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Appendix: List of stimuli sets

Frustrating situations explained using text and pictures.	Condition	Verbal response
1. Although it was a short distance to the destination, I take a taxi. The taxi driver says, "You can walk there."	SW	I will walk there.
	SWo	I should have taken a bus.
	OW	Please take me there.
	OWo	You shouldn't have said that.
2. After I am covered by mud splashed by a car on the road, the driver says, "I am sorry for splashing the mud."	SW	I will send it to the laundry.
	SWo	I shouldn't walk on this road.
	OW	You should get off a car first.
	OWo	Why can't you be careful?
3. When I am 5 minutes late for a part-time job, the boss says, "Do you know what time it is?"	SW	I'm sorry, I'll be careful from now on.
	SWo	I shouldn't have taken a part-time job.
	OW	Tell me what I should do now.
	OWo	You shouldn't get mad, it's only 5 minutes.
4. Although I want to go to the sixth floor by elevator, I push the button for the fifth floor by mistake. When the elevator stops at the fifth floor, a lady on the elevator says, "Is anyone getting off on the fifth floor?"	SW	Thank you for asking.
	SWo	I pushed the button for the fifth floor by mistake.
	OW	Please close the door.
	OWo	You should have noticed without asking.
5. I treat my assistant to sushi. Although he eats a lot of sushi, he says, "May I order more?"	SW	You may order and eat more.
	SWo	I shouldn't have treated him.
	OW	You should make sure you're hungry
	OWo	You shouldn't eat so much.
6. At the cash register of an expensive restaurant my friend says "I don't have any money on me, please pay the bill."	SW	I will pay the bill
	SWo	I should have chosen a less expensive restaurant.
	OW	I will wait while you go

		withdraw money.
	OWo	You should have brought enough money.
7. At the cash register of a restaurant at which I planned to use a coupon for a 30% discount, the cashier says, "You can't use this coupon today."	SW	I will pay with a credit card.
	SWo	I should have confirmed it in advance.
	OW	Call the store manager.
	OWo	You shouldn't have made such a confusing coupon.
8. I have eaten the last piece of cake in the refrigerator. My colleague says, "You should have left one for me."	SW	I will buy another cake.
	SWo	I shouldn't have eaten it.
	OW	You can buy another cake.
	OWo	You should have told me you wanted cake.
9. When I try to join a sports club, the receptionist says, "Students cannot register as club members."	SW	I will join after I graduate.
	SWo	I should have checked that.
	OW	Will you let me register as a member if I pay the fee?
	OWo	Why can't students become members?
10. I confidently ask a question at the conference, but the chairman says, "Don't you understand such a simple concept?"	SW	I will find the answer myself.
	SWo	It was a stupid question, wasn't it?
	OW	Can I get an answer soon?
	OWo	You shouldn't have said that.
11. When I get to the early morning lecture, "Today's lecture is canceled" is written on the blackboard.	SW	No way! I will take a nap here.
	SWo	I should have checked the bulletin board.
	OW	Is there someone who has nothing to do with?
	OWo	The teacher should have notified us.
12. When I try to get a ride in a friend's car, he says, "I have lost the car keys."	SW	I will ask another friend.
	SWo	I should have said I would walk.

	OW	You should look for the keys.
	OWo	You should have checked to see that you have them.
13. While walking down a narrow hallway, I bump into a stranger, and he says, "Shit! Look out."	SW	I'm sorry. I will walk closer to the wall.
	SWo	I shouldn't have walked down this narrow hallway.
	OW	You should give way.
	OWo	You shouldn't have said such a thing.
14. When I take out burnable garbage, a neighbor says, "Today is a non-burnable trash day."	SW	I will take out non-burnable garbage.
	SWo	I should have checked it.
	OW	When is the next burnable trash day?
	OWo	No one notified me.
15. After waiting for 2 hours at the hospital, I ask the receptionist, "How much longer do I have to wait?" She says, "You must wait a while because an emergency patient has come in."	SW	I will wait for a while.
	SWo	I should have gone to another hospital.
	OW	Please examine me soon.
	OWo	Do you know how long I have been waiting?
16. A friend returns a magazine that I have lent to him and says, "I'm sorry, my younger brother has torn this."	SW	OK, I will buy a new one.
	SWo	I shouldn't have lent it to him.
	OW	You should buy a new one.
	OWo	You shouldn't have let your brother see it.

In the actual acting task, subjects viewed the text and pictures explaining the frustrating situations. The original version was written in Japanese.

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Effects of the Higashi-Nihon Earthquake: Posttraumatic Stress, Psychological Changes, and Cortisol Levels of Survivors

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Abstract

On March 11, 2011, the Pacific side of Japan's northeast was devastated by an earthquake and tsunami. For years, many researchers have been working on ways of examining the psychological effects of earthquakes on survivors in disaster areas who have experienced aftershocks, catastrophic fires, and other damage caused by the earthquake. The goal of this study is to examine scores on psychological measures and salivary cortisol level in these individuals both before and three months after the earthquake. The participants had been measured for these variables before the earthquake. After the earthquake, we carried out PTSD screening using CAPS for participants for another experiment, and then again conducted the aforementioned tests. We collected saliva samples from all survivors. Our results show that social relationship scores on the WHO-QOL26, negative mood scores of the WHO-SUBI, total GHQ score, POMS confusion scores, and CMI emotional status score after the earthquake showed scores indicating significantly decreased compared to before the earthquake. On the other hand, salivary cortisol levels after the earthquake was significantly increased compared to before the earthquake. Moreover, the result of a multiple regression analysis found that negative mood score on the WHO-SUBI and social relationship score on the WHO-QOL26 were significantly related to salivary cortisol levels. Our results thus demonstrate that several psychological stress induced by the earthquake was associated with an increase in salivary cortisol levels. These results show similar findings to previous study. We anticipate that this study will provide a better understanding of posttraumatic responses in the early stages of adaptation to the trauma and expand effective prevention strategies and countermeasures for PTSD.

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Introduction

On March 11, 2011, at 2:46 pm, the Higashi-Nihon Earthquake (the Great East Japan Earthquake), the largest disaster to occur in Japan since World War II, hit three prefectures (Miyagi, Iwate, and Fukushima) on the Pacific side of northeastern Japan, with lesser damage in several other prefectures. These regions were severely damaged by the magnitude 9 earthquake and ensuing tsunami. The coastal communities of Kesennuma, Ishinomaki, and Minamisanriku were particularly devastated by the earthquake. More than 20,000 people were killed or went missing as a result of the tsunami and fires after the earthquake, and over 240,000 homes were damaged or destroyed. Immediately after an earthquake, people affected are damaged both physically and emotionally. Even now, the region is fighting intermittent aftershocks.

Over the past dozen years or so there have been several serious disaster events in Japan, including the Hokkaido Nansei-oki Earthquake of 1993, the Great Hanshin-Awaji earthquake of 1995, shocking cases such as the sarin gas attack on the Tokyo subway system in 1995, and so on. Many researchers have studied survivors' mental health and physical changes after such events [1–6]. According to many previous studies of survivors of disaster areas, prevalence of posttraumatic stress disorder (PTSD) ranging from approximately 5 percent to 60 percent is seen in the first 1–2 years after a disaster [7,8]. Further, more than 60 percent of survivors of disasters are at high risk of PTSD [9]. Fujimori and Fujimori (1996) have researched the mental health of survivors of the Hokkaido Nansei-oki Earthquake and pointed out that survivors can be in critical psychological condition six month after such a disaster [6]. Thus, it has been pointed out that mental health problems of survivors are most evident a certain amount of time after a disasters [10].

Previous studies have reported that based on individual difference and the type of disaster, the rate of psychiatric disorders among survivors either decreased after the second year or was prolonged and became chronic [5,6,11–13]. There are growing concerns about the development of PTSD in people from the disaster-affected areas. In the Great Hanshin-Awaji Earthquake in 1995, many survivors were injured in mind and body and had mental health problems [9]. Even now, some survivors of this earthquake suffer some sort of trauma.

