trait — in particular the aspect of alexithymia that involves having difficulty identifying one's feelings — is associated with the presence of chronic pain in the general population. This association also becomes nonsignificant when negative affect is controlled, suggesting that negative feelings such as depression and anxiety may mediate the association between alexithymia and chronic pain. This pattern of findings is consistent with previous

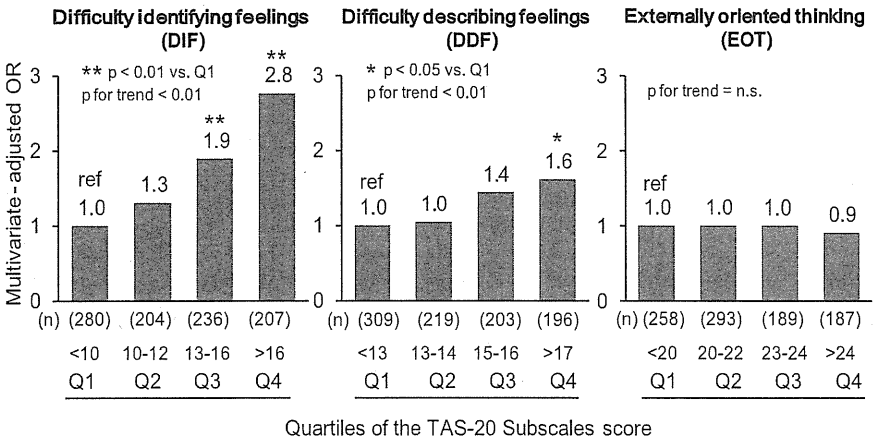

Figure 2. Odds ratios for chronic pain according to the TAS-20 subscales, adjusted for demographic factors in the general population.
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Table 3. The relationship between the TAS-20 score levels and the pain-related outcomes of the 439 participants with chronic pain.

	TAS-20 score				
	Low-normal	Middle-normal	High-normal	Alexithymic	p for trend
	<44	44–50	51–60	>60	
	n = 119	n = 116	n = 156	n = 48	
Pain intensity, mm	30 (15–50)	44 (20–54)	47 (24–65)	58 (36–80)	<0.001
Disability, mm	5 (0–15)	15 (0–31)	10 (0–38)	29 (3–61)	<0.001
Depression, score	0.7 (0.4–0.8)	0.7 (0.5–1.0)	0.9 (0.6–1.3)	1.4 (1.2–1.9)	<0.001
Anxiety, score	0.3 (0.2–0.6)	0.4 (0.2–0.6)	0.6 (0.4–0.8)	1.1 (0.8–1.6)	<0.001
Life satisfaction, mm	75 (50–89)	65 (47–81)	51 (40–71)	50 (38–61)	<0.001

Values are medians (interquartile range).
Pain intensity, disability and life satisfaction were evaluated by Visual Analogue Scale.
Depression and anxiety scores were evaluated by Symptom Check List-90-R.
doi:10.1371/journal.pone.0090984.t003

research involving samples of individuals with chronic pain [13,36].

In addition, our finding that the DIF and DDF domains of the TAS-20 were associated with the likelihood of chronic pain, while the EOT domain was not, is consistent with the findings of previous studies examining alexithymia and pain [7,8,11,14]. The finding may be due to poor reliability of the EOT subscale [37]. Given the cross-cultural consistency of the finding, however, it does not appear to be due to language issues or cultural differences.

