However, because these previous studies employed cross-sectional designs, longitudinal WMI changes within individuals remained unclear.

Our previous longitudinal investigation unveiled the causal relationships between WMI changes and psychological distress soon after a disaster [10]. In our previous study, we collected DTI data from a group of healthy subjects before the Japanese earthquake (pre). Then, we recruited 30 subjects (male/female = 24/6, age = 21.0 ± 1.6 yr, range = 19 to 25 yr) from this group and examined results from DTI and from psychological measures related to postearthquake distress 3 to 4 months after the earthquake (post) to examine short-term effects. We found that lower WMI in the right anterior Cg before the earthquake was a preexisting vulnerability factor for postearthquake distress, and that increased WMI in the left anterior Cg and Uf after the earthquake was an acquired sign of post-earthquake distress [10].

In the current study, we examined WMI changes in subjects from the previous investigation 1 year later (followup) [10]. We tried to identify WMI changes that occurred in early (pre to post) and late (post to followup) phases after this stressful life event and investigated when and where these WMI changes occurred. In particular, we focused on the prognosis of FA changes in the right anterior Cg and the left anterior Cg and Uf, which were identified as a preexisting vulnerability factor and an acquired sign of post-earthquake distress, respectively.

2. Materials and Methods

2.1. Subjects.
All subjects participated in our previous investigation [10, 11]. Of the 30 subjects in our previous DTI study [10], we rerecruited 25 subjects (male/female = 19/6, age = 21.7 ± 1.4 yr) and assessed their structural DTI results one year after the earthquake. We screened for neuropsychiatric disorders using the Mini International Neuropsychiatric Interview (M.I.N.I.) [12, 13]. Handedness was assessed using the Edinburgh Handedness Inventory [14]. All subjects provided written informed consent before participating in the current study, which examined the possible effects of psychological trauma on brain structure, in accordance with the Declaration of Helsinki [15]. 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 or tsunami. The current study was approved by the Ethics Committee of Tohoku University.

2.2. Psychological Evaluations.
All participants were interviewed by trained psychologists using the Japanese version of the clinician-administered PTSD scale (CAPS) structured interview [16, 17]. In accordance with the M.I.N.I., no subject was diagnosed as having PTSD. Levels of anxiety and depression were evaluated using the State-Trait Anxiety Inventory (STAI) [18, 19] and the Center for Epidemiologic Studies Depression Scale (CES-D) [20, 21]. Psychological traits related to resilience in response to stressful life events were assessed using the Japanese version of the Posttraumatic Growth Inventory (PTGI-J) [22, 23] and the Japanese version of the Rosenberg Self-Esteem Scale [24, 25]. All psychological measures were assessed at 3 to 4 months (post) and at 1 year (followup) after the earthquake.

2.3. Image Acquisition.
All MRI data were acquired with a 3-T Philips Intera Achieva scanner. The diffusion-weighted data were acquired using a spin-echo EPI sequence (TE = 55 ms, FOV = 22.4 cm, $2 \times 2 \times 2$ mm^3 voxels, 60 slices). The diffusion weighting was isotropically distributed along 32 directions (b value = 1,000 s/mm^2). Additionally, a dataset with no diffusion weighting (b value = 0 s/mm^2; b0 image) was acquired. The total scan time was 7 min 17 s. Then, fractional anisotropy (FA) values were calculated from the collected images. This information is of particular interest when making inferences regarding white matter microstructural properties, as diffusion is faster along axons than in the perpendicular direction. Consequently, diffusion in white matter is anisotropic (i.e., diffusion rates in different directions are unequal). By contrast, isotropic diffusion is equally fast in all directions. FA in each voxel was used as a measure of the degree of diffusion anisotropy. FA varies between 0 and 1, with 0 representing isotropic diffusion and 1 representing diffusion occurring entirely in one direction. After DTI image acquisition, FA map images were calculated from DTI using software preinstalled on the Philips MR console.

2.4. Preprocessing of Diffusion Imaging Data.
Preprocessing and data analysis were performed using statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks, Natick, MA, USA). First, our original b0 image template was created as follows. Using the affine and nonlinear spatial normalization algorithm, the b0 images from the pre-earthquake scans of all subjects in this study were spatially normalized to the SPM5 T2 template, which is based on averages taken from 152 brains from the Montreal Neurological Institute database. Then, we calculated a mean image of the normalized b0 images as our original b0 image template. Using the affine and nonlinear spatial normalization algorithm, the b0 image of each participant was normalized to our original b0 image template. Before normalization of the FA map, the postearthquake FA maps were coregistered with the pre-earthquake FA maps from each subject. Then, using the parameter for this affine and nonlinear normalization procedure, an FA map image of each participant was spatially normalized to yield images with $2 \times 2 \times 2$ mm voxels and spatially smoothed using a Gaussian kernel of 10 mm FWHM. The resulting maps representing FA were then subjected to the group regression analysis described below.

2.5. Statistical Analysis.
Differences in FA between before the earthquake (pre), 3-4 months after the earthquake (post), and 1 year after the earthquake (followup) were compared using analysis of covariance (ANCOVA) in SPM5. The analysis was performed with sex and period between MR acquisition and the earthquake as additional covariates. Differential FA between time periods was detected as a main effect (pre/post/followup) using F-contrasts in SPM. The significance level was set at P = 0.05, corrected for multiple comparisons (voxel-level family-wise error) and $k > 10$ to

TABLE 1: Psychological measures.

	Post	Followup	P value
CAPS (total)	6.6 ± 9.6	1.6 ± 2.9	0.04
CES-D score	12.1 ± 10.6	10.7 ± 9.3	n.s.
STAI scores			
State	44.1 ± 11.8	39.2 ± 10.4	n.s.
Trait	42.7 ± 9.6	43.2 ± 11.2	n.s.
Self-esteem	32.8 ± 8.2	32.8 ± 8.9	n.s.
PTGI-J (total)	33.8 ± 18.9	34.3 ± 19.3	n.s.

Values are shown as mean ± standard deviation.
CAPS: clinician-administered PTSD scale, CES-D: center for epidemiologic studies depression scale, STAI: state-trait anxiety inventory, and PTGI-J: Japanese version of the posttraumatic growth inventory.

TABLE 2: MNI coordinates, voxel sizes, F values, and P values for results of the SPM analyses.

Brain region	MNI coordinates			k (voxels)	F values	P values (FWE)
	x	y	z			
Rt anterior Cg	26	52	14	55	21.68	0.002
Rt Uf	8	46	−22	10	19.38	0.007
Lt Uf	−32	44	−6	72	33.49	0.000
Lt SLF	−28	−18	22	63	24.21	0.001
Lt thalamus	−10	−22	10	23	17.96	0.017

MNI: montreal neurological institute, Rt: right, Lt: left, Cg: cingulum, Uf: uncinate fasciculus, and SLF: superior longitudinal fissure.

suppress the possibility of small clusters arising by chance. Additionally, to check for structural changes between each period (pre versus post, pre versus followup, and post versus followup), paired t-tests were performed for each cluster identified as a main effect in the ANCOVA. Finally, to ascertain the 1-year prognosis of FA changes as a preexisting vulnerability factor and as an acquired sign of postearthquake distress, post hoc correlation analysis was performed including the scores for postearthquake distress (e.g., CAPS and STAI-state at post) and FA changes from pre to followup in the right anterior Cg (i.e., a preexisting vulnerability factor at Pre) as well as from post to followup in the left anterior Cg and Uf (i.e., an acquired sign at Post) within the clusters detected by the ANCOVA.

All FA tests were performed using an absolute threshold of FA >0.2 [26], such that if a voxel anywhere in the brain had an FA value >0.2 in all subjects, that voxel was included in the analysis. This measure was used because FA is more susceptible to errors arising from partial volumes [27], and this FA cut-off value allowed us to dissociate white matter structure from other tissue [28].

3. Results

As for psychological measures, the CAPS total score significantly recovered between post and followup (6.6 ± 11.2 to 1.6 ± 2.9, $P < 0.05$). Scores on STAI-state (44.1 ± 11.4 to 39.2 ± 10.4, n.s.), STAI-trait (42.7 ± 9.6 to 43.2 ± 11.2, n.s.), CES-D (12.1 ± 10.6 to 10.7 ± 9.3, n.s.), Rosenberg self-esteem scale (32.8 ± 8.2 to 32.8 ± 8.9, n.s.), and PTGI-J (33.8 ± 18.9 to 34.3 ± 19.3, n.s.) were not significantly changed from post to followup (Table 1).

We found differential FAs to be a significant main effect of time period (pre/post/followup) in the right anterior Cg, bilateral Uf, left superior longitudinal fasciculus (SLF), and the thalamus (Table 2, Figure 1). post hoc correlation analyses revealed a significant positive correlation between the FA changes in the right anterior Cg from pre to followup and CAPS scores at post (Spearman's Rho = 0.414, $P = 0.039$, Figure 2(a)) and a significant negative correlation between the FA changes in the left Uf from post to followup and STAI-state scores at post ($r = −0.440$, $P = 0.028$, Figure 2(b)).

4. Discussion

To the best of our knowledge, this is the first longitudinal study to track microstructural changes in the brain at three time points: before, a short time after, and a long time after a disaster. We found differential FA at each time point in the right anterior Cg, bilateral Uf, left SLF, and left thalamus. According to the results of additional comparisons, we categorized the data according to the following three types of FA changes: normalization from initial FA changes in the right anterior Cg and right Uf (Figures 1(a) and 1(b)), sustained FA changes from the early phase in the left Uf (Figure 1(c)), and FA changes appearing during the late phase in the left SLF and thalamus (Figures 1(d) and 1(e)).

Increased or decreased WMI both a short and a long time after a disaster is likely to be due to synaptic enhancement and shrinkage, respectively. Biologically, synaptic enhancement or shrinkage has been observed in altered white matter following stress [3]. These changes are caused by hyper-secretion of glucocorticoids, a stress hormone [29]. The effects of stress hormones on the brain are observed as an inverse
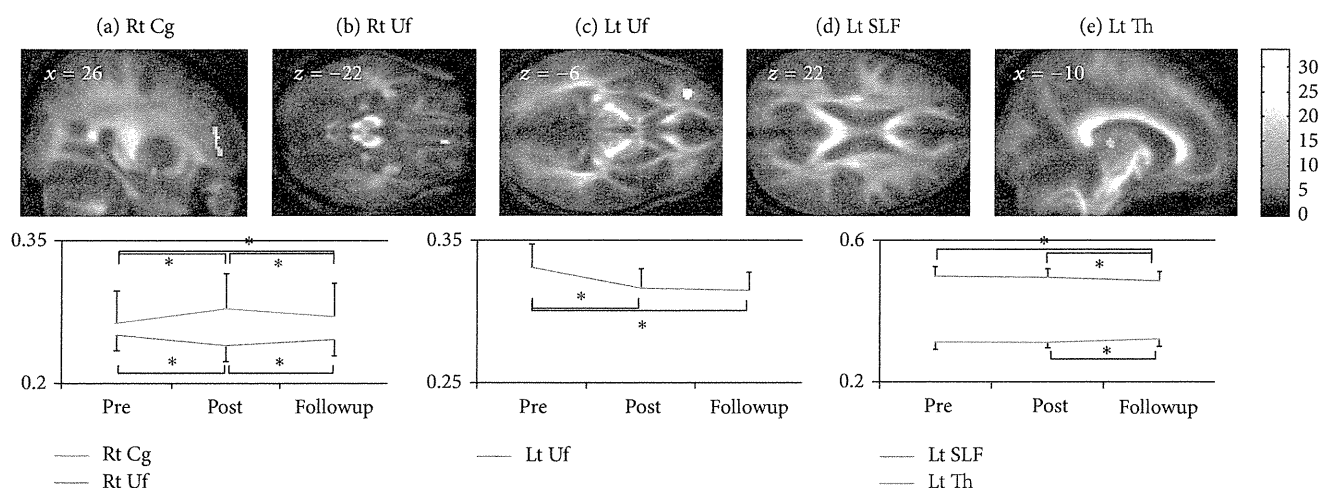
FIGURE 1: (a) FA in the right anterior Cg was significantly increased from pre to post ($P < 0.05$, paired t-test) and from pre to followup ($P < 0.05$, paired t-test), but it was significantly decreased from post to followup ($P < 0.05$, paired t-test). (b) FA in the right Uf was significantly decreased from pre to post ($P < 0.05$, paired t-test), but it was significantly increased from post to followup ($P < 0.05$, paired t-test). (c) FA in the left Uf was significantly decreased from pre to post ($P < 0.05$, paired t-test) and from pre to followup ($P < 0.05$, paired t-test). (d) FA in the left SLF was significantly decreased from pre to followup ($P < 0.05$, paired t-test) and from post to followup ($P < 0.05$, paired t-test). (e) FA in the left Th was significantly increased from post to followup ($P < 0.05$, paired t-test). These FA changes are illustrated by the plots at the bottom: vertical axes represent FA at peak voxels in each cluster, and horizontal axes indicate time periods. Error bars represent standard deviations. Colored bars represent F values. FA: fractional anisotropy; Rt: right; Lt: left; Cg: cingulum; Uf: uncinate fasciculus; SLF: superior longitudinal fasciculus; Th: thalamus.