With regard to the relationship between stress and the body, Cannon (1929) and Selye (1956) provide the foundation for the current interest in this physiological phenomenon [14–15]. In addition, McEwen and Stellar suggests that chronic stress responses involve actual physiological changes to body systems and organs, and considerable attention has been paid to acute physiological stress responses and how they might possibly lead to subsequent chronic stress responses [16]. Other previous studies suggest that PTSD is associated with behavioral and physiological pathology, which includes disruption of the hypothalamic–pituitary–adrenal (HPA) axis [15,17]. The HPA axis is involved in mediating physiological responses to stress and the secretion of the stress hormone cortisol [18]. Cortisol is considered an indicator of psychological and physiological stress and can be used in examining the pathophysiology of PTSD [19]. Some previous studies on cortisol data in PTSD report that cortisol level are high when people feel heavily stressed, a symptom of PTSD that can result from events including but not limited to earthquakes, war, accidents, abuse, or radioactive damage [20–22]. During the Hanshin-Awaji earthquake, people who had severe PTSD were found to have significantly higher cortisol levels [2]. Cortisol can be extracted from blood, urine, and saliva. Sampling by saliva collection has attracted attention for being a less stressful and invasive method for estimating cortisol levels than other methods of extraction [23–26]. Salivary cortisol level have been reported to reflect unbound forms of blood cortisol in particular, and a very high correlation has been reported between plasma and salivary cortisol levels [25–27]. To our knowledge, no study has yet examined psychological and physiological changes in survivors before and after the Great East Japan Earthquake.

In this study, we examined that these changes by collecting samples before the earthquake and three months after the earthquake. We hypothesized that psychological measures regarding the mental health of survivors, such as depression, anxiety would worsen and the saliva cortisol level of survivors would increase, three months after the earthquake, compared to before the earthquake. Our hypothesis was based on the previous studies mentioned above.

Methods

Ethics Statement

Written informed consent was obtained from each subject, in accordance with the Declaration of Helsinki (1991). This study was approved by the Ethics Committee of Tohoku University.

Participants

The study was performed three months after the Great East Japan Earthquake occurred. A total of 14 participants (men: 7; women: 7; age range: 19–26) were recruited from among undergraduate and postgraduate students at Tohoku University. All participants experienced the Great East Japan Earthquake. They live in Sendai and the surrounding areas, including the areas closest to the epicenter of the earthquake. All participants had participated in past psychological experiments and saliva cortisol experiments conducted in our laboratory, and had undergone psychological tests and saliva cortisol tests within the past six months and before the earthquake (experimental period: February 8 to March 7, 2011). All participants were screened for absence of neuropsychiatric disorders using the Mini-International Neuropsychiatric Interview (MINI) [28,29] and all participants were also interviewed by trained psychologists (initials: AO, NA, NS, and YW) using the Clinician-Administered PTSD Scale (CAPS) [30,31], a structured interview for screening for posttraumatic stress symptoms. CAPS generally requires that the interviewer undergo a psychiatric diagnostic interview. In accordance with the MINI, no participant was diagnosed as having PTSD. Of the 14 participants, each filled more than one but not all the criteria of three clusters of PTSD symptoms, including re-experiencing of the event, avoidance, and hyperarousal.

Psychological Measures

To assess any change in quality of life, happiness, and mental health of participants from before to after the earthquake, we administered the following questionnaires to participants.

World Health Organization Quality of Life 26 (WHO-QOL26). The World Health Organization Quality of Life 26 (WHO-QOL26) is a 26-item self-report measure designed to assess quality of life (QOL). Twenty-four items measure the four domains of QOL–physical, psychological, social, and environmental–and the other two items measure overall QOL and general health. The score for each question ranges from 1 to 5; higher scores reflect higher QOL. This study used the Japanese version of the WHO-QOL26, which was created by Tasaki and Nakane (1997) [32].

World Health Organization Subjective Well-being Inventory (WHO-SUBI). The World Health Organization Subjective Well-being Inventory (WHO-SUBI) is a 41-item self-report measure designed to assess subjective well-being [33,34]. The score for each question ranges from 1 to 3. The WHO-SUBI measures two types of subjective well-being. One is "positive affect," which is measured by the indices of good psychological health (19 items), while the other is "negative affect," which is measured by the indices of poor psychological health (21 items). Thus, the test evaluates the positive and negative aspects of 11 factors: sense of satisfaction, sense of achievement, self-confidence, sense of happiness, support of close relatives, social support, family relationships, sense of spiritual control, sense of physical ill health, and dissatisfaction with social ties. The reliability and validity of the Japanese version have been demonstrated by Ono et al. [35,36].

General Health Questionnaire (GHQ30). The General Health Questionnaire (GHQ30) is self-report measure designed to assess underlying psychological distress. This questionnaire comprises 30 questions covering a range of neurotic symptoms, with an emphasis on those typical of anxiety and depression and with a deliberate avoidance of those that might also reflect physical illness [37]. The responses are made on a four-point ordinal scale. The response for each item is scored from 0 to 3 and then summed over the 30 items (range 0–90). This study used the Japanese version of the GHQ30, which was created by Nakagawa and Daibo (1996) [38].

Profile of Mood States (POMS). The Profile of Mood States (POMS) is a 65-item self-report measure designed to assess seven aspects of mood (anxiety/tension, depression/dejection, anger/hostility, confusion/bewilderment, vigor/activity, fatigue/inertia, and friendship). Factor analyses by the developers failed to confirm the friendship domain, and although the guidelines for administration that were followed in this trial continue to include the seven friendship items, they are no longer reported as a POMS subscale or included in the TMD score [39]. Responses to each item range from 0 to 4, with higher scores indicating a more negative mood. This study used the Japanese version of the POMS, which was created by Yokoyama and Araki (1994) [40].

Cornell Medical Index (CMI). The Cornell Medical Index (CMI) consists of 18 sections and 195 items. The A–L sections (144 items) represent physical state and the M–R sections (51 items) represent mental state. Participants answered "yes" or "no" to indicate the presence or absence of a symptom or disorder. If the answer was "yes," it indicated that the patient had symptoms and received a score of 2. On the other hand, a "no" answer indicated that the patient had no symptoms and was scored at one point [41]. This study used the Japanese version of the CMI, which was created by Kanehisa and Fukamachi (1972) [42].

Saliva sampling. We collected saliva samples from participants to measure salivary cortisol level. In consideration of the circadian cortisol rhythms of the participants, we collected saliva samples across the board at 5 pm on weekdays, both pre-examination (before the earthquake) and post-examinations (after the earthquake). The reason we selected 5 pm is because people at this time of day are less affected by circadian cortisol rhythms [43] and we wished to consider participants' experimental spread-over. We also ordered participants to refrain from drinking, eating [44] and exercise [45] for two hours before saliva sampling.

Sampling Strategy

Saliva samples were collected using the salivette (Sarstedt, Nümbrecht, Germany) and centrifuged at 3,000 rpm for 5 minutes. We stored the supernatant solution in an airtight container at minus 80 degrees and measured cortisol using the solution. We measured the cortisol with a semi-microcolumn High Performance Liquid Chromatography (HPLC) system (Shiseido, Tokyo). For reagents, we used cortisol and cortisone (Nacalai Tesque, Inc., Kyoto).

The acetonitrile and methanol used were those available on the market. As for the standard solution of CS and CZ, the CS and CZ were dissolved in methanol so that 0.1 mg/ml each (CS: 275.9 nmol/ml, CZ: 277.5 nmol/ml) was used as the original liquid; this was then diluted with 100% methanol or 10% methanol (for CS and CZ, respectively) to be the standard solution used. As for the semi-microcolumns, we used the Capcell Pak MF Ph-1 (4.6 micrometer i.d. times 50 mm) from Shiseido Co., Ltd. as the semi-microcolumn for the preprocessing column, Capcell Pak C18 UG120 (1.5 micrometer i.d. times 250 mm) of Shiseido Co., Ltd. as the semi-microcolumn for the analytical column, and Capcell Pak C18 UG120 (2.0 micrometer i.d. times 35 mm) of Shiseido Co., Ltd. as the semi-microcolumn for the concentrating column.

For HPLC analysis, we set the following conditions: the mobile phase for preprocessing used 5 millimoles per liter phosphoric acid buffer solution (pH = 6.9) and acetonitrile at a ratio of 98/2, and the solution was sent at the flow rate of 1 ml/min. The mobile phase for measurements used 10 millimoles per liter phosphoric acid buffer solution (pH = 6.9) and acetonitrile at a ratio of 78/22, and the solution was sent at the flow rate of 0.1 ml/min. The column temperature was kept constant at 35 degrees Celsius with the detection wavelength set at 242 nm. The duration of salivary cortisol levels was 50 min per sample.

Experimental Procedure

In this study, participants were measured within subject, pretest (before the earthquake) and posttest (after the earthquake). Both of these experiments followed the same procedure. Participants were tested in the lab of university at weekday afternoon. Participants received experimental suggestions from experimenter and were answered all psychological measures prepared by experimenters in the time given. Participants were allowed 60 min as response time to psychological measures. Then, participants took a saliva sampling at 5 pm. Saliva sampling time was for about five minute. Total experimental time was 65 minutes.