3. Possible mechanism underlying the association between alexithymia and chronic pain

Various theories linking alexithymia and physical illness have been conceptualized at the physiological level (e.g., the hypothalamic-pituitary-adrenal axis, chronic sympathetic hyperarousal, inflammation, and impaired immune status), the behavioral level, and the cognitive level (e.g., illness behavior, somatic amplification) [38,39]. Some neuroimaging studies of alexithymia and chronic pain have been conducted recently, and their findings may contribute to our understanding of the mechanism of the relationship. First, neuroimaging data indicate not only hyperactivity in pain perception areas such as the insular cortex, but also hypoactivity in pain-processing regulatory areas such as the prefrontal cortex. Lack of an emotional regulation system might cause hypersensitivity to aversive bodily sensations and prolonged, pain-related affective reactions such as distress [40,41]. Second, a possibility is related to the known negative effect of depression on the descending inhibitory system [42]. That is, alexithymia may lead to increased risk of depression, which may then interfere with an individual's ability to reduce or inhibit pain.

4. Clinical implications

Our analyses of the subgroup of participants with chronic pain supported a link between alexithymia and a number of measures of the key functioning domains in these individuals, including pain intensity, disability, depression and anxiety (positive associations), and life satisfaction (negative association). To the extent that these associations are causal — a conclusion that cannot yet be drawn due to the correlational nature of the current and previous findings — then treatments that decrease alexithymia could potentially have significant benefits across multiple quality of life domains for individuals with chronic pain. Thus, our findings support the need for research to develop and test interventions [43,44] that could help individuals identify and describe their feelings, and to determine whether these interventions promote health-related quality of life and reduce the risk for chronic pain as a general health policy.

5. Study strengths and limitations

The study has a number of important strengths, including its large sample size and a population-based study design. Some limitations should be noted, however.

One primary limitation is that the data are cross-sectional. We thus cannot conclusively determine if alexithymia influences the presence and severity of negative affect and pain, if negative affect and pain influence alexithymia, or if there is an unidentified third variable that influences all three. However, experts generally agree that alexithymia is a trait that develops early in life and that it rarely changes without active intervention [45]. Thus, the possibility that alexithymia has a greater impact on pain and depression than these variables have on alexithymia remains viable. Prospective longitudinal studies are needed to clarify the contribution of alexithymia to the development of chronic pain and other negative outcomes. A second limitation is related to the possibility of selection bias, because approximately one-half of the individuals who participated in the regular Hisayama Study survey did not participate in our research. Certainly, we cannot deny the possibility that people with physical or mental complaints were more willing to participate in the study than were people without. In contrast, health-conscious people might have been more likely to participate in the study than non-health-conscious people. The fact that the present study population had many more females than males (601 women, 326 men) may support these possibilities [46]. Therefore, the generalizability of our findings to all individuals in the community may be limited. Nevertheless, we believe that our findings provide important information to consider alexithymia as a cognitive factor that may exacerbate physical symptoms such as chronic pain. Third, our questions about the presence of chronic pain have not clearly determined temporal patterns of chronic pain (e.g., it is unclear how a patient with recurrent pain would respond to the questions). A fourth limitation is that the causes of pain were not assessed in this study. It will be informative to explore whether or not the magnitude of the associations between alexithymia and chronic pain is different between participants with pain disorders that have or do not have

one or more established biological causes. However, this limitation is unlikely to alter our conclusion, because previous studies have shown a positive correlation between alexithymia and pain-related outcomes regardless of the presence or absence of biological cause [12,26,27,44,47]. Lastly, pain intensity, disability, and life satisfaction were each assessed with a single-item measure using a VAS, which may have limited reliability of a part of the results compared to assessment that uses multiple-item questionnaires.

Conclusions

The results of the present study indicate that alexithymia is significantly associated with a greater prevalence of chronic pain in the general population and that individuals with alexithymia have more pain intensity, disability, and depression and anxiety symptoms, and less life satisfaction than those without alexithymia. Our findings highlight certain clinically important concepts; i.e., that adverse psychological factors and personality traits play a significant role in the etiology of chronic pain. The early identification of alexithymia and negative affect may be beneficial in preventing chronic pain and reducing the clinical and economic burdens of chronic pain. Further prospective studies and interventional studies are needed to confirm this hypothesis.