U shape, depending on dose and time [30]. Additionally, stress-induced structural and functional alterations have been shown to be reversible, at least in the prefrontal cortex [31, 32]. In the context of these considerations, we assumed that FA changes in the right anterior Cg were consistent with the aforementioned concept and that increased FA in the thalamus and decreased FA in the Uf and SLF reflected the rising and falling components, respectively, of the inverse U-shaped curve that characterizes such changes.

The results of correlation analyses and our previous findings [10] led us to speculate that, in some subjects, the WMI changes reflected normalization after initial changes. Such reversible WMI changes are congruent with the aforementioned biological conceptualizations [30–32]. As discussed below, we interpreted such WMI changes as not only signs of recovery from emotional distress shortly after a disaster but also as predictors of a better prognosis for subjects with more pronounced psychological responses to a stressful event, namely, following two cases.

First, the WMI changes in the left Uf identified in some subjects who reported distress indicated that recovery from emotional distress is possible following a stressful event. Our previous study demonstrated that the WMI was greater in the left Uf after the earthquake as compared with before the earthquake and was positively correlated with state anxiety levels, suggesting that the increased WMI in the left Uf was an acquired sign of emotional distress soon after a disaster [10]. In the present study, the WMI in the left Uf decreased from soon after (Post) to one year after (followup) the earthquake in subjects who had had higher state anxiety

levels soon after the earthquake (Post). The Uf, which is also involved in emotional processing [33], is a principal white matter tract that connects the orbitofrontal cortex (OFC) and limbic regions, including the amygdala and the anterior temporal cortices [34, 35]. Neural responses in the OFC are preferentially enhanced, along with those in the amygdala, during extinction [36] and this relationship is crucial to the voluntary regulation of emotion [37]. Taking the functional roles of the Uf into account, the current results suggest that WMI in the Uf, which was elevated soon after the earthquake, reflecting the requirements of emotional regulation related to postearthquake stress, declined 1 year after the earthquake.

Next, the WMI changes in the right anterior Cg in some subjects who reported subclinical PTSD symptoms also suggested that a stressful event would strengthen structural connectivity, particularly in vulnerable subjects. The anterior Cg bundle is a part of the principal white matter tract in the Papez circuit, which includes the ACC and the amygdala [38]. Reduced WMI in the anterior Cg is frequently reported in patients with anxiety disorders such as PTSD [6–8, 39], social anxiety disorder (SAD) [40], and generalized anxiety disorder (GAD) [41] and in healthy subjects with high trait anxiety [42, 43]. It has been suggested that reduced WMI in the Cg represents dysfunctional emotion processing in such patients [6–8, 39–41]. Our previous study revealed that lower WMI in the right anterior Cg was a preexisting vulnerability factor for emotional distress soon after a disaster [10]. The current results showing the positive correlation between increased WMI in the right anterior Cg and CAPS scores demonstrated that those who had more PTSD symptoms
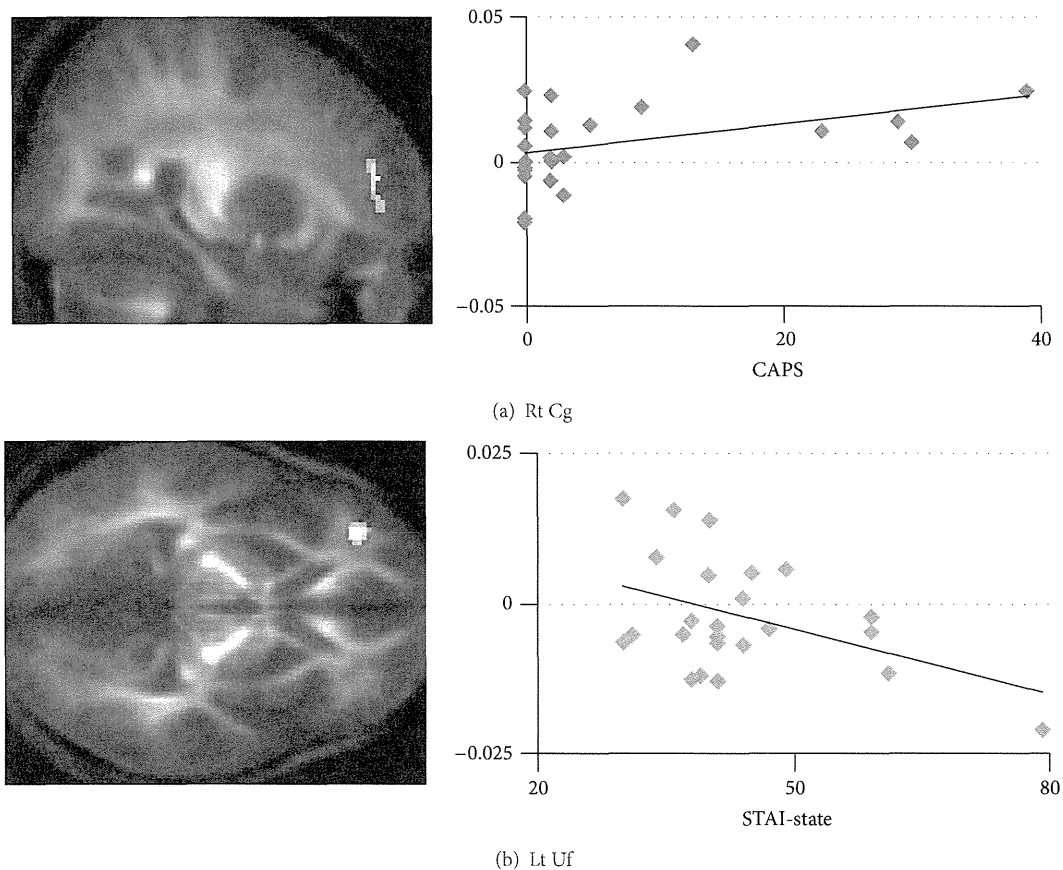
(a) Rt Cg

(b) Lt Uf

FIGURE 2: (a) CAPS scores were positively associated with FA changes from pre to followup in the right anterior Cg (Spearman's Rho = 0.414, $P = 0.039$), and (b) STAI-state scores were positively associated with FA changes from post to followup in the left Uf ($r = -0.440$, $P = 0.028$), as illustrated by the scatter plots on the right. Vertical axes represent FA changes at peak voxels in each cluster, and horizontal axes indicate (a) CAPS scores and (b) STAI-state scores. FA: fractional anisotropy; Rt: right; Lt: left; Cg: cingulum; Uf: uncinate fasciculus.

soon after the earthquake displayed increased structural connectivity in the anterior Cg from before to 1 year after the earthquake. Furthermore, although depression and anxiety levels did not improve from 3-4 months after to 1 year after the earthquake, none of the subjects in this study developed clinical PTSD. Together, the findings suggest that dynamic WMI changes in the Cg predict a better prognosis, whereas persistently lower WMI represents cognitive dysfunction, implying the development of anxiety disorders (e.g., PTSD, SAD, and GAD).

White matter changes due to maturation and/or aging should be taken into account when interpreting the results, because this study did not include a control group, which is a limitation of this study. This is particularly problematic with respect to interpreting WMI changes, such as the increased WMI in the thalamus and the decreased WMI in the SLF, without evaluating their correlation with psychological measures. A recent study that investigated WMI changes due to maturation and/or aging revealed that peak FAs in the Cg, Uf, and SLF were observed in subjects older than the age range of our subjects (19 to 25 yr) [44]. Another study reported increased FA in thalamic radiations with age [45]. In contrast, another recent study investigating longitudinal FA

changes at younger ages found that FA in the Uf decreased by almost half in subjects ranging in age from 19 to 25 [46]. Thus, decreased WMI in the SLF is unlikely to have occurred in our subjects, whereas it is difficult to reject the possibility that our finding of the increased WMI in the thalamus is a result of maturation. Nevertheless, the interpretation of WMI changes, such as the increased WMI in the Cg and the decreased WMI in the Uf, and their correlation with psychological measures are less problematic. We believe that the current study provides sufficient evidence of the short- and long-term effects on the brain microstructure despite the absence of a control group.

5. Conclusions

The present followup DTI study showed the long lasting effects of stressful events on brain microstructure. Our findings suggest that microstructures within the brain change due to stress and recovery. We assumed that brain microstructural changes due to stressful life events were not static but dynamic through life. Recently, the alteration of functional and structural connectivity, including regions adjacent to the Cg and the Uf, was reported in subjects soon after a disaster

[47, 48]. Therefore, further longitudinal investigations using multimodal approaches are necessary to examine whether the stress-induced alterations in brain structure are reversible.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

All authors contributed to the concept and design of the study. Atsushi Sekiguchi, Yuka Kotozaki, Motoaki Sugiura, Tsuyoshi Araki, Sugiko Hanawa, Seishu Nakagawa, and Carlos Makoto Miyauchi contributed to data acquisition. Atsushi Sekiguchi, Motoaki Sugiura, Yuka Kotozaki, Rui Nouchi, Hikaru Takeuchi, Tsuyoshi Araki, Yasuyuki Taki, and Ryuta Kawashima contributed to the data analysis and interpretation. Atsushi Sekiguchi, Motoaki Sugiura, Rui Nouchi, Hikaru Takeuchi, Tsuyoshi Araki, Yasuyuki Taki, and Ryuta Kawashima provided statistical expertise. Atsushi Sekiguchi wrote the paper. Motoaki Sugiura, Rui Nouchi, Hikaru Takeuchi, Yasuyuki Taki, and Ryuta Kawashima reviewed/revised the paper. All authors discussed the results and commented on the paper. All authors gave their final approval for the paper to be submitted.

Acknowledgments

References

[1] G. A. Van Wingen, E. Geuze, E. Vermetten, and G. Fernández, "Perceived threat predicts the neural sequelae of combat stress," Molecular Psychiatry, vol. 16, no. 6, pp. 664–671, 2011.

[2] G. A. Van Wingen, E. Geuze, E. Vermetten, and G. Fernández, "The neural consequences of combat stress: long-term follow-up," Molecular Psychiatry, vol. 17, no. 2, pp. 116–118, 2012.

[3] M. Popoli, Z. Yan, B. S. McEwen, and G. Sanacora, "The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission," Nature Reviews Neuroscience, vol. 13, no. 1, pp. 22–37, 2012.

[4] D. Le Bihan, "Looking into the functional architecture of the brain with diffusion MRI," Nature Reviews Neuroscience, vol. 4, no. 6, pp. 469–480, 2003.

[5] O. Abe, H. Yamasue, K. Kasai et al., "Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism," Psychiatry Research, vol. 146, no. 3, pp. 231–242, 2006.

[6] L. Zhang, Y. Zhang, L. Li et al., "Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions," Journal of Affective Disorders, vol. 133, no. 1, pp. 294–299, 2011.

[7] S. J. Kim, D.-U. Jeong, M. E. Sim et al., "Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder," Neuropsychobiology, vol. 54, no. 2, pp. 120–125, 2007.

[8] M. J. Kim, I. K. Lyoo, S. J. Kim et al., "Disrupted white matter tract integrity of anterior cingulate in trauma survivors," NeuroReport, vol. 16, no. 10, pp. 1049–1053, 2005.