Statistical Analyses

The statistical analyses of psychological and salivary cortisol data between participants the high PTSD score group and the low PTSD score group were analyzed using the statistical software PASW Statistics 18 for Windows (SPSS Inc, Chicago). Pre- and post-levels of measured variables were analyzed by a paired t-test, and exacerbating factors in salivary cortisol were analyzed by multiple regression analysis. We set the significance level at $p<0.05$.

Results

First, we examined sex differences in salivary cortisol level, because several previous studies have indicated that it shows a sex difference in stress response [46–48]. The result showed no significant differences between males and females (Table 1). We thought that males and females might not differ in the face of the statistics, so we put all of the data together and analyzed it.

Next, the comparison results for the data obtained from these tests are shown in Table 2. First, we examined changes in the scores of the psychological measurements before and after the earthquake. According to the results of the paired t-test, positive scores on the WHO-SUBI, negative scores on the WHO-SUBI, and the social relationship score of the WHO-QOL26 significantly increased (positive score of the WHO-SUBI: $t = 2.166$, degree of freedom [df] = 13, $p = 0.05$; negative score of the WHO-SUBI: $t = 3.183$, $df = 13$, $p = 0.01$; social relationship score of the WHO-QOL26: $t = 2.222$, $df = 13$, $p = 0.05$). Emotional status per the CMI and confusion score per the POMS also significantly increased (emotional status: $t = -2.471$, $df = 13$, $p<0.05$; confusion score: $t = -3.633$, $df = 13$, $p<0.01$).

Next, we measured cortisol levels from after the earthquake. The results of the comparison of salivary cortisol level before and after the earthquake are given in Table 2; they show that salivary cortisol level had increased by three months after the earthquake, a difference with statistical significance ($t = -2.745$, $df = 13$, $p<0.05$).

To pinpoint the exacerbating factors in salivary cortisol level, a multiple regression analysis was conducted using the difference between salivary cortisol level before and after the earthquake as the objective variable. The CAPS score, positive score on the WHO-SUBI, negative score on the WHO-SUBI, and the social relationship score of the WHO-QOL26 were used as explanatory variables. The results of the multiple regression analysis are shown in Table 3. It was found that negative scores on the WHO-SUBI and the social relationship score of the WHO-QOL26 were factors significantly related to salivary cortisol level.

Discussion

To investigate psychological changes among the survivors in the disaster area before and three months after the earthquake, we

Table 1. Sex differences of the participants.

	Men (N = 7)	Women (N = 7)	P value
Before the earthquake (mean±SD)	4.3529±2.8122	4.153±2.8992	0.898[a]
After the earthquake (mean±SD)	14.3546±12.6064	9.2219±5.5099	0.343[a]

[a]: an independent-samples t-test.
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Table 2. Characteristics of the participants.

Age [years], (mean±SD)	**20.64±2.53**		
CAPS Total score, (mean±SD)	**17.07±9.38**		
	Before the earthquake	**After the earthquake**	***P value***
The WHO-QOL26 Physical functioning, (mean±SD)	3.07±0.63	2.81±0.38	0.09[b]
The WHO-QOL26 Psychological functioning, (mean±SD)	3.26±0.6	3.27±0.59	0.865[b]
The WHO-QOL26 Social relationship, (mean±SD)	3.67±0.87	3.26±0.83	**0.045**[b]
The WHO-QOL26 Environmental functioning, (mean±SD)	3.63±0.64	3.46±0.5	0.202[b]
The WHO-QOL26 Global functioning, (mean±SD)	3.54±0.5	3.61±0.86	0.789[b]
The WHO-SUBI positive score, (mean±SD)	41.43±7.71	37.5±5.68	**0.05**[b]
The WHO-SUBI negative score, (mean±SD)	52.36±6.54	47.14±5.63	**0.007**[b]
GHQ score, (mean±SD)	5.64±5.88	7.79±6.59	0.375[b]
POMS Tension-Anxiety score, (mean±SD)	53.36±10.4	54.36±12.29	0.77[b]
POMS Depression-Dejection score, (mean±SD)	51.71±10.58	46.0±17.47	0.381[b]
POMS Anger-Hostility score, (mean±SD)	44.57±7.14	47.21±17.26	0.615[b]
POMS Vigour-Activity score, (mean±SD)	50.86±7.42	47.86±15.33	0.577[b]
POMS Fatigue-Inertia score, (mean±SD)	52.64±10.12	53.07±15.83	0.915[b]
POMS Confusion score, (mean±SD)	51.0±9.54	65.14±13.92	**0.003**[b]
POMS Total Mood Disturbance score, (mean±SD)	202.43±38.84	217.93±29.96	0.3[b]
CMI somatic status score, (mean±SD)	14.57±8.67	18.21±15.74	0.278[b]
CMI emotion status score, (mean±SD)	7.64±6.33	19.14±21.07	**0.028**[b]
Salivary cortisol level, (mean±SD)	4.25±2.45	11.79±9.72	0.17[b]

[b]: Paired t-test.
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used psychological measures and salivary cortisol level. The results show that salivary cortisol levels increased after the earthquake. The exacerbating factors in this increase were negative scores on the WHO-SUBI and (higher) social relationship score of the WHO-QOL26. Our findings were consistent with the results of previous studies, such as those on the Hanshin-Awaji earthquake of 1995 and the Wenchuan earthquake of 2008 which were associated with higher cortisol level [2,4]. The relationship between higher cortisol levels and psychological stress suggests that high stress conditions induce an alteration in the HPA axis and stimulate the release of cortisol [49–51].

Some exacerbating factors in salivary cortisol level may have included anxiety as a result of the disruption of access to daily information, damage to homes or businesses, and lifeline damage such as interruption of water supply, gas supply, or electrical power supply. Another possible factor was logistical disruption and resultant shortages of food, drinking water, and gasoline. Many people who were in the disaster still spend their days feeling stress, fear, fatigue, helplessness, disappointment [11], and so on. It would appear that these factors still influence psychological responses to the disaster three months after the earthquake. Previous studies have suggested that psychological responses in times of disaster can be categorized into three steps: "Reactions,"

Table 3. Results of a multiple regression analysis of change in salivary cortisol levels before and after the earthquake.

Explanatory variable	**Objective variable**	
	Change in salivary cortisol levels before and after the earthquake	
	β	**p**
CAPS score	1.02	**0.004**
Positive score of the WHO-SUBI	−0.022	0.923
Negative score of the WHO-SUBI	0.717	**0.021**
Social relationship score of the WHO-QOL26	0.653	**0.029**
R^2	0.696	

*β: Standardized Coefficients.
R^2 : R Squar.
P: Significance probability.
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"Factors," and "Psychodynamics" [52,53]. "Reactions" are the psychological states associated with the stress situation, "Factors" are the various kinds of circumstance said to contribute to the reactions observed, and "Psychodynamics" are the character and mode of operation of the alleged relationships between the normal or abnormal reactions observed and the factors contributing to them [52]. The current situation in the disaster area is in transition from Factors to Psychodynamics. There are cases of spontaneous psychological recovery; however, many survivors still have strong negative feelings such as depression, anger, and disconcertment around the earthquake. It would appear that living conditions changed dramatically soon after the earthquake disaster because of temporary living in evacuation centers, the inconvenience of getting things, lack of essential utilities, etc. Moreover, as people had to live in an environment that was complex and unfamiliar, it is considered that they felt more anxiety and fatigue than usual in their daily living and human relationship [54]. With these points in mind, we consider that the altered daily life environment and psychological stress caused by the disaster influenced an increase in salivary cortisol level. In summary, our study demonstrated that the severe psychological stress induced by the Great East Japan Earthquake was associated with salivary cortisol level and that psychological changes resulted from this earthquake, although the difference was not significant.

In the way of limitations of this study, four points should be noted. 1) The sample size of this study was very small. This is because the psychological and saliva cortisol data from before the earthquake were conducted for the purpose of collecting baseline data for other preliminary experiments, and the number of participants in the preliminary experiment was 14. This study compared the data of these 14 participants before the earthquake and three months after the earthquake. 2) We could not consider gender-differentiated salivary cortisol levels or psychological measures, because the numbers of men and women in participants was very small and because the salivary cortisol levels of participants showed no significant difference by gender. 3) Because this study compared data before the earthquake three months after the earthquake, we did not use new depression scales such as the Center for Epidemiologic Studies Depression scale (CES-D) or the Self-rating Depression Scale (SDS). 4) We did not check or consider coping behavior or resilience of survivors, for the same reason as in point 3.