Supporting Information

Figure S1 Flow chart of the participant recruitment.
(EPS)

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Author Contributions

Conceived and designed the experiments: MS MH. Performed the experiments: MS MH KA SM RI K. Yamashiro TY YI. Analyzed the data: MS TN K. Yonemoto YK. Contributed reagents/materials/analysis tools: MS MH. Wrote the paper: MS TN MPJ KA CK NS YK MH.

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Temperament and character profiles of Japanese university students with depressive episodes and ideas of suicide or self-harm: A PHQ-9 screening study

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Abstract

Objective: The aim of our study was to reveal the personality traits of individuals with major and other depressive episodes among the young adult population. Furthermore, character traits of individuals with ideas of suicide or self-harm were also investigated in this study.
Methods: The subjects of this study were 1421 university students who completed the Patient Health Questionnaire (PHQ-9) and the Temperament and Character Inventory (TCI). The subjects were divided into three separate groups: the major depressive episode group (N = 41), the other depressive episode group (N = 97), and the non-depressive controls (N = 1283). This separation was achieved using the PHQ-9 algorithm diagnosis. We compared the TCI scores using an analysis of variance. Moreover, the Cochran-Armitage trend test was used to determine the diagnosis, ideas of suicide or self-harm, and analysis of *character profiles*.
Results: The major depressive episode group had significantly higher HA ($P < 0.001$), lower RD ($P < 0.001$), lower SD ($P < 0.001$), and lower C ($P < 0.001$) scores than non-depressive controls. The other depressive episode group had significantly higher HA scores ($P < 0.001$) and lower SD scores ($P < 0.001$) than non-depressive controls. The Cochran-Armitage trend test revealed that the prevalence of depressive episodes decreased as the character profiles matured ($\chi^2_{trend} = 57.2$, $P < 0.0001$). The same tendency was observed in individuals who had ideas of suicide or self-harm ($\chi^2_{trend} = 49.3$, $P < 0.0001$).
Conclusion: High HA and low SD scores were common personality traits among young adults with major depressive episodes. Furthermore, the immaturity of *character profiles* was clearly associated with depressive episodes and ideas of suicide or self-harm.

1. Introduction

Kessler et al. reported that the highest risk of initial suicide ideation, planning, and attempts took place during an individual's late teens to early 20s [1]. Accordingly, it is very important to study depression and ideas of suicide or self-harm in young adults to prevent suicide. Several studies have examined the pathogenic and predictive role of personality in depressive symptoms among the young adult population using the Temperament and Character Inventory (TCI) [2–5]. The TCI is a widely used self-rating scale for assessing personality among adult samples. The TCI consists of four dimensions of temperament [i.e., novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P)] and three dimensions of character [i.e., self-directedness (SD), cooperativeness (C), and self-transcendence (ST)].

Among the four temperament dimensions, high HA scores were consistently associated with depressive symptoms in both clinical samples and general populations [6]. Recently, Kampman et al. reviewed 12 studies that focused on the relationship between TCI temperament dimensions and depressive symptoms. He concluded that high HA scores were associated with both current depressive symptoms and a depressive trait [6]. Four recent studies, comprised of young adult participants, also demonstrated the correlation

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between depressive symptoms and HA scores [2–5]. In these studies, the Beck Depression Inventory (BDI), Self-Rating Depression Scale (SDS), and the Hospital Anxiety and Depression Scale (HADS) were used to evaluate depressive symptoms. These instruments can be used as continuous measures of depression severity, but they cannot make a criteria-based diagnosis of depression. Therefore, it is difficult to differentiate threshold and sub-threshold depressive episodes, i.e., major and minor depressive episodes, using the BDI, SDS, and HADS. Hence, these previous studies did not properly judge the temperaments of individuals with major depressive episodes among the young adult population. Moreover, the relationship between minor depressive disorder and personality has yet to be reported. Although minor depressive disorder is thought to be a risk factor for developing major depressive disorder [7–9], the personality traits of minor depressive disorder have not been made clear.