[9] L. Chen, S. Lui, Q.-Z. Wu et al., "Impact of acute stress on human brain microstructure: an MR diffusion study of earthquake survivors," Human Brain Mapping, vol. 34, no. 2, pp. 367–373, 2013.

[10] A. Sekiguchi, M. Sugiura, Y. Taki et al., "White matter microstructural changes as vulnerability factors and acquired signs of post-earthquake distress," PLoS ONE, vol. 9, no. 1, Article ID e83967, 2014.

[11] A. Sekiguchi, M. Sugiura, Y. Taki et al., "Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress," Molecular Psychiatry, vol. 18, no. 5, pp. 618–623, 2013.

[12] D. V. Sheehan, Y. Lecrubier, K. H. Sheehan et al., "The Mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10," The Journal of Clinical Psychiatry, vol. 59, 20, pp. 22–33, 1998.

[13] T. Otsubo, K. Tanaka, R. Koda et al., "Reliability and validity of Japanese version of the mini-international neuropsychiatric interview," Journal of Psychiatry and Clinical Neurosciences, vol. 59, no. 5, pp. 517–526, 2005.

[14] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," Neuropsychologia, vol. 9, no. 1, pp. 97–113, 1971.

[15] "Declaration of helsinki," Law, Medicine & Health Care, vol. 19, pp. 264–265, 1991.

[16] D. D. Blake, F. W. Weathers, L. M. Nagy et al., "The development of a clinician-administered PTSD scale," Journal of Traumatic Stress, vol. 8, no. 1, pp. 75–90, 1995.

[17] N. Asukai and A. Nishizono-Maher, "The Japanese version of clinician-administered PTSD scale," Tokyo Institute of Psychiatry, Tokyo, Japan, 1998.

[18] C. Spielberger, R. Gorsuch, R. Lushene, P. Vagg, and G. Jacobs, Manual for the State-Trait Anxiety Inventory, Consulting Psychologists Press, Palo Alto, Calif, USA, 1983.

[19] K. Nakazato and T. Mizuguchi, "How to use STAI," Sankyoubou, Kyoto, Japan, 1982.

[20] L. S. Radloff, "The CES-D scale: a self-report depression scale for research in the general population," Applied Psychological Measurement, vol. 1, no. 3, pp. 385–401, 1977.

[21] S. Shima, T. Shikano, T. Kitamura, and M. Asai, "New self-rated scale for depression," Japanese Journal of Clinical Psychiatry, vol. 27, pp. 717–723, 1985 (Japanese).

[22] R. G. Tedeschi and L. G. Calhoun, "The posttraumatic growth inventory: measuring the positive legacy of trauma," Journal of Traumatic Stress, vol. 9, no. 3, pp. 455–471, 1996.

[23] K. Taku, L. G. Calhoun, R. G. Tedeschi, V. Gil-Rivas, R. P. Kilmer, and A. Cann, "Examining posttraumatic growth among Japanese university students," Anxiety, Stress and Coping, vol. 20, no. 4, pp. 353–367, 2007.

[24] M. Rosenberg, Society and the Adolescent Self-Image, Princeton University Press, Princeton, NJ, USA, 1965.

[25] M. Yamamoto, Y. Matsui, and Y. Yamanari, "Substructure of self-recognition," *Japanese Journal of Educational Psychology*, vol. 30, pp. 64–68, 1982.

[26] J. Albrecht, P. R. Dellani, M. J. Müller et al., "Voxel based analyses of diffusion tensor imaging in Fabry disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 78, no. 9, pp. 964–969, 2007.

[27] A. Pfefferbaum and E. V. Sullivan, "Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming," *Magnetic Resonance in Medicine*, vol. 49, no. 5, pp. 953–961, 2003.

[28] D. H. Salat, D. S. Tuch, D. N. Greve et al., "Age-related alterations in white matter microstructure measured by diffusion tensor imaging," *Neurobiology of Aging*, vol. 26, no. 8, pp. 1215–1227, 2005.

[29] R. M. Sapolsky, "Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders," *Archives of General Psychiatry*, vol. 57, no. 10, pp. 925–935, 2000.

[30] M. Joëls, "Corticosteroid effects in the brain: U-shape it," *Trends in Pharmacological Sciences*, vol. 27, no. 5, pp. 244–250, 2006.

[31] J. J. Radley, A. B. Rocher, W. G. M. Janssen, P. R. Hof, B. S. McEwen, and J. H. Morrison, "Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress," *Experimental Neurology*, vol. 196, no. 1, pp. 199–203, 2005.

[32] C. Liston, B. S. McEwen, and B. J. Casey, "Psychosocial stress reversibly disrupts prefrontal processing and attentional control," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 3, pp. 912–917, 2009.

[33] H. T. Ghashghaei and H. Barbas, "Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey," *Neuroscience*, vol. 115, no. 4, pp. 1261–1279, 2002.

[34] H. T. Ghashghaei, C. C. Hilgetag, and H. Barbas, "Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala," *NeuroImage*, vol. 34, no. 3, pp. 905–923, 2007.

[35] U. Ebeling and D. V. Cramon, "Topography of the uncinate fascicle and adjacent temporal fiber tracts," *Acta Neurochirurgica*, vol. 115, no. 3-4, pp. 143–148, 1992.

[36] J. A. Gottfried and R. J. Dolan, "Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value," *Nature Neuroscience*, vol. 7, no. 10, pp. 1144–1152, 2004.

[37] K. N. Ochsner and J. J. Gross, "The cognitive control of emotion," *Trends in Cognitive Sciences*, vol. 9, no. 5, pp. 242–249, 2005.

[38] M. B. Hamner, J. P. Lorberbaum, and M. S. George, "Potential role of the anterior cingulate cortex in PTSD: review and hypothesis," *Depression and Anxiety*, vol. 9, no. 1, pp. 1–14, 1999.

[39] N. Schuff, Y. Zhang, W. Zhan et al., "Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: an MRI study," *NeuroImage*, vol. 54, no. 1, pp. S62–S68, 2011.

[40] V. Baur, A. B. Brühl, U. Herwig et al., "Evidence of frontotemporal structural hypoconnectivity in social anxiety disorder: a quantitative fiber tractography study," *Human Brain Mapping*, vol. 34, no. 2, pp. 437–446, 2011.

[41] J. M. Hettema, B. Kettenmann, V. Ahluwalia et al., "Pilot multimodal twin imaging study of generalized anxiety disorder," *Depression and Anxiety*, vol. 29, no. 3, pp. 202–209, 2012.

[42] M. J. Kim and P. J. Whalen, "The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety," *Journal of Neuroscience*, vol. 29, no. 37, pp. 11614–11618, 2009.

[43] V. Baur, J. Hänggi, and L. Jäncke, "Volumetric associations between uncinate fasciculus, amygdala, and trait anxiety," *BMC Neuroscience*, vol. 13, no. 1, article 4, 2012.

[44] C. Lebel, M. Gee, R. Camicioli, M. Wieler, W. Martin, and C. Beaulieu, "Diffusion tensor imaging of white matter tract evolution over the lifespan," *NeuroImage*, vol. 60, no. 1, pp. 340–352, 2012.

[45] B. D. Peters, P. R. Szeszko, J. Radua et al., "White matter development in adolescence: diffusion tensor imaging and meta-analytic results," *Schizophrenia Bulletin*, vol. 38, no. 6, pp. 1308–1317, 2012.

[46] C. Lebel and C. Beaulieu, "Longitudinal development of human brain wiring continues from childhood into adulthood," *Journal of Neuroscience*, vol. 31, no. 30, pp. 10937–10947, 2011.

[47] S. Lui, X. Huang, L. Chen et al., "High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 36, pp. 15412–15417, 2009.

[48] S. Lui, L. Chen, L. Yao et al., "Brain structural plasticity in survivors of a major earthquake," *Journal of Psychiatry & Neuroscience*, vol. 38, no. 6, Article ID 120244, pp. 381–387, 2013.
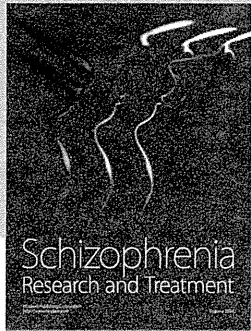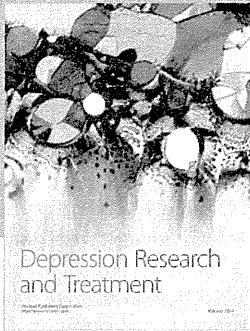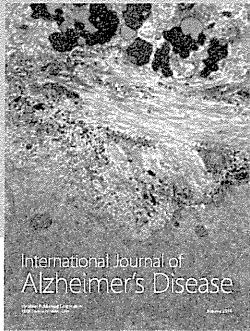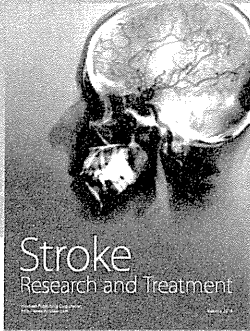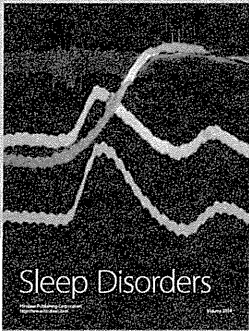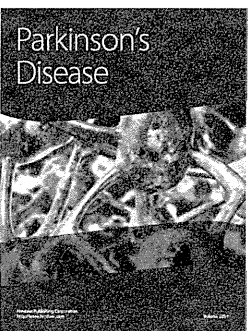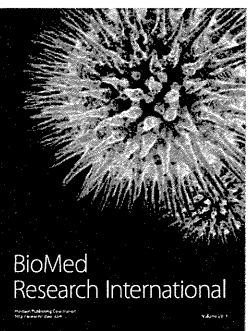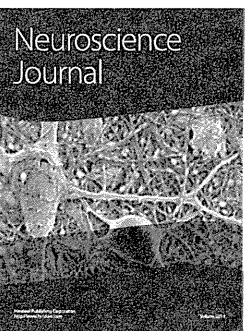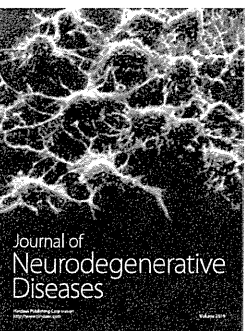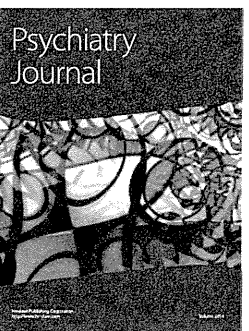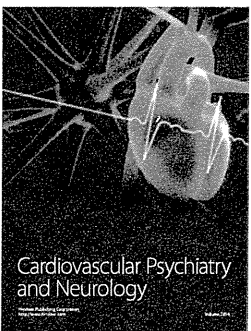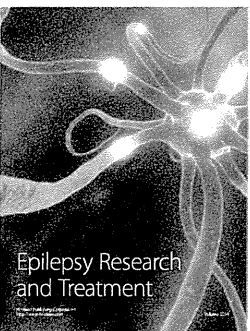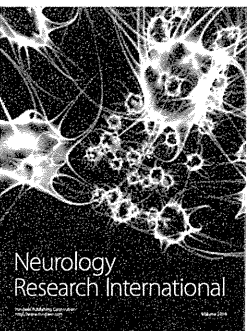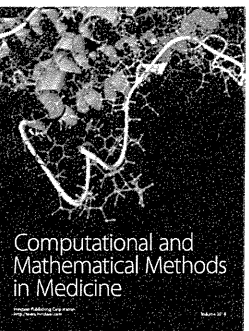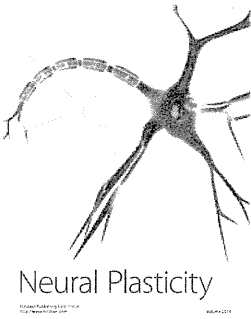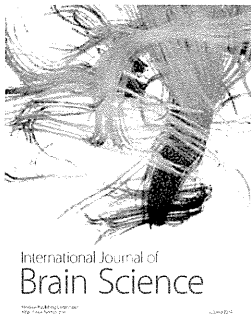
White Matter Microstructural Changes as Vulnerability Factors and Acquired Signs of Post-Earthquake Distress