In the future, we plan to examine the following three points: 1) First, we will examine change in activity of natural killer cells before and after the earthquake, because these cells are associated with cortisol levels and immune activity in stress conditions [55]. We already have blood samples from participants, obtained before and three months after the earthquake. Therefore, we will immediately analyze the change in activity of natural killer cells in the blood. 2) Second, we will examine the same variables in the same participants six months, twelve months, or three years after the earthquake, as a follow-up study. Some previous studies about earthquakes have done follow-ups a few years later [56–59]. We consider it very important for the mental health of survivors to track psychological changes and salivary cortisol levels over time. 3) As an additional experiment, we are considering studying survivors living in the coastal area devastated by the earthquake. This study was conducted with survivors living in Sendai and the surrounding, areas which were less affected by the earthquake. The reason we were unable to study coastal survivors was that we did not have psychological and saliva data from them before the earthquake. However, time has passed since the Great East Japan Earthquake, and we think that it is important to conduct a longitudinal study of the mental health of survivors living in the area most severely affected by the earthquake. And not only that, we need to consider the importance of examining the new lifestyles and psychological support for survivors based on the outcomes of studies. To gather further data, we feel that a cohort study of these individuals is important; although we will not have data from before the earthquake to fall back on, we will be able to assess changes over time using the longitudinal cohort model. Therefore, we want to examine these issues after improvements of the methodology used in this study.

In conclusion, more than half a year after the earthquake, rebuilding efforts in the disaster area are very slow. Many survivors still have to confront painful situations such as life stress after the earthquake, disparity between survivors in the disaster area, employment problems, and the effect of radiation. Especially in the worst-affected coastal area, survivors have become extremely unstable. Our overarching mission is to assess about change over time in physical and mental health of many people damaged by earthquake using scientific methods.

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Author Contributions

Conceived and designed the experiments: YK RK. Performed the experiments: YK. Analyzed the data: YK. Contributed reagents/materials/analysis tools: YK. Wrote the paper: YK.

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Causal Relationship Between Psychological Distress After a Severe Earthquake and Brain Structural Changes

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Abstract— **Brain gray and white matter structural alternations in several brain regions including hippocampus, amygdala, the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) were reported in patients with posttraumatic stress disorder (PTSD) or stressful life events. However, the causal relationship between psychological distress after stressful life events and the structural alteration has remained unclear, because of difficulties with prospective studies. A magnitude 9.0 earthquake hit Japan on March 11, 2011. Many survivors, even those without PTSD, needed psychological support. Since we had much structural MRI data from subjects living around Sendai city area before the quake, this tragedy provided a rare opportunity to investigate longitudinal brain structural changes associated with such a disaster. In this article, we introduce our recent investigations which revealed the brain structural alternations as (a) vulnerability factors and (b) acquired signs of psychological distress after the disaster. Actually, we had collected structural MRI data from a group of healthy subjects before the quake, and we recruited 42 subjects from this group to examine their structural MR images 3 to 4 months after the quake. We demonstrated that smaller regional grey matter volume (rGMV) in the right ventral ACC, and lower fractional anisotropy (FA) in the right cinglum (Cg) before the earthquake were vulnerability factors of psychological distress after the earthquake, and decreased rGMV in the left OFC and increased FA in the left Cg and uncinate fasciculus (Uf) from before to after the earthquake were acquired signs of psychological distress after the earthquake. The findings provide further evidence that the ACC/Cg and the OFC/Uf, which are involved in fear conditioning, and emotional regulation, play an important role in the pathogenesis of PTSD.**

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I. Introduction

The Great East Japan Earthquake, a severe earthquake with a magnitude of 9.0, hit Japan on March 11, 2011. Stress-related disorders such as acute stress disorder and posttraumatic stress disorder (PTSD) are likely to occur among a large number of survivors following a severe disaster [1], and even those without PTSD often require psychological support [2]. In fact, many survivors maintain high anxiety levels due to the earthquake aftermath including frequent aftershocks and dispersed radioactive material leaking from nuclear plants [3]. Distinguishing neurological underpinnings as a vulnerability factor from the acquired signs of psychological distress soon after a disaster among non-PTSD survivors might contribute to a better understanding of posttraumatic responses, early detection of PTSD, and PTSD prevention among survivors.

The neurological underpinnings of patients with PTSD [4–6] as well as those of non-PTSD subjects after stressful life events [7, 8] have been well characterized. Previous neuroimaging studies of patients with PTSD revealed morphological changes in several brain regions, including the hippocampus [4], amygdala [4], anterior cingulate cortex (ACC) [9–11], insula [12] and orbitofrontal cortex (OFC) [13–15], which were also found in healthy adults after stressful life events [7, 8]. Recently, diffusion-tensor imaging (DTI) [16] was used to investigate white matter structural changes in patients with PTSD [17–20], also in health survivor of a disaster [21]. DTI is used to measure the magnitude and direction of water diffusion [i.e., fractional anisotropy (FA)] in brain tissue. FA is modulated by the degree of myelination, axonal membrane thickness and diameter, and/or the amount of axon parallel organization [22, 23] and is thus an indicator of white matter pathway strength or integrity. Previous DTI studies suggest that PTSD patients have altered white matter integrity in the anterior cingulum (Cg) which is adjacent to the anterior cingulate cortex (ACC) [17–20].

Nevertheless, the causal relationships between the brain structural changes and the psychological response to stressful life events remained unclear, because of difficulties with prospective studies [24]. Although, some longitudinal studies had examined patients with PTSD after traumatic events, they failed to find longitudinal brain structural changes [13, 25, 26]. Longitudinal changes of white matter integrity in subject with PTSD or stressful life events were unexamined. Even a recent longitudinal study revealed that decreased volumes in the ACC and hippocampus/ parahippocampus were associated with the number of stressful life events, the impacts of stress related responses on brain structure were not examined [7]. Evaluation of monozygotic twin pairs with combat-related PTSD has provided evidence that smaller hippocampal volume is a vulnerability factor for PTSD [27], and smaller pregenual ACC represents an acquired sign of PTSD [10]; however, the significance of longitudinal structural changes within individuals as vulnerability factors and acquired signs of psychological distress have remained unclear.

In this article, we introduce our recent investigations which revealed the brain structural alternations as vulnerability factors and acquired signs of psychological distress after the earthquake [28, 29], based on a longitudinal study of structural MRI data obtained before and after the earthquake in normal subjects. In fact, we had collected much structural MRI data from a group of healthy subjects before the quake. Therefore, this tragedy provided a rare opportunity to investigate brain structural changes associated with such a disaster. Forty two subjects were recruited from this group to examine MR images 3–4 months after the earthquake. PTSD symptoms were also assessed using the Japanese version of the clinician-administered PTSD scale (CAPS) structural interview [30]. Anxiety levels were assessed by using the Japanese version of the State–Trait Anxiety Inventory (STAI) [31, 32]. We hypothesized that (a) vulnerability factors for psychological distress after the earthquake could be detected by a significant association with individual differences of bran structures before the earthquake, and (b) the acquired signs could be detected by a significant association with individual difference of brain structural changes from before to after the earthquake around brain regions previously implicated in PTSD.

II. Materials and Methods

A. Recruitment and selection of participants

Eligible participants were recruited from undergraduate and postgraduate students of the Tohoku University community, who met the eligibility criteria of having no history of neuropsychiatric disorders and right-handed. All candidates had participated in past MR imaging experiments conducted in our laboratory undergone structural MR imaging within the 2 years before the earthquake, and declared agreements for re-analyses of MR images scanned before the earthquake in advance. Since all the candidates lived around Sendai city, where was strongly affected by the earthquake, we did not plan to recruit control subjects without experiencing the earthquake. Neuropsychiatric disorders were screened by using the mini international neuropsychiatric interview (M.I.N.I.) [33, 34]. Handedness was assessed by the Edinburgh Handedness Inventory [35]. Among numerous candidates in our database of the past experiments, we could contact with forty two of them. All candidates met above eligible criteria and made written informed consents before participating in the current study to examine possible effect of psychological trauma on brain structure, in accordance with the Declaration of Helsinki [36]. The M.I.N.I. confirmed that no subject had any history of psychiatric illness including PTSD and no subjects were exposed to life-threatening experiences due to the earthquake and tsunami, as well. The current study and all previous studies were approved by the Ethics Committee of Tohoku University.