Concerning *character profiles*, several previous studies conducted in clinical settings [10,11] have reported that depressive symptoms are associated with character immaturity. This character immaturity was indicated by the presence of low SD and low C scores [12]. In a general adult sample, depressive symptoms are often observed in individuals who have an immature *character profile* [13]. Moreover, a low SD score was suggested as one of the predictors of vulnerability to a future major depressive disorder [14]. Focusing on the young adult population, previous studies reported that SD scores are negatively correlated with depressive symptoms [2–5]. The other character dimensions, C [2–4] and ST [2], are also negatively correlated with depressive symptoms. Cloninger et al. proposed eight *character profiles* based on eight possible configurations of high or low scores of SD, C, and ST [15]. For example, the *character profile* that includes low scores in three different character dimensions will most likely embody a depressive personality. The melancholic *character profile* is the most common in depression [15]. Although the link between character immaturity and depression is anticipated among the young adult population, the prevalence of depressive episodes among young adults who fit one of Cloninger's eight *character profiles* has not yet been reported. Another reason for major depressive episode screening among the general population is the early detection of individuals with a high suicide risk. Few studies, at least among the young adult population, have analyzed the association between personality and ideas of suicide or self-harm. According to clinical studies, individuals who had previously attempted suicide [16,17] and had suicidal thoughts, [16] along with depression, showed high HA scores and low SD scores. Our recent study demonstrated that young adults who completed suicide consistently had high HA scores [18]. The association between ideas of suicide or self-harm and *character profiles* has not yet been studied among the young adult population.

This study aims to verify a number of hypotheses regarding young adults. First, young adults with major depressive episodes have higher HA scores and lower SD scores than did non-depressive controls. Second, young adults with other depressive episodes defined by the PHQ-9 also have higher HA scores and lower SD scores than non-depressive controls. Third, major or other depressive episodes are more often observed in individuals with low SD scores and low C *character profiles* than those with high SD scores and high C *character profiles*. Fourth, ideas of suicide or self-harm are more often observed in individuals with low SD scores and low C *character profiles* than those with high SD scores and high C *character profiles*. To screen for major and other depressive episodes and ideas of suicide or self-harm and to study the relationship between these disorders and personality, we administered the PHQ-9, a self-report questionnaire, and TCI to university students. Though the PHQ-9 requires less than 1 minute for patients to complete, it is as good a screener for major depression as longer instruments in various settings, countries, and populations, and has a validity for measuring its severity [19–21].

2. Methods

2.1. Subjects

The PHQ-9 and TCI were administered to 2117 university students who enrolled in Hokkaido University in April 2010. Both self-rating scales were completed by 1421 students (67.1%). We defined these 1421 students as the "subjects" of our study. According to the PHQ-9 algorithm diagnosis, 41 (2.9%) were classified as having a major depressive episode, 97 (6.8%) were classified as having other depressive episodes, and 1283 (90.3%) were classified as non-depressive controls (NC).

Written informed consent was obtained from all subjects prior to completion of the TCI and PHQ-9. This study was approved by the Ethical Committee of Hokkaido University Graduate School of Medicine and was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki (amended in Seoul, October 2008).

2.2. Measures

2.2.1. PHQ-9

The PHQ was developed as a self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD). It was designed for the criteria-based diagnosis of several mental disorders commonly observed in primary care [19]. The validity of the depression module (PHQ-9) of the PHQ for screening major depressive episodes was confirmed in primary care, medical outpatient services and specialist medical services [20,22]. Two recent meta-analyses have reliable sensitivity numbers (0.80 and 0.77, respectively) and specificity data (0.92 and 0.94, respectively) for the PHQ-9. These numbers correspond with the DSM-IV diagnosis of major depressive disorder or major depressive episodes in primary care clinics and non-psychiatric clinics [20,22]. In this study, we used the Japanese version of the PHQ-9. The