Atsushi Sekiguchi[1,2]*, Motoaki Sugiura[2,3], Yasuyuki Taki[1,4,5], Yuka Kotozaki[6], Rui Nouchi[3,6,7], Hikaru Takeuchi[4], Tsuyoshi Araki[6], Sugiko Hanawa[2], Seishu Nakagawa[2], Carlos Makoto Miyauchi[2,8], Atsushi Sakuma[2,9], Ryuta Kawashima[2,4,6]

1 Division of Medical Neuroimage Analysis, Department of Community Medical Supports, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan, 2 Department of Functional Brain Imaging, Institute of Development, Aging and Cancer (IDAC), Tohoku University, Sendai, Japan, 3 International Research Institute of Disaster Science, Tohoku University, Sendai, Japan, 4 Division of Developmental Cognitive Neuroscience, IDAC, Tohoku University, Sendai, Japan, 5 Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, 6 Department of Advanced Brain Science, Smart Ageing International Research Center, IDAC, Tohoku University, Sendai, Japan, 7 Japanese Society for the Promotion of Science, Tokyo, Japan, 8 Graduate Schools for Law and Politics, The University of Tokyo, Tokyo, Japan, 9 Department of Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan

Abstract

Many survivors of severe disasters need psychological support, even those not suffering post-traumatic stress disorder (PTSD). The critical issue in understanding the psychological response after experiencing severe disasters is to distinguish neurological microstructural underpinnings as vulnerability factors from signs of emotional distress acquired soon after the stressful life event. We collected diffusion-tensor magnetic resonance imaging (DTI) data from a group of healthy adolescents before the Great East Japan Earthquake and re-examined the DTIs and anxiety levels of 30 non-PTSD subjects from this group 3–4 months after the earthquake using voxel-based analyses in a longitudinal DTI study before and after the earthquake. We found that the state anxiety level after the earthquake was negatively associated with fractional anisotropy (FA) in the right anterior cingulum (Cg) before the earthquake ($r = -0.61$, voxel level $p < 0.0025$, cluster level $p < 0.05$ corrected), and positively associated with increased FA changes from before to after the earthquake in the left anterior Cg ($r = 0.70$, voxel level $p < 0.0025$, cluster level p < 0.05 corrected) and uncinate fasciculus (Uf) ($r = 0.65$, voxel level $p < 0.0025$, cluster level p < 0.05 corrected). The results demonstrated that lower FA in the right anterior Cg was a vulnerability factor and increased FA in the left anterior Cg and Uf was an acquired sign of state anxiety after the earthquake. We postulate that subjects with dysfunctions in processing fear and anxiety before the disaster were likely to have higher anxiety levels requiring frequent emotional regulation after the disaster. These findings provide new evidence of psychophysiological responses at the neural network level soon after a stressful life event and might contribute to the development of effective methods to prevent PTSD.

Introduction

The Japanese earthquake, a severe earthquake with a magnitude of 9.0, hit Japan on March 11, 2011. Many survivors maintain high anxiety levels due to the earthquake aftermath including frequent aftershocks and dispersed radioactive material leaking from nuclear plants[1]. Therefore, even those without posttraumatic stress disorder (PTSD) often require psychological support [2].

The neurological characteristics of subjects with PTSD [3] or stressful life events [4], [5] have been well characterized. Recently, diffusion-tensor magnetic resonance imaging (DTI) [6] was used to investigate white matter structural changes in patients with PTSD [7–10], also in healthy survivors of a disaster [11], suggesting the white matter integrity (WMI) changes in the anterior cingulum (Cg). However, a causal relationship with stressful life events

remains unclear because of the cross-sectional designs. Detecting neurological underpinnings as a vulnerability factor and the acquired signs of emotional distress soon after stressful life events might contribute to a better understanding of psychological responses to stressful life events and early detection and prevention of PTSD for normal population. A previous study from our lab demonstrated longitudinal changes in grey matter volume from before to after the earthquake [12], suggesting that the reduced volume in the right anterior cingulate cortex before the earthquake was a pre-existing vulnerability factor, and the decreased volume in the left orbitofrontal cortex from before to after the earthquake was an acquired sign of post-earthquake stress. Beyond grey matter volume changes, investigating longitudinal FA changes before and after an earthquake can provide detailed evidence of microstructural abnormalities, particularly in structural connectivity related to emotional distress, after stressful life events.

This study attempted to identify WMI changes representing vulnerability factors and acquired signs of survivors' reports of emotional distress based on a longitudinal study of DTI data obtained from normal subjects before and after the earthquake. In fact, multiple studies performed in our laboratory collected DTI data from a group of healthy subjects before the earthquake. Therefore, this tragedy provided a rare opportunity to investigate WMI changes associated with such a disaster. Thirty subjects were recruited from this group to examine DTI 3~4 months after the earthquake. Anxiety levels were assessed as a measure of emotional distress following the disaster using the Japanese version of the State–Trait Anxiety Inventory (STAI) [13],[14]. State anxiety represents a psychological response to a stressful event, whereas trait anxiety represents a stable feature of one's personality. Therefore, we assumed that state anxiety scores were more appropriate than trait anxiety scores for assessing the psychological distress experienced soon after the earthquake, and we used state anxiety scores as a measure of the psychological distress experienced soon after the earthquake. We hypothesized that (a) vulnerability factors for anxiety levels after the earthquake could be detected by a significant association between state anxiety and FA before the earthquake (Pre FA) around brain regions previously implicated in PTSD and (b) the acquired signs could be detected by a significant association between state anxiety and WMI changes from before to after the earthquake (Post – Pre FA).

Methods and Materials

Recruitment and selection of participants

Eligible right-handed participants with no history of neuropsychiatric disorders were recruited from the undergraduate and postgraduate student population of the Tohoku University community. All candidates had participated in previous Magnetic Resonance Imaging (MRI) experiments conducted in our laboratory, had undergone DTI in the 2 years before the earthquake, and had agreed in advance to re-analyses of MRI scans taken before the earthquake. Because all candidates lived near the city of Sendai, which was seriously affected by the earthquake, control subjects with no experience with the earthquake were not recruited. Screening for neuropsychiatric disorders was conducted using the Mini-International Neuropsychiatric Interview (M.I.N.I.) [15], [16]. Handedness was assessed using the Edinburgh Handedness Inventory [17]. Among the numerous candidates in our database of past experiments, 30 could be contacted. All candidates enrolled in this study were part of a previous study conducted in our lab investigating grey matter volume before and after the earthquake [12]. Among the participants in this study [12], those who did not undergo DTI were excluded from the current investigation. All candidates met the above eligibility criteria and provided written informed consent before participating in the study. The M.I.N.I. confirmed that no subject had a history of psychiatric illness, including PTSD. Additionally, no subjects were taking medications for psychiatric symptoms according to a self-report questionnaire written both before and after the earthquake. This study and all previous studies were approved by the Ethics Committee of Tohoku University School of Medicine.

Psychological evaluation

All participants were evaluated for levels of anxiety using the STAI [13], [14]. The STAI measures state anxiety levels by asking subjects about their feelings "right now," whereas it measures trait anxiety levels by asking about their "usual" feelings. Levels of depression were assessed by the Center for Epidemiologic Studies Depression scale (CESD) [18], [19]. Coping styles used in daily life were assessed using the Stress Coping Inventory (SCI) [20]; Japanese version developed by the Japanese Institute of Health [21]. The SCI includes two major factors: 1) cognitive coping strategy, and 2) emotional coping strategy.

All participants were also interviewed by trained psychologists using the Japanese version of the Clinician-Administered PTSD Scale (CAPS) structured interview [22], [23]. In accordance with the M.I.N.I., no subject was diagnosed with PTSD. As for criterion A in CAPS, seven subjects experienced the earthquake as a supra-threshold psychological trauma. Although they did not experience direct life-threatening events due to the earthquake or tsunami, some of them thought that the houses or buildings that they were in at the time of the earthquake might collapse, and some of them thought that the leakage of radioactive materials from nuclear plants might be life threatening. As a result, these seven subjects were assessed to have satisfied criterion A. Actually, four of the seven subjects who met criterion A did not have any PTSD symptoms. As for criteria B, C and D in CAPS, of the 30 participants, seven met more than one criterion but none met all criteria for the three clusters of PTSD symptoms, which include re-experiencing the event, avoidance, and hyperarousal. Four of the seven subjects who had more than one PTSD symptom also did not experience life-threatening events due to the earthquake or tsunami. Specifically, the PTSD symptoms of these four subjects were mainly caused not by the earthquake directly but by the leakage of radioactive materials from nuclear plants or differences in interpersonal relationships after the earthquake. We believe that psychological stress from this kind of disaster comes not only from the disaster itself but also from continuous stressful events after the disaster. Additionally, the highest total CAPS score was 39, which is categorized as subthreshold PTSD [24]. Therefore, all subjects were regarded as "non-PTSD." The structured diagnostic interview and MRI analysis were conducted 3~4 months after the earthquake.

All psychological measurements were evaluated after the earthquake. The demographic characteristics of the subjects are presented in Table 1.

Image acquisition

All MRI data were acquired with a 3-T Philips Intera Achieva scanner. The diffusion-weighted data were acquired using a spin-echo echo-planar imaging (EPI) sequence (TR = 10,293 ms, TE = 55 ms, big delta (Δ) = 26.3 ms, little delta (δ) = 12.2 ms, FOV = 22.4 cm, $2\times2\times2$ mm^3 voxels, 60 slices, SENSE reduction factor = 2, number of acquisitions = 1). The diffusion weighting was isotropically distributed along 32 directions (b value = 1,000 s/mm^2). Additionally, a dataset with no diffusion weighting (b value = 0 s/mm^2; b0 image) was acquired. The total scan time was 7 min 17 s. Then, FA values were calculated from the collected images. This information is of particular interest when making inferences regarding white matter microstructural properties, as diffusion is faster along axons than in the perpendicular direction. Consequently, diffusion in white matter is anisotropic (i.e., diffusion rates in different directions are unequal). By contrast, isotropic diffusion is equally fast in all directions. FA in each voxel was used as a measure of the degree of diffusion anisotropy. FA varies between 0 and 1, with 0 representing isotropic diffusion and 1 representing diffusion occurring entirely in one direction. After DTI image acquisition, FA map were calculated from DTI data using the software that was pre-installed on the Philips MR console.

Table 1. Demographic characteristics of the non-PTSD survivors.

Number of subjects (male/female)	30 (24/6)
Age (years)	21.0±1.6
Number of previous lifetime traumas	1.97±1.0
Period between pre- and post-earthquake MR imaging (days)	271.4±122.9
CAPS	
Total	7.0±11.5
Re-experience	1.7±2.7
Avoidance	2.5±5.1
Hyperarousal	2.8±5.1
CESD score	11.3±10.0
STAI scores	
State	42.9±11.2
Trait	42.5±9.1
SCI scores	
Co	32.7±14.2
Em	30.7±9.8

Values are shown as means ± standard deviations.
CAPS, clinician-administered PTSD scale; CESD, Center for Epidemiologic Studies Depression scale; STAI, State–Trait Anxiety Inventory; SCI, Stress Coping Inventory; Co, cognitive coping strategy; Em, emotional coping strategy.
doi:10.1371/journal.pone.0083967.t001

Pre-processing of diffusion imaging data and statistical analysis

Pre-processing and data analysis were performed using statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks, Natick, MA, USA). First, our original b0 image template was created as follows. Using the affine and nonlinear spatial normalization algorithm, the b0 images from the pre-earthquake scans of all subjects in this study were spatially normalized to the SPM5 T2 template, which is based on averages taken from 152 brains from the Montreal Neurological Institute database. Then, we calculated a mean image of the normalized b0 images as our original b0 image template. Using the affine and nonlinear spatial normalization algorithm, the b0 image of each participant was normalized to our original b0 image template. Before normalization of the FA map, the post-earthquake FA maps were co-registered with the pre-earthquake FA maps from each subject. Then, using the parameter for this affine and nonlinear normalization procedure, an FA map of each participant was spatially normalized to yield 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 subjected to the group regression analysis described below.