B. Psychological evaluations

All participants were interviewed by trained psychologists using the CAPS structured interview [30, 37]. In accordance with the M.I.N.I., no subject was diagnosed as having PTSD. Of the 42 participants, 8 subjects filled more than one but not all criteria of three clusters of PTSD symptoms including re-experiencing of the event, avoidance and hyperarousal. In addition, the highest total CAPS score was 39, which is categorized as subthreshold PTSD [38]. Therefore, we could regard all subjects as non-PTSD. Levels of anxiety and depression were evaluated using the state-trait anxiety inventory [31, 32] and the Center for Epidemiologic Studies Depression Scale [39, 40]. The diagnostic structured interview and MR imaging were conducted at 3 to 4 months after the earthquake. All psychological measurements were evaluated only after the earthquake. Demographic characteristics of the subjects are shown in Table 1.

Table 1. Demographic characteristics of non-PTSD survivors

Number of subjects (male/female)	42 (33/9)
Age (years)	21.7 ± 1.7
Number of previous lifetime traumas	1.98 ± 0.98
Periods (days) from pre- to post-earthquake MR scans	244.4 ± 137.8
CAPS	
Total	5.7 ± 10.0
Re-experience	1.6 ± 2.5
Avoidance	2.0 ± 4.4
Hyperarousal	2.1 ± 4.5
CESD score	11.6 ± 10.2
STAI scores	
State	41.6 ± 11.4
Trait	43.0 ± 10.0

Values are shown as mean ± standard deviation.

CESD, Center for Epidemiologic Studies Depression; STAI, state-trait anxiety inventory.

C. Image acquisition

All MR imaging data acquisition was conducted with a 3-T Philips Intera Achieva scanner. Using a MPRAGE sequence, high-resolution T1-weighted structural images (240 × 240 matrix, repetition time = 6.5 ms, echo time = 3 ms, field of view = 24 cm, 162 slices, 1.0 mm slice thickness) were collected from all the subjects. Of the 42 subjects, 30 subjects who had undergone DTIs before the earthquake underwent DTIs after the earthquake, as well. The diffusion-weighted data were acquired using a spin-echo EPI sequence (TE = 55 ms, FOV = 22.4 cm, 2 × 2 × 2 mm^3 voxels, 60 slices). The diffusion weighting was isotropically distributed along 32 directions (*b* value = 1,000 s/mm^2). Additionally, a data set with no diffusion weighting (*b* value = 0 s/mm^2; b0 image) was acquired. Detailed information about MR images data acquisition were described in our previous articles [28, 29].

D. Pre-processing of MR imaging data and statistical analysis

(1) MR imaging data analysis for rGMV

Pre-processing and data analysis of rGMV were performed following steps. First, post-earthquake images were coregistered with pre-earthquake images in each subject on SPM2. Preprocessing of the morphological data was performed with VBM2 software [41], an extension of SPM2. The resulting maps representing the rGMV before the earthquake (Pre rGMV) and the rGMV change between before and after the earthquake (Post-Pre rGMV) were then forwarded to the group-level analysis. The group level analysis tested for the relationship between individual severity of PTSD symptoms measured by the CAPS and rGMV. Voxel-by-voxel multiple regression analyses were performed using the CAPS scores for Pre rGMV and Post-Pre rGMV on SPM5. The analysis was performed with age, total brain volume, and periods between pre- and post-earthquake MR imaging data acquisition as additional covariates. A significant level was set at $P = 0.05$ corrected for multiple comparisons. Small volume correction (SVC) [42] was performed to examine each ROI with a hypothesis (amygdala, hippocampus, insula, ACC and OFC) [4, 9–15] using a lenient threshold of $P = 0.001$ uncorrected, and a $\kappa = 100$ to suppress the possibility of small clusters arising by chance. Finally, to verify the effect of the structural changes on the CAPS scores, regression analysis was performed employing Pre rGMV and Post-Pre rGMV at peak voxels in each cluster as explanatory variables, and total scores of CAPS as independent variables.

(2) Diffusion tensor imaging data analysis for FA

Pre-processing and data analysis of diffusion tensor images were performed using statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA, USA). The FA map image of each participant was spatially normalized to give images with 2 × 2 × 2 mm voxels and spatially smoothed using a Gaussian kernel of 10 mm FWHM. The resulting maps representing the FA were then forwarded to a group regression analysis. The group-level analysis tested for a relationship between individual state anxiety as measured by the STAI and regional FA. Voxel-by-voxel multiple regression analyses (VBA) were performed using the state anxiety for Pre FA and Post – Pre FA in VBM5 on SPM5. The analysis was performed with sex and period between pre- and post-earthquake MR imaging data acquisition as additional covariates. All tests of FA were performed using an absolute threshold of FA >0.2 [43]. Significant regions were inferred using cluster-level statistics [44]. Only clusters with a *p*-value <0.05 after correction for multiple comparisons at cluster size and an uncorrected voxel-level cluster-determining threshold of $p < 0.0025$ were considered statistically significant in this analysis [45]. Finally, to evaluate the relative association strength between white matter structural changes and state anxiety level, we applied structural equation modeling (SEM) by employing state anxiety scores from STAI, Pre FA, and Post – Pre FA at peak voxels in each cluster as observed variables.

Detailed information about MR imaging data and statistical analysis were described in our previous articles [28, 29].

TABLE 2. MNI COORDINATES, VOXEL SIZES, Z SCORES AND *P* VALUES FOR RESULTS OF THE SPM ANALYSES

Brain region	MNI coordinates			κ (voxels)	z scores	*P* values (SVC)
	x	y	z			
Pre						
Rt ACC	6	34	0	145	3.76	0.020
Post-Pre						
Lt OFC	−24	52	−6	124	4.03	0.034

MNI, Montreal Neurological Institute; Rt, right; Lt, left.

ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; Rt, right; Lt, left

III. RESULTS

A. VBM results for rGMV

After controlling for age, total brain volume, and periods between pre- and post-earthquake MR imaging data acquisition, the total scores of CAPS were significantly associated with smaller Pre rGMV in the right ventral ACC (Montreal Neurological Institute [MNI] coordinates coordinates, x = 6, y = 32, z = 0; Fig. 1a, Table 2), and decreased rGMV from Pre to Post earthquake in the left OFC (MNI coordinates, x = −20, y = 52, z = −6, Fig. 1b, Table 2), based on region of interest (ROI) analysis. Post hoc regression analysis revealed that Pre rGMV in the right ventral ACC and Post-Pre rGMV in the left OFC accounted for 49% score variance in the CAPS ($F(2, 39) = 18.28$, $R^2 = 0.48$, $P < 0.001$, Fig. 1c).

B. VBA results forFA

After controlling for sex and period between pre- and post-earthquake MRI data acquisition, the state anxiety scores were negatively associated with Pre FA in the right Cg (MNI coordinates, x = 20, y = 36, z = 0; Fig. 2a, Table 3) and positively associated with Post – Pre FA in the left

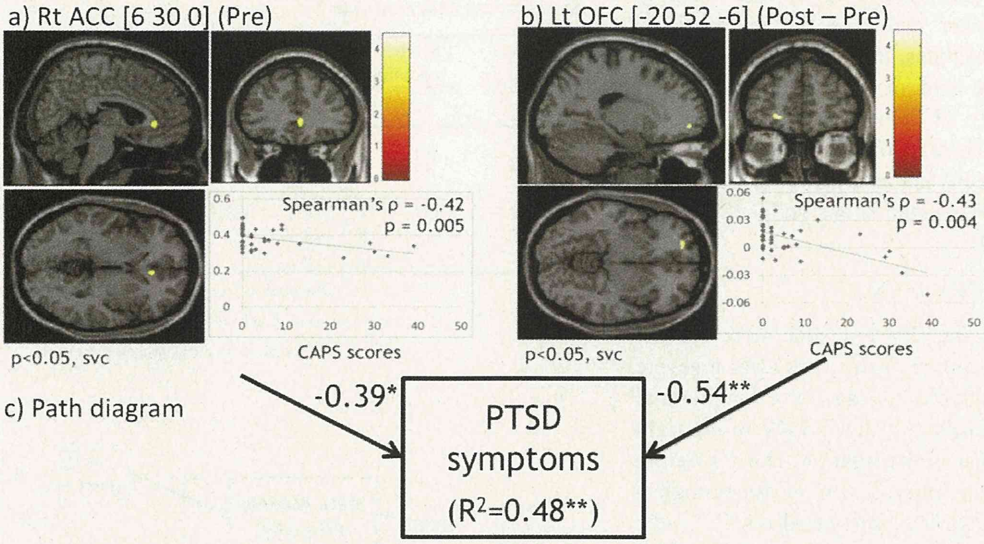

Fig. 1. Relationship between total CAPS scores and rGMV [28]
Total CAPS scores were negatively associated with Pre rGMV in the right ACC (**a**, Spearman's Rho = −0.42, $P = 0.005$) and Post-Pre rGMV in the left OFC (**b**, Spearman's Rho = −0.43, $P = 0.004$), illustrated by the scatter plots on the right side. Vertical axes represent rGMV at peak voxels in each cluster, and horizontal axes indicate total CAPS scores. c) Post hoc regression analysis implemented on a path diagram. The relationships between total CAPS scores and Pre rGMV in the right ventral ACC ($\beta = -0.39$, $P < 0.005$), and between total CAPS scores and Post-Pre rGMV in the left OFC ($\beta = -0.54$, $P < 0.001$) are shown. The predictor brain regions are shown on the left, which predicts PTSD symptoms evaluated by CAPS. Rt, right; Lt, left.

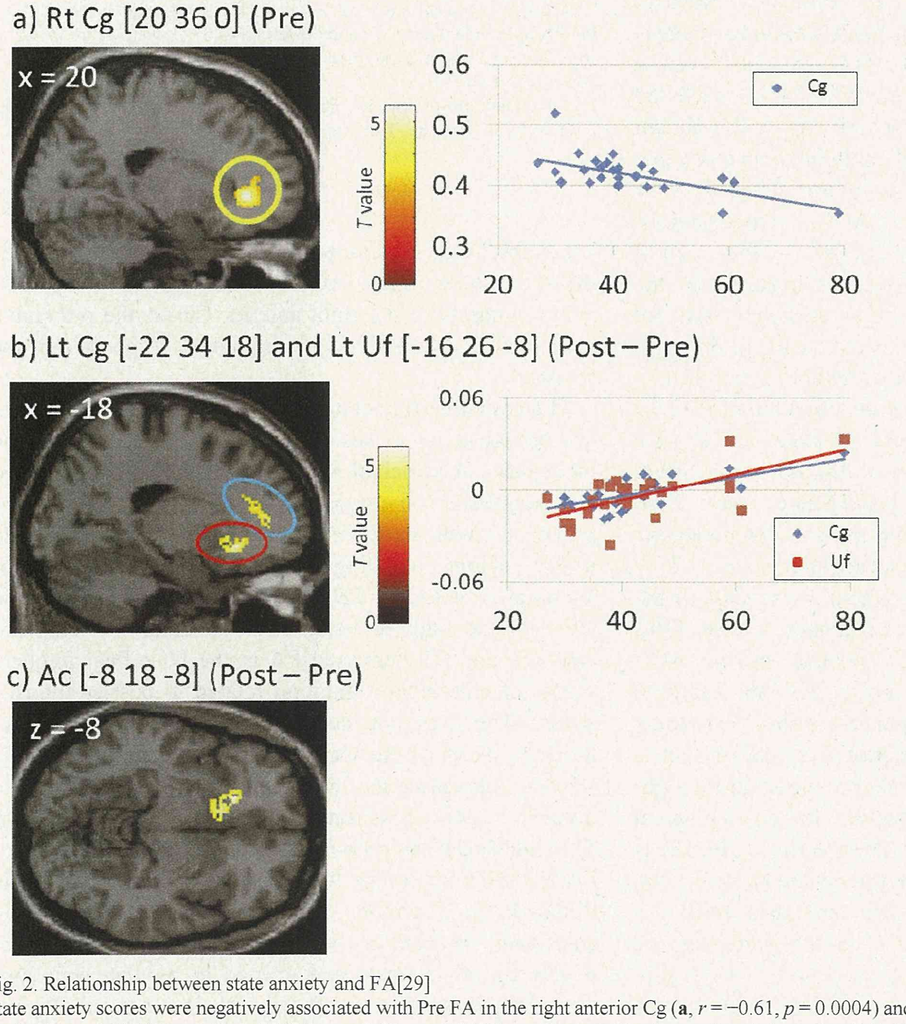

Fig. 2. Relationship between state anxiety and FA[29]
State anxiety scores were negatively associated with Pre FA in the right anterior Cg (**a**, $r = -0.61$, $p = 0.0004$) and Post – Pre FA in the left anterior Cg (**b**, $r = 0.70$, $p = 0.00002$) and the left Uf (**b**, $r = 0.65$, $p = 0.0001$), as illustrated by the scatter plots on the right. Vertical axes represent FA values at peak voxels in each cluster and horizontal axes indicate total state anxiety scores. The left Uf and the Ac were included in the same cluster.
FA, fractional anisotropy; Rt, right; Lt, left; Cg, cingulum; Uf, uncinate fasciculus.

anterior Cg (MNI coordinates, x = −22, y = 34, z = 18; Fig. 2b; Table 3), and a cluster including the left uncinate fasciculus (Uf; MNI coordinates, x = −18, y = 26, z = −8; Fig. 2b, Table 3) and the anterior commissure (Ac; MNI coordinates, x = −10, y = 18, z = −8; Fig. 2c, Table 3). Furthermore, SEM data showed that Pre FA in the right anterior Cg and Post – Pre FA in the left anterior Cg and the left Uf accounted for 60% of the score variance in state anxiety ($R^2 = 0.60$; Fig. 3).

IV. Discussion

This article introduces the first evidence of the causal relationship between psychological distress after a severe earthquake and brain structural changes. The longitudinal MRI studies demonstrated that smaller rGMV in the right ventral ACC, and lower FA in the right anterior Cg before the earthquake were vulnerability factors of psychological distress after the earthquake, and decreased rGMV in the left OFC and increased FA in the left anterior Cg and Uf from before to after the earthquake were acquired signs of psychological distress after the earthquake.

Our longitudinal studies provide further evidence of the causal relationships between brain structural changes and psychological responses to the disaster. Previous longitudinal studies investigating brain structural changes only after the traumatic events [13, 25, 26], even a prospective study of combat related PTSD [46], have failed to find the longitudinal brain structural changes in patient with PTSD. Another longitudinal study have revealed that the number of stressful life events are associated with the decreased volumes in the ACC, hippocampus/ parahippocampus in healthy subjects, the causal relationship between psychological responses to the stressful events and brain structural changes were not examined [7]. On the other hand, in contrast to our findings, smaller hippocampal volume as a vulnerability factor [27], and smaller pregenual ACC as an acquired sign of PTSD [10] were unveiled by investigations of same monozygotic twin pairs with PTSD. Apparent discrepancy existed; however, the reason of the discrepancy came from fundamental differences in study designs. Monozygotic twin studies could not distinguish an acquired sign of PTSD from an acquired one from birth to trauma, because of the cross-sectional design after the traumatic events [10]. Taken our present findings into account, smaller ACC volume is not an acquired sign, but an acquired vulnerability of PTSD before exposed to traumatic events.

Several evidence support the notion that smaller ventral ACC volume and lower white matter integrity in the right anterior Cg are vulnerability factors for psychological responses to a stressful life event. The anterior Cg bundle is a part of the principal white matter tract in the Papez circuit, which includes the ACC and the amygdala [47]. An essential role of the ventral ACC is the processing of anxiety and fears [48], which is supposed to be highly related to the manifestation of the clinical symptoms of PTSD [5]. In fact, smaller ACC volume and lower white matter integrity in Cg are robust findings in patients with PTSD [9–11, 18–20], also in normal subjects after stressful life events [7, 8, 21]. Our present findings provide evidence that the smaller ventral ACC volume and the lower white matter integrity in the right anterior Cg are the pretrauma vulnerability factors for psychological responses to the disaster.

The cognitive functions of the OFC and the Uf indicate psychological responses of the survivors soon after the earthquake. A principal function of the OFC is associated with regulation of emotions [49, 50]. Then, the Uf is a principal white matter tract that connects the OFC and limbic regions including the amygdala and the anterior temporal cortices [51, 52]. We supposed that the decreased OFC volume might reflect difficulty in cognitive control of emotion, and the increased FA in the Uf reflect frequent access of emotional regulation related to post-earthquake stress. The frequent access strengthens white matter integrity, based on the notion of previous cognitive training studies suggesting the white matter integrity related to trained cognitive functions in question increased [53, 54]. This interpretation is consistent with the interpretation of FA elevation caused by temporary activation of the Cg in PTSD [17]. Therefore, those who have difficulty in emotional regulation were likely to have higher psychological distress, and needed to regulate emotions more frequently than did those with lower psychological distress soon after the earthquake.