Statistical analyses

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 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 the pre- and post-earthquake MRI data acquisition as additional covariates. According to the relevant guidelines[25], this study, which had a sample size of 30, should be limited to two variables. Therefore, we made it a priority to control the effects of sex and

period, and age was not included in the analysis as a covariate. All tests of FA were performed using an absolute threshold of FA >0.2 [26], such that if a voxel anywhere in the brain had an FA value >0.2 in all subjects, that voxel was included in the analysis. This measure was used because FA is more susceptible to errors arising from partial volumes [27], and this FA cut-off value allowed us to dissociate white matter structure from other tissue [28].

Significant regions were inferred using cluster-level statistics [29]. In this procedure, the null hypothesis was rejected when the clusters had a large spatial extent. The distribution of cluster sizes was found by parametric methods based on the theory of Gaussian random fields, which accounts for image volume, smoothness, and the cluster-defining threshold. At the cluster level, inference is determined according to the cluster size; that is, the probability that any cluster is larger than the critical cluster size is controlled. Only clusters with a p-value <0.05 after correction for multiple comparisons related to cluster size and an uncorrected voxel-level cluster-determining threshold of $p<0.0025$ were considered statistically significant in this analysis [30]. Next, to evaluate the strength of the association between white matter structural changes and state anxiety levels, we performed structural equation modeling (SEM) using the state anxiety scores from the STAI, Pre FA, and Post–Pre FA at peak voxels in each cluster as observed variables. Finally, we performed *post hoc* correlation analyses between the FA values in the regions of interest (ROIs) found in the aforementioned whole-brain analyses for trait anxiety scores, CAPS, and the two main factors of the SCI.

Results

The demographic characteristics of subjects are presented in Table 1. The distribution of anxiety levels is illustrated in Table 2. The state anxiety scores show significant positive correlations with both trait anxiety (r = 0.66, p = 0.0001) and CAPS scores (r = 0.50, p = 0.005). We also found a significant negative correlation between the state anxiety scores and the factor representing emotional coping strategy on the SCI (r = −0.54, p = 0.002).

After controlling for sex and the period between pre- and post-earthquake MRI data acquisition, state anxiety scores were negatively associated with Pre FA in the right Cg (Montreal Neurological Institute [MNI] coordinates, x = 20, y = 36, z = 0; Fig. 1a, Table 3) and positively associated with Post–Pre FA in the left anterior Cg (MNI coordinates, x = −22, y = 34, z = 18; Fig. 1b; Table 3) and with a cluster including both of the left uncinate fasciculus (Uf; MNI coordinates, x = −18, y = 26, z = −8; Fig. 1b, Table 3) and the anterior commissure (Ac; MNI coordinates, x = −10, y = 18, z = −8; 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 ($R2$ = 0.60; Fig. 2). Additionally, the *post hoc* correlation analysis revealed that the Post–Pre FA in the left Uf was negatively correlated with the factor of cognitive coping strategy (r = −0.40, p = 0.029) and emotional coping strategy on

Table 2. Distribution of anxiety levels.

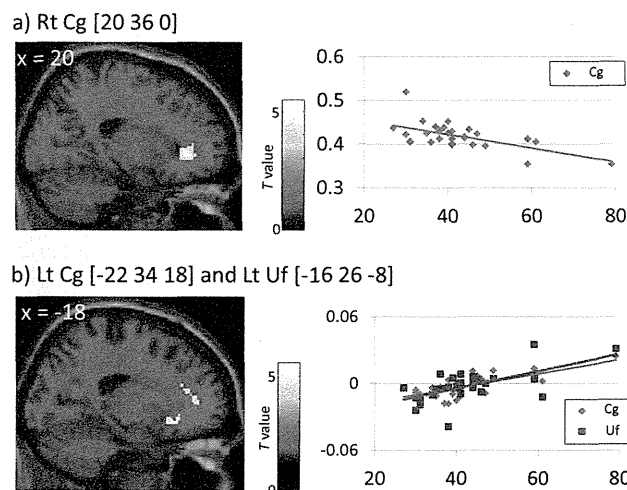|	Extremely low	Low	Normal	High	Extremely high
State	0	5	10	10	5
Trait	0	3	16	6	5

STAI, State–Trait Anxiety Inventory.
doi:10.1371/journal.pone.0083967.t002

the SCI ($r = -0.44$, $p = 0.015$). Also, the trait anxiety scores were negatively correlated with the Pre FA in the right Cg ($r = -0.47$, $p = 0.010$) and positively correlated with the Post – Pre FA in the left Cg ($r = 0.42$, $p = 0.022$) and the left Uf ($r = 0.36$, $p = 0.049$). No significant correlations were observed between the FA values in each ROI and CAPS scores.
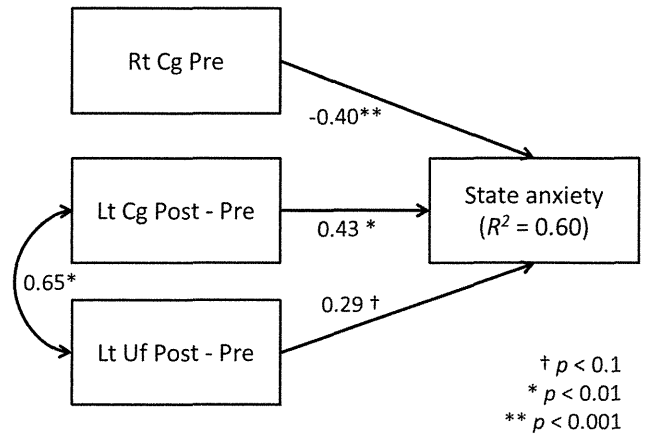
Discussion

State anxiety scores were negatively associated with Pre FA in the right anterior Cg and positively associated with Post–Pre FA in the left anterior Cg, the left Uf, and the left Ac. According to our hypothesis, lower WMI in the right anterior Cg and increased WMI in the left anterior Cg, the left Uf, and the left Ac were white matter structural changes that respectively represented vulnerability factors and acquired signs of anxiety level after the earthquake.

Several lines of evidence support the notion that lower WMI in the right anterior Cg is a vulnerability factor for anxiety after stressful events. The anterior Cg bundle is a part of the principal white matter tract in the Papez circuit, which includes the ACC and the amygdala [31]. Decreased anterior Cg WMI in patients with PTSD has been frequently reported [8–10]. Also, smaller dorsal and ventral ACC volumes are reported in patients with PTSD [32], [33] and in normal subjects after stressful life events [4]. Regarding vulnerability factors, a previous study from our lab found that a smaller right ventral ACC volume was a pre-trauma vulnerability factor for PTSD symptoms [12], which is congruent with the present findings. On the other hand, investigations of monozygotic twin pairs with PTSD have found that smaller hippocampal volume was a vulnerability factor [34] and that a smaller rostral ACC was an acquired sign of PTSD [35]. Although there are apparent discrepancies between our findings and the monozygotic twin studies, it is postulated that the discrepant findings result from fundamental differences in study designs. Monozygotic twin studies cannot distinguish acquired signs of

Figure 2. SEM implemented on a path diagram. 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.
doi:10.1371/journal.pone.0083967.g002

PTSD from acquired signs from birth to trauma because of the cross-sectional design of the study, which occurs after the traumatic events [35]. Based on our findings, the lower WMI in the right anterior Cg is a pre-trauma vulnerability factor for anxiety levels after a stressful event. This may have been identified as an acquired sign in the monozygotic twin study.

The functional roles of the anterior Cg and Uf indicate that psychological responses of survivors occur soon after the earthquake. The Uf, also involved in the emotional processing [36], is a principal white matter tract that connects the orbitofrontal cortex (OFC) and limbic regions including the amygdala and the anterior temporal cortices [37] [38]. In fact, neural responses in the OFC are preferentially enhanced with those in the amygdala during extinction [39] and this relationship is crucial to the voluntary regulation of emotion [40]. Given our finding that scores for

Figure 1. Relationship between state anxiety and FA. 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.
doi:10.1371/journal.pone.0083967.g001

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

Brain region	MNI coordinates			k (voxels)	z-scores	P-values
	x	y	z			(cluster level)
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	−8	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.
doi:10.1371/journal.pone.0083967.t003

cognitive coping strategy were negatively correlated with scores for increased FA in Uf, those who were unlikely to have a cognitive coping strategy in daily life may have increased their WMI in Uf soon after the earthquake; this may have been induced by frequent reliance on emotional regulation due to post-earthquake stress. Based on previous cognitive training studies suggesting that the integrity of the white matter related to trained cognitive functions increases [41], [42], this would be expected to strengthen the integrity of the white matter. Therefore, subjects with the increased WMI in the left Uf and Cg would be required to regulate their emotions more frequently, but failed to regulate. Then they had higher state anxiety levels than subjects with decreased WMI in the left Uf and Cg.

In contrast, there is an apparent discrepancy with previous DTI studies demonstrating lower WMI in the anterior Cg and/or the Uf in patients with anxiety disorders such as PTSD [8–10], social anxiety disorder (SAD) [43], and generalized anxiety disorder (GAD) [44] and in healthy subjects with high anxiety levels [45], [46] [11]. It was suggested that lower WMI in the Cg and/or Uf represents a dysfunction of emotion regulation in patients with anxiety disorders [8–10], [43], [44]. We believe that this discrepancy between increased and lower WMI could be explained by a difference in early stage and long lasting anxiety levels. High anxiety levels soon after a stressful life event would be associated with frequent access to the anterior Cg and the Uf cognitive functions, which are involved in emotional processing and emotional regulation, respectively. Conversely, long lasting high anxiety levels, which is also common in the aforementioned anxiety disorders, induces cognitive dysfunction, which is associated with lower WMI in the anterior Cg and Uf. This interpretation is consistent with that of diffusional anisotropy elevation caused by temporary activation of the Cg in PTSD [7], which is also supported by our findings that state anxiety scores, which represent possibly temporary anxiety levels experienced soon after the earthquake, were more strongly correlated with increased WMI in these regions than were trait anxiety and CAPS scores. Together, these findings indicate that increased WMI in the anterior Cg and the Uf represents early-stage psychological responses to a stressful life event, and decreased WMI represents the late stage, which is reflected in the development of anxiety disorders (e.g., PTSD, SAD, and GAD).

In addition, these findings indicate asymmetrical characteristics of anterior Cg psychological responses to a stressful life event in normal subjects. Previous neuroimaging studies investigating patients with PTSD revealed right hemisphere predominance [47], left hemisphere dysfunction [48], and asymmetrical WMI reduction in the anterior Cg [9]. Asymmetrical functional connectivity in the cognitive division of the ACC exists in healthy subjects as well [49]. A possible interpretation of the current results is that those with low right anterior Cg function are likely to become anxious but are protected against the development of PTSD by the maintenance of left anterior Cg function.

Some limitations should be considered when interpreting our results. First, psychological data related to emotional distress, such as anxiety levels before the earthquake, were not available. This was a predetermined limitation of the study because pre-earthquake dataset were not obtained to address the emotional issues. Additionally, because the STAI is designed to assess general anxiety in a non-specific manner, we could not determine whether the anxiety levels were caused by the earthquake. However, all subjects had no history of psychiatric diseases, suggesting their

anxiety levels before the earthquake were within normal levels. Also, the significant correlation between state anxiety levels and CAPS scores indicates that the anxiety levels were raised by the earthquake, because CAPS scores were definitely results of the earthquake. Furthermore, the SEM analysis supports the model in which the direction from brain structural changes to anxiety levels was suggested. The results of these analyses complement the lack of psychological data before the earthquake. Second, this study did not include subjects with supra-threshold PTSD symptoms, because most candidates in our pre-earthquake database were assumed to have been affected by the earthquake to some extent but not to have been exposed to life-threatening experiences. Therefore, the scope of the current study was the neural correlates of individual differences in state anxiety levels in the normal population after experiencing the disaster, regardless of psychological trauma. We believe that investigation of subjects with subclinical PTSD symptoms can provide sufficient evidence, an assumption that has been made in previous studies [4], [5], [11], [50], [51], [52], which would namely contribute to early detection and prevention of PTSD. In any case, a further longitudinal study of patients with supra-threshold PTSD symptoms caused by traumatic events is necessary to examine whether the neural microstructural connectivity changes observed in the current investigation are applicable to such individuals. Third, the majority of our subjects were males. To deal with this issue, sex was treated as an additional covariate. However, the possibility that the unbalanced sex distribution of subjects distorted the results remains. Fourth, the participants in the present study were limited to university students. Thus, the results may not generalize to older populations.