Table 3. MNI coordinates, voxel sizes, z-scores and P-values for results of the SPM analyses

Brain region	MNI coordinates			κ (voxels)	z scores	p-values (cluster level)
	x	y	z			
Pre						
Rt Cg	20	36	0	310	4.62	0.010
Post-Pre						
Lt Cg	−22	34	18	128	4.34	0.026
Lt Uf	−18	26	−s8	161	4.12	0.013
Ac*	−10	18	−8		3.83	

MNI, Montreal Neurological Institute; Rt, right; Lt, left.

Cg, cingulum; Uf, uncinate fasciculus; Ac, anterior commissure

* The Ac is included in the same cluster as the Lt Uf.

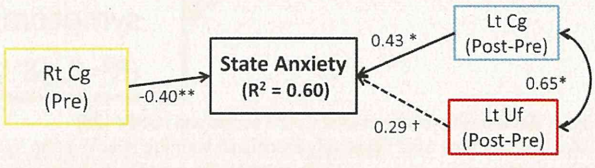

Fig. 3. SEM implemented on a path diagram [29]

The strength of the path coefficients between state anxiety scores and Pre FA in the right anterior Cg (−0.40, $p < 0.001$) and between state anxiety scores and Post – Pre FA in the left anterior Cg (0.43, $p < 0.01$) and the left Uf (0.29, $p = 0.06$) are shown. The path coefficient strength between Post – Pre FA in the left anterior Cg and the left Uf (0.65, $p < 0.005$) are shown as well. The brain regions that predict state anxiety level evaluated by STAI are shown on the left.

FA, fractional anisotropy; Rt, right; Lt, left; Cg, cingulum; Uf, uncinate fasciculus; STAI, State–Trait Anxiety Inventory

V. Conclusion

The longitudinal investigations distinguished structural brain changes that distinguish a vulnerability factor rather than an acquired sign of psychological distress after the disaster. These findings might be essential for discriminating between survivors with and without emotional distress soon after a disaster and between survivors who will and will not experience elevated levels of psychological distress, even in the normal population. These kinds of brain structural studies allow us to infer cognitive functions, dysfunctions, and personalities associated with the brain structures in question. Therefore, the findings improve our understanding of the psychophysiological responses to disasters and might contribute to the development of effective methods to prevent stress-related disorders in the normal population, specifically PTSD. In particular, the findings let us know what kind of cognitive functions, dysfunctions, and personalities we should screen for in a disaster area. In addition, the cognitive functions and personalities would be a target of psychotherapy for stress-related disorders. We also believe that investigations of normal populations without PTSD make a significant social contribution in that a large population was resilient to the disaster.

Finally, we present the future directions of our on-going investigations. First, we plan to follow the subjects for least 2 years after the earthquake. These follow-up investigations will allow us to observe whether the brain structural changes recovered or continued. In addition, we will be able to detect late-onset brain structural changes, as the present study detected brain structural changes soon after the disaster only. Second, we will attempt to recruit a control group that did not experience the earthquake. The lack of a control group was a predetermined limitation of the present study, because most of the candidates in our pre-earthquake database were believed to be living near Sendai, which was affected by the earthquake. To overcome this issue, we plan to make a longitudinal magnetic resonance imaging (MRI) dataset of healthy subjects who did not experience the disaster. We have started to obtain brain MR images and psychological data from such healthy subjects. Finally, we propose combining the brain MRI data, psychological data, and genomic information to explore genomic vulnerability factors for brain structural changes and psychological distress after a disaster.

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Psychological Effects of the Great East Japan Earthquake: Posttraumatic Stress, Psychological Effects and the Cortisol Levels in Women Who Live in the Coastal Disaster Areas

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Abstract— **The Pacific side of northeast Japan was devastated by the seismic activity and resulting tsunami generated from the Great East Japan Earthquake in 2011. People living in the coastal disaster areas witnessed firsthand the danger of the tsunami and subsequent horrible sights and were more shocked than people living inland of the disaster area. This study attempts to reveal the psychological effects of these experiences on women living in the coastal areas, using psychological measures and salivary cortisol levels, 6 months after the earthquake. We anticipate that this study will provide a better understanding of posttraumatic responses to the earthquake and tsunami in the early stages of adaptation and to effectively expand prevention strategies and countermeasures for posttraumatic stress disorder (PTSD). Fifty-four right-handed women with mild PTSD who were living in the disaster area participated in this study. Six months after the earthquake, all subjects completed PTSD screening using the Clinician-Administered PTSD Scale (CAPS), then they completed psychological measures and collected saliva samples. We used the following psychological measures to investigate psychological effects: the quality of life, psychological distress, physical symptoms and depressive symptoms. The results showed that the loss group had significantly lower lifestyle evaluations after the earthquake than the non-loss group. They had significantly lower scores of psychological health, social relationships and the environment subscale of the WHO-QOL26 than the non-loss group. In addition, the loss group had significantly higher salivary cortisol levels than the non-loss group. Moreover, in the loss group, the physical health scores of the WHO-QOL26 were significant negative correlations with salivary cortisol levels. Also, the psychological scores of the WHO-QOL26 were significant negative correlations with the salivary cortisol levels. The novelty of this study is that there are identified the psychological effects on women with mild PTSD derived from natural disasters such as earthquakes. Our results demonstrate that several psychological stressors related to the survivors' QOL induced by the disaster are associated with increased salivary cortisol levels. The findings that the physical health scores and the psychological health scores of the WHO-QOL26 in the loss group were low indicate that the conditions of the components of these domains are worst. Based on these results, we propose strongly that the immediate psychological and social support for women with loss experience is necessary.**

Keywords: Earthquake, Disaster area, Women, Loss experience, Psychological effect

I. Introduction

The Pacific Coast regions of the Tohoku area suffered significantly from the Great East Japan Earthquake that occurred on March 11, 2011. Particularly, the coastal areas of Miyagi, including Kesennuma, Ishinomaki and Minamisanriku, were destructive damage by the earthquake and tsunami. In the aftermath of the earthquake, the affected people were damaged both physically and psychologically. Two years have passed since the earthquake, the region continues to fight intermittent aftershocks. Many researchers have studied the mental health and physical changes that occur in survivors after serious events [1–5]. Previous studies have suggested that survivors' mental health problems are most evident after a certain amount of time following a disaster [6], and have also suggested that prevalence rates of posttraumatic stress disorder (PTSD) ranging from approximately 5% to 60% are seen in the first one to two years after a disaster [7–8]. Other previous studies have reported that depending on individual differences and the type of disaster, the rate of psychiatric disorders among survivors either decreases after

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the second year or is prolonged and becomes chronic [5,6,9–10]. In the case of the Great Hanshin-Awaji Earthquake of 1995, many survivors damaged mentally and physically by the earthquake and many of they had the problem of some mental health. [11]. Some survivors of the Great East Japan Earthquake is still suffering from trauma by this disaster.

Chronic stress responses involve actual physiological changes to body systems and organs, also there are been paid to acute physiological stress responses. It has been suggested that such physiological changes may subsequently lead to chronic stress responses [12]. PTSD, which develops under intense stress conditions, is associated with behavioral and physiological pathologies, including disruption of the hypothalamic–pituitary–adrenal (HPA) axis [13]. The HPA axis mediates physiological stress responses and the secretion of the stress hormone cortisol [14]. Cortisol is an indicator of psychological and physiological stress and can be used to examine PTSD pathophysiology [15]. Previous studies have shown that the cortisol levels are high when people feel heavily stressed; this symptom of PTSD can result from events including but not limited to earthquakes, war, accidents, abuse and radioactive damage [16–18]. During the Hanshin-Awaji Earthquake, for example, people with severe PTSD were found to have significantly higher cortisol levels than those without PTSD [2]. Cortisol can be extracted from blood, urine and saliva. The use of sampling via saliva collection has attracted attention as a less stressful and invasive method of estimating the cortisol levels compared to other methods of extraction [19–22]. In particular, the salivary cortisol levels have been reported to reflect unbound blood cortisol, and a very high correlation has been reported between the plasma and salivary cortisol levels [21–23]. Also, cortisol production has a circadian rhythm [24]. The cortisol levels peak in the early morning and drop to their lowest concentration at night [25]. In addition, the cortisol levels increase independently of the circadian rhythm in response to stress [26]. Several studies of the psychological effects on survivors induced by natural disaster have been performed thus far [27]. The subjects of these studies included both men and women [28–31], only men [1, 32–33] and children [34–37]. However, there is very little study focusing only women by natural disaster. Previous studies between men and women suggest that women are more likely than men to have PTSD in addition to high levels of anxiety and anxiety disorders after natural disasters [27, 31, 37–41]. However, there have been few reports on psychological effects of women induced by the East Japan Great Earthquake. We therefore focused on this point. We believe that the information obtained in this study will be useful for providing support at the time of disasters in Japan, especially for women. The purpose of this study was to investigate psychological effects in women who live in the disaster area through the use of psychological and biochemical data collected six months after the earthquake, particularly comparing women who lost a member of their household and/or a relative and those who did not. We hypothesized that the psychological conditions of the women who lost a relative would be poor compared with those of women who did not.

II. Materials and Methods

A. Subjects

Fifty-four healthy, right-handed women participated in this study as part of our ongoing project to investigate the associations between brain structure and mental health. All subjects who took part in this study also participated in our interventional studies and underwent psychological tests and MRI scans that are not described in this study but were performed together with those described in this study. The subjects were recruited using a newspaper advertisement. With regard to the ability of subjects to make judgments, one of the criteria applied during open recruitment was that candidate was to have no past medical history, including treatment or hospitalization for mental illness. The mean subject age was 43.4 years (standard deviation [SD], 8.8). All subjects were survivors of the Great East Japan Earthquake of March 11, 2011 and were living in the disaster area at the time of study. The subjects lived in cities that were devastated by the disaster, including Ishinomaki, Onagawa and Higashi-Matsushima in Miyagi Prefecture. The majority of the subjects were married (96.3%). Only eight people (14.8%) lived alone, while 46 (85.2%) lived with their spouse or relatives. In terms of damage from the earthquake, 17 people (31.5%) lost their homes (completely destroyed), 19 people (35.2%) sustained damage to their homes (semi-destroyed) and 20 people sustained slight damage to their homes. People with completely destroyed or semi-destroyed homes lived in rental houses in other areas, relatives' homes or temporary houses. Furthermore, 22 people (40.7%) lost members of their households and/or relatives.

During the PTSD screening, a clinical psychologist reviewed the candidate's condition using an interview. When any candidate showed even the slightest sign of an abnormal condition, the clinical psychologist consulted a doctor of psychosomatic medicine who was a member of the research project to decide whether to exclude the subject from participation. Having taken such measures, the subjects of this study were considered to be subjects with the capacity to give consent and render judgment. The subjects were verified as having no neuropsychiatric disorders via the Mini-International Neuropsychiatric Interview (MINI) [42, 43] as a check of their competence to give consent. We used the CAPS to assess whether the volunteers had PTSD [44-46]. The CAPS scores were divided into the following categories: 0–19 (asymptomatic/ few symptoms), 20–39 (mild PTSD/sub-threshold), 40–59 (moderate PTSD/above threshold), 60–79 (severe PTSD symptoms) and ≥80 (extreme PTSD symptoms). Trained psychologists (A.O., N.A., M.S., N.S., S.T. and Y.W.) administered the Japanese version of the CAPS [46] to all subjects in structured psychiatric diagnostic interviews to screen for posttraumatic stress symptoms. Consequently, all subjects were diagnosed with mild PTSD via the M.I.N.I and the CAPS. The M.I.N.I. and CAPS were administered before examination. Subjects answered to the face sheets a household member and/or relative perished in the earthquake and those who did not. After that, they were assigned to the loss group and the non-loss group. The number of subjects in the loss group was 22 (mean age:

42.7 years old, SD: 8.8). The mean CAPS score of the loss group was 32.8 ± 6.1 points. The number of subjects in the non-loss group was 32 (mean age: 43.8 years, SD: 8.9). The mean CAPS score of the non-loss group was 30.41 ±6.6 points. Other information for each group is shown in Table 1. Written informed consent was obtained from each subject in accordance with the Declaration of Helsinki (1991). This study was approved by the Ethics Committee of Tohoku University School of Medicine.

B. Experimental procedure

The scores on the psychological measures were compared between the two groups. Subjects received instructions from the experimenter about the experiment and completed psychological measures and saliva sampling in the time allotted. The subjects were given 120 minutes to complete the psychological measures. Then, the subjects underwent saliva sampling at 4:00 p.m. for five minutes. Therefore, the experimental time was 125 minutes. The subjects also completed certain psychological tests and an MRI scan that were not used in this study while they waited for the next procedure.

C. Psychological measures

To assess any effects in terms of the quality of life, happiness and mental health of the subjects, we administered the following psychological measures: (a) a face sheet consisting of facts such as age, home damage and a lifestyle evaluation after the earthquake (responses rated from 0 [worst] to 8 [good]); (b) the World Health Organization Quality of Life 26 (WHO-QOL26) questionnaire, which measures a survivor's quality of life [47]; (c) the General Health Questionnaire 30 (GHQ30), which measures psychological distress and physical symptoms [48, 49]; and (d) the Center for Epidemiologic Studies Depression Scale (CES-D), which measures the level of depressive symptoms occurring within the past week [50, 51].

D. Saliva sampling

We collected saliva samples from subjects to measure their levels of salivary cortisol. Distressing psychological stimuli are associated with increased cortisol levels [52]. Taking into consideration the subjects' circadian cortisol rhythms, we collected all saliva samples at 4:00 p.m. on weekdays, as people are less affected by circadian cortisol rhythms at this time of day [53]. The collection time for the saliva samples was determined in reference to a previous study showing that it is preferable to collect saliva samples during a timeslot with little circadian variation (for example, 3:00 p.m. or 4:00 p.m.) when performing saliva sample collection two or more times [54]. The subjects also refrained from drinking, eating [55] and exercise [56] for two hours before the saliva sampling.

E. Sampling strategy

(1) Measurement of salivary cortisol

To assess physiological stress, we used the same technique to measure salivary cortisol as that used in a previous study [57]. The saliva samples were collected using a salivette apparatus (Sarstedt, Nümbrecht, Germany) and centrifuged at 3,000 rpm for five minutes. We stored the supernatant solutions in airtight containers at −80°C and measured the salivary cortisol levels in these solutions. We measured salivary cortisol using a semi-microcolumn high-performance liquid chromatography (HPLC) system (Shiseido, Tokyo). The following conditions were used for the HPLC analysis: the mobile phase for preprocessing used a 5-mmol/L phosphoric acid buffer solution (pH = 6.9) and acetonitrile at a ratio of 98:2, with the solution flowing through the columns at a rate of 1 mL/min. The mobile phase for measurement used a 10-mmol/L phosphoric acid buffer solution (pH = 6.9) and acetonitrile at a ratio of 78:22, with the solution flowing through the columns at a rate of 0.1 mL/min. The column temperature was maintained at 35°C, and the detection wavelength was 242 nm. Increased cortisol levels are associated with distressing psychological stimuli [52].

(2) Statistical analyses

The psychological and salivary data were analyzed using the PASW statistical software package (ver. 18 for Windows; SPSS, Inc., Chicago, IL, USA). Comparisons of demographic and clinical data, psychological measures and the salivary cortisol levels between the loss group and the non-loss group performed with a two-sample t-test (marital status, family composition after the earthquake, and damage to housing performed with Pearson's chi-square test). To evaluate the correlations between each psychological variable and the salivary cortisol levels, Pearson's correlation coefficients were determined. All p values were two-tailed, and values of ≤ 0.05 were considered to be significant.

III. Results

A. Psychological measures

The demographic and clinical data of the subjects are shown in Table 1. Age, the CAPS scores, marital status, and of the percentage of semi-destroyed house, which is part of damage to housing did not differ significantly between the loss and non-loss groups. The loss group exhibited significantly lower lifestyle evaluations after the earthquake compared to the non-loss group [t = 4.83, degrees of freedom [df] = 52, $p < 0.001$]. Additionally, the loss group exhibited significantly higher the percentage of living alone and completely-destroyed house which is part of damage to housing compared to the non-loss group [the percentage of living alone: χ^2=8.505, df=1, p<.01; the percentage of completely-destroyed house which is part of damage to housing: χ^2=13.12, df=1, p<.001]. The loss group also exhibited significantly lower the percentage of living together with a spouse or a relative and no damage which is part of damage to housing compared to non-loss group [the percentage of living together with a spouse or a relative: χ^2=8.505, df=1, p<.01; the percentage of no damage which is part of damage to housingχ^2=9.82, df=1, p<.01]. The comparison results for the data obtained from these tests are shown in Table 2. The loss group demon-

Table 1. Baseline demographic and clinical data of the study subjects