Despite these limitations, this is the first longitudinal study distinguished WMI changes that represent a vulnerability factor from structural changes that represent an acquired sign of high state anxiety. Additionally, the results demonstrating increased FA in the left anterior Cg and the Uf provide new evidence of temporal FA elevation in the early-stage response to stressful life events before anxiety disorders (e.g., PTSD, SAD, and GAD) develop. Such disorders are characterized by decreased FA in these areas. These findings may be helpful for discriminating between survivors with and without emotional distress soon after a stressful life event, and between survivors who will and will not, in future, experience anxiety after a stressful life event, even in the normal population. These findings provide a better understanding of psychophysiological responses to a stressful life event at the neural network level and may contribute to the development of effective methods to prevent stress-related disorders, namely PTSD, in the normal population.

Acknowledgments

Author Contributions

Conceived and designed the experiments: A. Sekiguchi MS YT YK TA SH SN CMM A. Sakuma RK. Performed the experiments: A. Sekiguchi MS YK TA SH SN CMM. Analyzed the data: A. Sekiguchi YK. Contributed reagents/materials/analysis tools: A. Sekiguchi MS YT YK RN HT AT. Wrote the paper: A. Sekiguchi. Revised the article: A. Sekiguchi MS YT RN HT RK.

References

1. McCurry J (2011) Anxiety over radiation exposure remains high in Japan. Lancet 378: 1061–1062.
2. Furukawa K, Arai H (2011) Earthquake in Japan. Lancet 377: 1652.
3. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, et al. (2012) Biological studies of post-traumatic stress disorder. Nature reviews Neuroscience 13: 769–787.
4. Papagni SA, Benetti S, Arulanantham S, McCrory E, McGuire P, et al. (2011) Effects of stressful life events on human brain structure: a longitudinal voxel-based morphometry study. Stress 14: 227–232.
5. Ganzel BL, Kim P, Glover GH, Temple E (2008) Resilience after 9/11: multimodal neuroimaging evidence for stress-related change in the healthy adult brain. Neuroimage 40: 788–795.
6. Le Bihan D (2003) Looking into the functional architecture of the brain with diffusion MRI. Nature reviews Neuroscience 4: 469–480.
7. Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, et al. (2006) Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. Psychiatry Res 146: 231–242.
8. Zhang L, Zhang Y, Li L, Li Z, Li W, et al. (2011) Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions. J Affect Disord 133: 294–299.
9. Kim SJ, Jeong DU, Sim ME, Bae SC, Chung A, et al. (2006) Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder. Neuropsychobiology 54: 120–125.
10. Kim MJ, Lyoo IK, Kim SJ, Sim M, Kim N, et al. (2005) Disrupted white matter tract integrity of anterior cingulate in trauma survivors. Neuroreport 16: 1049–1053.
11. Chen L, Lui S, Wu QZ, Zhang W, Zhou D, et al. (2013) Impact of acute stress on human brain microstructure: An MR diffusion study of earthquake survivors. Hum Brain Mapp 34: 367–373.
12. Sekiguchi A, Sugiura M, Taki Y, Kotozaki Y, Nouchi R, et al. (2013) Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. Mol Psychiatry 18: 618–623.
13. Spielberger C, Gorsuch R, Lushene R, Vagg P, Jacobs G (1983) Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press.
14. Nakazato K, Mizuguchi T (1982) How to use STAI. Kyoto: Sankyoubou Corp.
15. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 22-33;quiz 34–57.
16. Otsubo T, Tanaka K, Koda R, Shinoda J, Sano N, et al. (2005) Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. Psychiatry Clin Neurosci 59: 517–526.
17. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9: 97–113.
18. Radloff L (1977) The CES-D scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1: 385–401.
19. Shima S, Shikano T, Kitamura T, Asai M (1985) New self-rated scale for depression (in Japanese). Japanese Journal of Clinical Psychiatry 27: 717–723.
20. Lazarus RS, Folkman S (1984) Stress, appraisal, and coping. New York: Springer Publishing.
21. Japanese Institute of Health Psychology (1996) Lazarus Type Stress Coping Inventory. Tokyo: Jitsumu Kyoiku Shuppan.
22. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, et al. (1995) The development of a Clinician-Administered PTSD Scale. J Trauma Stress 8: 75–90.
23. Asukai N, Nishizono-Maher A (1998) The Japanese Version of Clinician-Administered PTSD Scale Tokyo: Tokyo Institute of Psychiatry.
24. Weathers FW, Keane TM, Davidson JR (2001) Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety 13: 132–156.
25. Tabachnick GB, Fidell SL (1996) Using multivariate statistics. New York: HarperCollins College Publishers.
26. Albrecht J, Dellani PR, Muller MJ, Schermuly I, Beck M, et al. (2007) Voxel based analyses of diffusion tensor imaging in Fabry disease. J Neurol Neurosurg Psychiatry 78: 964–969.
27. Pfefferbaum A, Sullivan EV (2003) Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 49: 953–961.
28. Salat DH, Tuch DS, Greve DN, van der Kouwe AJ, Hevelone ND, et al. (2005) Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiology of aging 26: 1215–1227.
29. Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996) Detecting activations in PET and fMRI: levels of inference and power. Neuroimage 4: 223–235.
30. Poline JB, Worsley KJ, Evans AC, Friston KJ (1997) Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 5: 83–96.
31. Hamner MB, Lorberbaum JP, George MS (1999) Potential role of the anterior cingulate cortex in PTSD: review and hypothesis. Depress Anxiety 9: 1–14.
32. Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, et al. (2003) Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. Proc Natl Acad Sci U S A 100: 9039–9043.
33. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, et al. (2006) Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry 59: 582–587.
34. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, et al. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5: 1242–1247.
35. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, et al. (2008) Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry 63: 550–556.
36. Ghashghaei HT, Barbas H (2002) Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience 115: 1261–1279.
37. Ghashghaei HT, Hilgetag CC, Barbas H (2007) Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. Neuroimage 34: 905–923.
38. Ebeling U, von Cramon D (1992) Topography of the uncinate fascicle and adjacent temporal fiber tracts. Acta neurochirurgica 115: 143–148.
39. Gottfried JA, Dolan RJ (2004) Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nat Neurosci 7: 1144–1152.
40. Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends Cogn Sci 9: 242–249.
41. Scholz J, Klein MC, Behrens TE, Johansen-Berg H (2009) Training induces changes in white-matter architecture. Nat Neurosci 12: 1370–1371.
42. Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, et al. (2010) Training of working memory impacts structural connectivity. J Neurosci 30: 3297–3303.
43. Baur V, Bruhl AB, Herwig U, Eberle T, Rufer M, et al. (2013) Evidence of frontotemporal structural hypoconnectivity in social anxiety disorder: A quantitative fiber tractography study. Hum Brain Mapp 34: 437–446.
44. Hettema JM, Kettenmann B, Ahluwalia V, McCarthy C, Kates WR, et al. (2012) Pilot multimodal twin imaging study of generalized anxiety disorder. Depress Anxiety 29: 202–209.
45. Kim MJ, Whalen PJ (2009) The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J Neurosci 29: 11614–11618.
46. Baur V, Hanggi J, Jancke L (2012) Volumetric associations between uncinate fasciculus, amygdala, and trait anxiety. BMC neuroscience 13: 4.
47. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, et al. (1996) A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 53: 380–387.
48. Lanius RA, Williamson PC, Densmore M, Boksman K, Neufeld RW, et al. (2004) The nature of traumatic memories: a 4-T FMRI functional connectivity analysis. Am J Psychiatry 161: 36–44.
49. Yan H, Zuo XN, Wang D, Wang J, Zhu C, et al. (2009) Hemispheric asymmetry in cognitive division of anterior cingulate cortex: a resting-state functional connectivity study. Neuroimage 47: 1579–1589.
50. Carrion VG, Weems CF, Richert K, Hoffman BC, Reiss AL (2010) Decreased prefrontal cortical volume associated with increased bedtime cortisol in traumatized youth. Biol Psychiatry 68: 491–493.
51. Cohen RA, Grieve S, Hoth KF, Paul RH, Sweet L, et al. (2006) Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biol Psychiatry 59: 975–982.
52. Lui S, Huang X, Chen L, Tang H, Zhang T, et al. (2009) High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China. Proc Natl Acad Sci U S A 106: 15412–15417.

ORIGINAL ARTICLE

Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress

A Sekiguchi[1], M Sugiura[1,2], Y Taki[3], Y Kotozaki[4], R Nouchi[4,5], H Takeuchi[4], T Araki[4], S Hanawa[1], S Nakagawa[1], CM Miyauchi[1], A Sakuma[1,6] and R Kawashima[1,3,4]

Many survivors of severe disasters, even those without posttraumatic stress disorder (PTSD), need psychological support. To understand the pathogenesis of PTSD symptoms and prevent the development of PTSD, the critical issue is to distinguish neurological abnormalities as vulnerability factors from acquired signs of PTSD symptoms in the early stage of adaptation to the trauma in the normal population. The neurological underpinnings of PTSD have been well characterized, but the causal relationships with the traumatic event are still unclear. We examined 42 non-PTSD subjects to find brain morphometric changes related to the severity of PTSD symptoms in a longitudinal magnetic resonance imaging study extending through the Great East Japan Earthquake. We found that regional grey matter volume (rGMV) in the right ventral anterior cingulate cortex (ACC) before the earthquake, and decreased rGMV in the left orbitofrontal cortex (OFC) through the earthquake were negatively associated with PTSD symptoms. Our results indicate that subjects with smaller GMV in the ACC before the earthquake, and subjects with decreased GMV in the OFC through the earthquake were likely to have PTSD symptoms. As the ACC is involved in processing of fear and anxiety, our results indicate that these processing are related to vulnerability for PTSD symptoms. In addition, decreased OFC volume was induced by failing to extinct conditioned fear soon after the traumatic event. These findings provide a better understanding of posttraumatic responses in early stage of adaptation to the trauma and may contribute to the development of effective methods to prevent PTSD.

INTRODUCTION

The Great East Japan Earthquake, a severe magnitude 9.0 earthquake, hit Japan on 11 March 2011. The eastern half of Japan was severely affected, and the northeast coast suffered widespread destruction caused by a massive tsunami triggered by this earthquake. More than 15 000 people have been confirmed dead, and ~4000 remain missing 6 months after the earthquake. Stress-related disorders such as acute stress disorder and posttraumatic stress disorder (PTSD) are likely to occur among the large number of survivors,[1-3] but even those without PTSD will require psychological support.[4] However, survivors without PTSD are likely to hesitate to ask for psychological supports and may not receive help, in contrast to those with PTSD. Distinguishing neurological abnormalities as a vulnerability factor from the acquired signs of PTSD symptoms in the early stage of adaptation to the trauma is essential both to understand the pathogenesis of PTSD and to prevent survivors from developing PTSD. Such information may provide a better understanding of posttraumatic responses and the development of effective methods to prevent PTSD.

The neurological underpinnings of PTSD have been well characterized, but the causal relationships to the traumatic event remain unclear, because of difficulties with prospective studies.[5] Previous neuroimaging studies of patients with PTSD revealed

morphological changes in several brain regions, including the hippocampus/parahippocampus,[6] amygdala,[6] anterior cingulate cortex (ACC),[7-9] insula[10] and orbitofrontal cortex (OFC),[11-13] which were also found in healthy adults after stressful life events.[14,15] Evaluation of monozygotic twin pairs with combat-related PTSD has provided evidence that smaller hippocampal volume is a vulnerability factor for PTSD,[16] and smaller pregenual ACC represents an acquired sign of PTSD.[8] However, longitudinal structural changes as a vulnerability factor and an acquired sign of PTSD symptoms remain unclear. Some longitudinal studies have examined patients with PTSD after traumatic events, but failed to find subsequent brain structural changes.[11,17,18] A recent long-itudinal study revealed that decreased volumes in the ACC and hippocampus/parahippocampus were associated with the number of stressful life events, but the impacts of stress-related responses on brain structure were not examined.[14] Therefore, the significance of longitudinal structural changes caused by posttraumatic response remained unclear.

This study tried to identify brain structural changes representing vulnerability factors and acquired signs of PTSD symptoms in non-PTSD survivors, based on a longitudinal study of structural magnetic resonance (MR) images obtained before and after the earthquake. In fact, we had obtained extensive structural MR imaging database from a group of healthy adolescents before the

[1]Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan; [2]International Research Institute of Disaster Science, Tohoku University, Sendai, Japan; [3]Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan; [4]Smart Ageing International Research Center, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan; [5]Japanese Society for the Promotion of Science, Tokyo, Japan and [6]Department of Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan. Correspondence: Dr A Sekiguchi, Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan.
E-mail: asekiguchi@idac.tohoku.ac.jp

2

earthquake in multiple studies performed in our laboratory. Therefore, this extremely miserable episode provided a rare opportunity for investigating brain structural changes associated with such a disaster. We recruited 42 subjects from this group to examine structural MR images at 3–4 months after the earthquake. PTSD symptoms were also assessed using the Japanese version of the clinician-administered PTSD scale (CAPS) structural interview.[19] We hypothesized that the vulnerability factors for PTSD could be detected by a significant association between the CAPS scores and smaller regional grey matter volume (rGMV) before the earthquake (Pre rGMV) in brain regions previously implicated in PTSD, and that the acquired signs could be detected by a significant association between the CAPS scores and decrease in rGMV from before to after the earthquake (Post-Pre rGMV). More specifically, based on previous monozygotic twin studies,[8,16] we could predict that smaller rGMV in the hippocampus would be identified as a pre-trauma vulnerability factor, and smaller rGMV in the ACC as an acquired sign of PTSD symptoms.

MATERIALS AND METHODS

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 dominance. All candidates had participated in past MR imaging experiments conducted in our laboratory, and had undergone structural MR imaging within 2 years before the earthquake, and had agreed to re-analyses of MR images obtained before the earthquake in advance. As all candidates lived around Sendai city, which was strongly affected by the earthquake, we did not plan to recruit control subjects unaffected by the earthquake. Neuropsychiatric disorders were screened using the mini international neuropsychiatric interview (M.I.N.I.).[20,21] Handedness was assessed by the Edinburgh Handedness Inventory.[22] We were able to contact 42 of the numerous candidates in our database of past experiments. All candidates satisfied the eligibility criteria and provided written informed consents before participating in the current study to examine the possible effects of psychological trauma on brain structure, in accordance with the Declaration of Helsinki Principles.[23] 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. This study and all previous studies were approved by the Ethics Committee of Tohoku University.

Psychological evaluations

All participants were interviewed by trained psychologists (A Omoto, N Aikawa, N Saito, Y Watanabe and YK) using the CAPS structured interview.[19,24] 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.[25] Therefore, we could regard all subjects as non-PTSD. The levels of anxiety and depression were evaluated using the state-trait anxiety inventory[26,27] and the Center for Epidemiologic Studies Depression Scale.[28,29] The diagnostic structured interview and MR imaging were conducted at 3–4 months after the earthquake. All psychological measurements were evaluated only after the earthquake.

Image acquisition

All MR imaging data acquisition was conducted with a 3-T Philips Intera Achieva scanner (Best, Netherlands). By 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.

Voxel-based morphometry analysis

To investigate the structural changes as vulnerability factors and acquired signs of PTSD symptoms in non-PTSD patients, voxel-based morphometry (VBM) was conducted. 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,[30] an extension of SPM2. Default parameter settings were used.[30] In order to reduce the scanner-specific bias, a customized grey matter anatomical template was created from the pre-earthquake data of all participants in this study. Next, the T1-weighted structural images of each subject were segmented into grey and white matter partitions using the new grey and white matter prior probability maps. The resulting images included the extracted grey and white matter partitions in the native space. The grey matter partition was then normalized to the new grey matter probability map. The normalization parameters determined from this initial step were then applied to the native T1-weighted structural image. These normalized T1-weighted structural data were then segmented into grey and white matter partitions. The volumes of global grey matter, white matter and cerebrospinal fluid space were calculated using segmented and modulated images by adding a value derived from the voxel volume and multiplied by the value of each voxel. To facilitate optimal segmentation, normalization parameters were estimated with the previously reported protocol.[31] In addition, a correction was performed for volume changes (modulation) by modulating each voxel with the Jacobian determinants derived from the spatial normalization, to test for regional differences in the absolute amount of grey matter.[32] All images were subsequently smoothed by convolving with an isotropic Gaussian kernel of 8-mm full-width at half-maximum. Finally, the signal change in rGMV between pre- and post-earthquake images was calculated at each voxel for each participant. Only voxels that showed GMV values > 0.10 in both pre- and post-earthquake images were included to avoid possible partial volume effects around the borders between grey matter and white matter, as well as between grey matter and cerebrospinal fluid. 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 described below.

Statistical 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. Total brain volume was summation of segmented global grey matter and white matter volume in each subject. A significant level was set at $P = 0.05$ corrected for multiple comparisons. Small volume correction[33] was performed to examine each region of interest with a hypothesis (amygdala, hippocampus, insula, ACC and OFC)[6–13] using a lenient threshold of $P = 0.001$, uncorrected as a cluster determined threshold, and a $\kappa = 100$ to suppress the possibility of small clusters arising by chance, as used in previous neuroimaging studies.[7] Small volume correction was applied to each region of interest using anatomical masks (amygdala, hippocampus, insula, ACC and OFC in each hemisphere) from the WFU_PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas)[34,35] and the Anatomical Automatic Labelling Region of Interest package,[36] as used in previous VBM studies of PTSD,[7,8,37,38] as well as functional MR imaging studies.[39,40] Finally, to verify the effect of the structural changes on the CAPS scores, regression analysis was performed using Pre rGMV and Post-Pre rGMV at peak voxels in each cluster as explanatory variables, and total scores of CAPS as independent variables.

RESULTS

Demographic characteristics of the subjects are shown in Table 1. The distribution of the CAPS scores is illustrated in Figure 1. After controlling for age, total brain volume, and periods between pre- and post-earthquake MR imaging data acquisition, the total

51

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
From pre-earthquake MR scans *to* the earthquake	142.6 ± 135.4
From the earthquake to post-earthquake MR scans	101.8 ± 8.2
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

Abbreviations: CAPS, clinician-administered PTSD scale; CESD, Center for Epidemiologic Studies Depression; MR, magnetic resonance; PTSD, posttraumatic stress disorder; STAI, state-trait anxiety inventory. Values are shown as mean ± s.d.
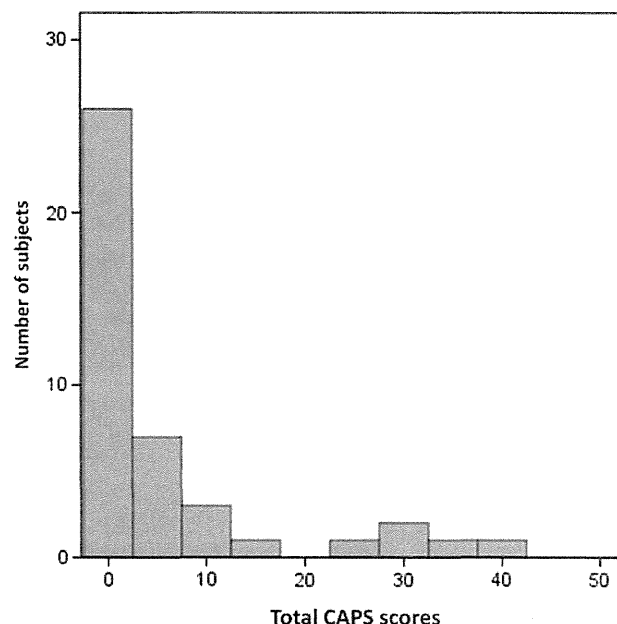

Figure 1. Distribution of total clinician-administered PTSD scale (CAPS) scores. Highest total CAPS score was 39, which is categorized as subthreshold posttraumatic stress disorder (PTSD), according to the following diagnostic categorization of PTSD by CAPS scores; 0–19 (asymptomatic/few symptoms), 20–39 (mild PTSD/subthreshold), 40–59 (moderate PTSD/threshold), 60–79 (severe PTSD symptomatology) and ⩾80 (extreme PTSD symptomatology).[25] All subjects were confirmed as non-PTSD survivors.

scores of CAPS were significantly associated with smaller Pre rGMV in the right ventral ACC ($x = 6, y = 32, z = 0$; Figure 2a, Table 2), and decreased Post-Pre rGMV in the left OFC ($x = -20, y = 52, z = -6$; Figure 2b, Table 2), based on region of interest analysis. *Post hoc* regression analysis revealed that Pre rGMV in the right ventral ACC and Post-Pre rGMV in the left OFC accounted for 48% score variance in the CAPS ($F(2, 39) = 18.28, R^2 = 0.48, P < 0.001$; Figure 3).

DISCUSSION

The aim of this study was to investigate the brain structural changes as vulnerability factors and acquired signs of PTSD symptoms in non-PTSD survivors. We found the total scores of CAPS were negatively associated with Pre rGMV in the right ventral ACC, and negatively associated with Post-Pre rGMV in the left OFC.

According to our hypothesis, smaller Pre rGMV in the right ventral ACC and decreased Post-Pre rGMV in the left OFC are structural changes representing vulnerability factor and acquired sign of PTSD symptoms, respectively. Additionally, these structural changes could explain approximately half of the observed PTSD symptoms.

Our longitudinal study provides further evidence of the causal relationships between brain structural changes and posttraumatic responses. Previous longitudinal studies have investigated brain structural changes only after the traumatic events,[11,17,18] but failed to find any brain volume reduction in patients with PTSD. Another longitudinal study revealed that the number of stressful life events is associated with decreased volumes in the ACC and hippocampus/parahippocampus in healthy subjects, but the causal relationship between psychological responses to the stressful events and brain structural changes was not examined.[14] On the other hand, in contrast to our findings, investigations of monozygotic twin pairs with PTSD revealed smaller hippocampal volume as a vulnerability factor,[16] and smaller pregenual ACC as an acquired sign of PTSD.[8] We suppose that these discrepant findings result from fundamental differences in study designs. Monozygotic twin studies cannot distinguish acquired signs of PTSD from acquired signs from birth to trauma, because of the cross-sectional design only after the traumatic events.[8] On the basis of our present findings, smaller ACC volume is not an acquired sign, but an acquired vulnerability of PTSD before exposure to traumatic events, which could have been identified as an acquired sign of PTSD in the monozygotic twin study.[8]

Several lines of evidence support the notion that smaller ventral ACC volume is a vulnerability factor for PTSD symptoms. An essential role of the ventral ACC is the processing of anxiety and fears,[41] which is supposed to be highly related to the manifestation of the clinical symptoms of PTSD.[42] In fact, smaller ACC volume is one of the more robust VBM findings in patients with PTSD,[7–9] also in normal subjects after stressful life events.[14,15] Whether such a smaller volume in the ventral ACC represents an acquired abnormality or a pretrauma vulnerability factor for PTSD is still under discussion.[8] Our present findings provide evidence that smaller ventral ACC volume is a pretrauma vulnerability factor for PTSD.

rGMV in the ACC is associated with personality traits related to PTSD symptoms. Harm avoidance,[43] which is predictive of increased PTSD symptom severity,[44] is positively associated with anatomical variability of the ACC.[45] Individuals with alexithymia, which is positively associated with PTSD symptoms,[46] had smaller ACC volume.[47] Combined with our findings, these observations support the possibility that these psychological characteristics are also vulnerability factors for PTSD.

The cognitive functions of the OFC indicate posttraumatic responses of the survivors soon after the earthquake. A principal function of the OFC is associated with extinction of conditioned fear. Previous lesion studies revealed that OFC lesion caused resistance to the extinction of conditioned fear in both non-human primates[48] and human patients with OFC lesions.[49] Neural responses in the OFC were preferentially enhanced with those in the amygdala during extinction,[50] and this relationship is crucial in the voluntary regulation of emotions.[51,52] In particular, the left lateral part of the OFC is involved in emotional distraction. The left OFC is also involved in suppression of emotional distracters during working memory performance.[53] In fact, patients with PTSD had less activity in the OFC than normal control subjects during extinction to conditioned fear[54] and emotion regulation.[55] Given the previous

4

a   Rt ACC [6 32 0]

T value

0   4

b   Lt OFC [-20 52 -6]
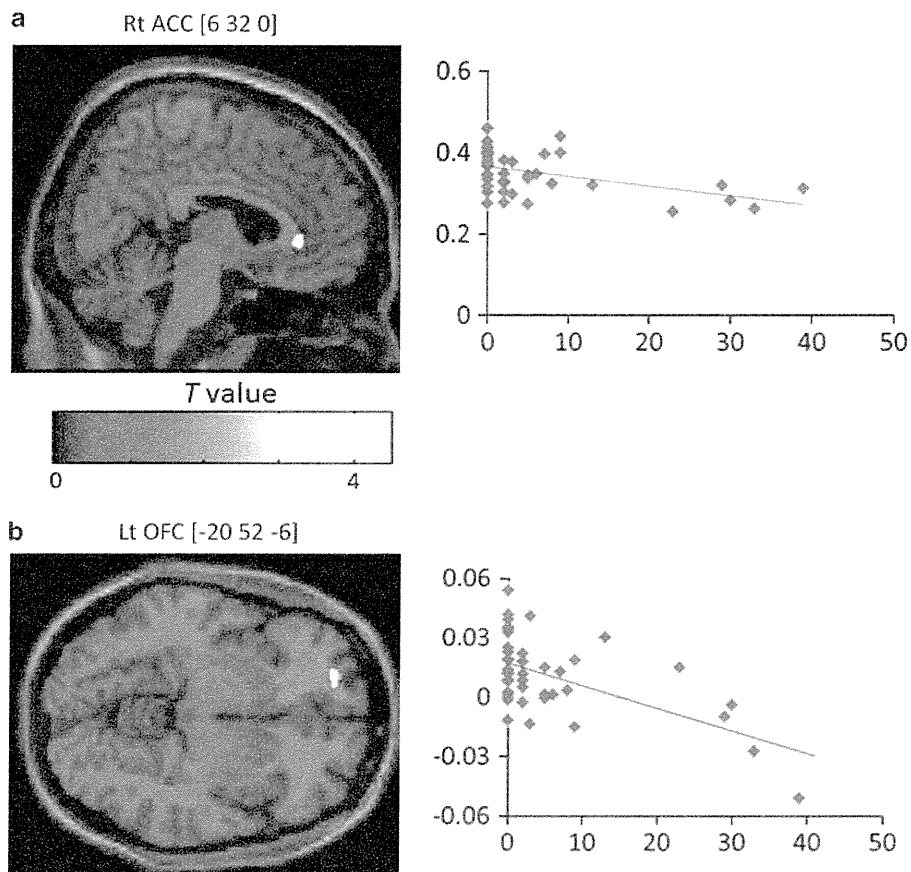
Figure 2. Relationship between total clinician-administered PTSD scale (CAPS) scores and regional grey matter volume (rGMV). Total CAPS scores were negatively associated with Pre rGMV in the right anterior cingulate cortex (ACC; **a**, Spearman's $\rho = -0.42$, $P = 0.005$) and Post-Pre rGMV in the left orbitofrontal cortex (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. The predictor brain regions are shown on the left. Rt, right; Lt, left.

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	−20	52	−6	124	4.03	0.034

Abbreviations: ACC, anterior cingulate cortex; Lt, left; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; Rt, right; SVC, small volume correction.

findings, our results indicate that decreased OFC volume might reflect difficulty in distracting emotional memories of experiences related to the earthquake. Therefore, survivors with high CAPS scores are likely to have more difficulty in distracting emotional memories compared with those with low CAPS scores.

Some limitations should be considered when interpreting the present results. First, our study included no subjects with supra-threshold PTSD symptoms and no control group without experience of the earthquake. These were predetermined limitations of this study, because most of the candidates in our pre-earthquake database were supposed to have been affected by the earthquake to some extent, but not exposed to life-threatening experiences.

We believe that the investigation of subjects with subclinical PTSD symptoms can provide sufficient evidence, like previous studies.[14,15,56-59] However, a further longitudinal study of patients with supra-threshold PTSD symptoms caused by traumatic events is necessary to examine whether the brain structural changes in our current investigation is applicable to such individuals.

Second, the CAPS scores were not normally distributed across subjects (Figure 1). As this distribution may be consistent with the expected distribution in the normal population, investigating such a population was inevitable. Even if multiple regression analysis on SPM allows independent values of non-normal distribution, the distorted distribution of the CAPS score may reduce the statistical power. Actually, of the 42 participants, 37 scored 0 to 19 and 5 scored 20 to 39 in the CAPS, which are categorized as asymptomatic and subthreshold PTSD, respectively.[25] By applying these two categories to group comparison analysis (that is, two sample *t*-test) as non-PTSD and subclinical PTSD groups, respectively, we found that similar brain regions including the Pre rGMV in the right ventral ACC and the Post-Pre rGMV in the left OFC were negatively associated with the CAPS scores ($P < 0.05$, small volume correction in each region of interest). However, another problem is that the sample size for subjects with subthreshold PTSD was too small to perform group comparison. We could not exclude the possibility that regions other than the ACC and OFC may show significant association with the CAPS scores, if the sample size was improved.

Third, although all subjects were diagnosed as normal, it was suspected that the anxiety level of subjects was relatively high. We
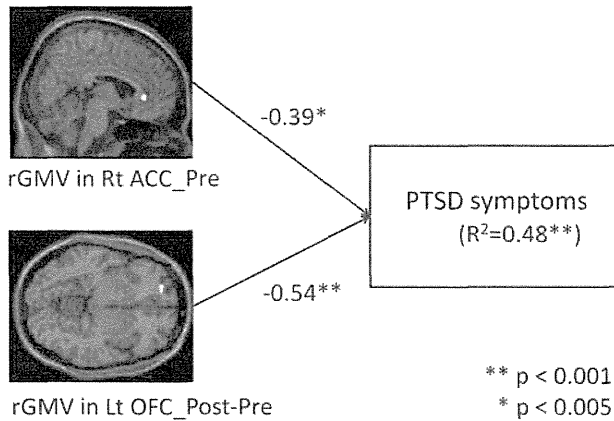
Figure 3. *Post hoc* regression analysis implemented on a path diagram. The relationships between total clinician-administered PTSD scale (CAPS) scores and Pre regional grey matter volume (rGMV) in the right ventral anterior cingulate cortex (ACC; $\beta = -0.39$, $P < 0.005$), and between total CAPS scores and Post-Pre rGMV in the left orbitofrontal cortex (OFC; $\beta = -0.54$, $P < 0.001$) are shown. The predictor brain regions are shown on the left, which predicts posttraumatic stress disorder (PTSD) symptoms evaluated by CAPS. Rt, right; Lt, left.

supposed that such high anxiety level might be caused by the aftermath of the earthquake, such as frequent afterquakes and dispersed radioactive material leaking from the nuclear plants.[60] The high anxiety levels may have some effects on the MR imaging findings. However, even if we adjusted both state and trait anxiety scores as additional covariates, we showed that similar brain regions, including the Pre rGMV in the right ventral ACC and the Post-Pre rGMV in the left OFC, were negatively associated with total CAPS scores ($P < 0.001$, uncorrected). Therefore, our MR imaging findings were robust despite the high anxiety level.

Fourth, numerous studies revealed smaller rGMV associated with PTSD in the amygdala and hippocampus,[6] and also smaller hippocampal volume represented vulnerability factor for PTSD,[16] but we failed to detect these brain regions either as a vulnerability factor or an acquired sign of PTSD. VBM may not detect such small and localized GMV reduction, because false-positive or false-negative VBM findings may arise from the change of spatial normalization.[7,61] Actually, when applying more lenient thresholds ($P < 0.01$, uncorrected) to this study, we could find negative associations between the CAPS scores and both Pre rGMV and Post-Pre rGMV in the hippocampus.

Despite these limitations, the present longitudinal study could distinguish structural changes representing a vulnerability factor from structural changes representing an acquired sign of PTSD symptoms in the early stage of adaptation to trauma. These findings may be essential to discriminate between survivors with and without PTSD symptoms soon after a traumatic event, and between survivors who will and will not develop PTSD, even in the normal population. These findings provide a better understanding of the posttraumatic responses in the early stage of adaptation to trauma, and may contribute to the development of effective methods to prevent PTSD in the normal population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Fukuda S, Morimoto K, Mure K, Maruyama S. Posttraumatic stress and change in lifestyle among the Hanshin-Awaji earthquake victims. *Prev Med* 1999; **29**: 147–151.
2 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995; **52**: 1048–1060.
3 Perrin MA, DiGrande L, Wheeler K, Thorpe L, Farfel M, Brackbill R. Differences in PTSD prevalence and associated risk factors among World Trade Center disaster rescue and recovery workers. *Am J Psychiatry* 2007; **164**: 1385–1394.
4 Furukawa K, Arai H. Earthquake in Japan. *Lancet* 2011; **377**: 1652.
5 Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ et al. Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. *Ann N Y Acad Sci* 2006; **1071**: 242–254.
6 Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev* 2006; **30**: 1004–1031.
7 Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O et al. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci USA* 2003; **100**: 9039–9043.
8 Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol Psychiatry* 2008; **63**: 550–556.
9 Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry* 2006; **59**: 582–587.
10 Chen S, Xia W, Li L, Liu J, He Z, Zhang Z et al. Gray matter density reduction in the insula in fire survivors with posttraumatic stress disorder: a voxel-based morphometric study. *Psychiatry Res* 2006; **146**: 65–72.
11 Hakamata Y, Matsuoka Y, Inagaki M, Nagamine M, Hara E, Imoto S et al. Structure of orbitofrontal cortex and its longitudinal course in cancer-related post-traumatic stress disorder. *Neurosci Res* 2007; **59**: 383–389.
12 Woodward SH, Schaer M, Kaloupek DG, Cediel L, Eliez S. Smaller global and regional cortical volume in combat-related posttraumatic stress disorder. *Arch Gen Psychiatry* 2009; **66**: 1373–1382.
13 Eckart C, Stoppel C, Kaufmann J, Tempelmann C, Hinrichs H, Elbert T et al. Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. *J Psychiatry Neurosci* 2011; **36**: 176–186.
14 Papagni SA, Benetti S, Arulanantham S, McCrory E, McGuire P, Mechelli A. Effects of stressful life events on human brain structure: a longitudinal voxel-based morphometry study. *Stress* 2011; **14**: 227–232.
15 Ganzel BL, Kim P, Glover GH, Temple E. Resilience after 9/11: multimodal neuroimaging evidence for stress-related change in the healthy adult brain. *Neuroimage* 2008; **40**: 788–795.
16 Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002; **5**: 1242–1247.
17 Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK et al. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am J Psychiatry* 2001; **158**: 1248–1251.
18 De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry* 2001; **50**: 305–309.
19 Asukai N, NishizonoMaher A. *The Japanese Version of Clinician-Administered PTSD Scale Tokyo*. Tokyo Institute of Psychiatry, 1998.
20 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59**(Suppl 20): 22–33, ; quiz 4–57.
21 Otsubo T, Tanaka K, Koda R, Shinoda J, Sano N, Tanaka S et al. Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. *Psychiatry Clin Neurosci* 2005; **59**: 517–526.
22 Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; **9**: 97–113.

6

23 World Medical Association. Declaration of Helsinki. *Law Med Health Care* 1991; **19**: 264–265.

24 Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS *et al.* The development of a Clinician-Administered PTSD Scale. *J Trauma Stress* 1995; **8**: 75–90.

25 Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. *Depress Anxiety* 2001; **13**: 132–156.

26 Spielberger C, Gorsuch R, Lushene R, Vagg P, Jacobs G. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1983.

27 Nakazato K, Mizuguchi T. *How to use STAI*. Kyoto: Sankyoubou Corp, 1982.

28 Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; **1**: 385–401.

29 Shima S, Shikano T, Kitamura T, Asai M. New self-rated scale for depression (in Japanese). *Japn J Clin Psychiatry* 1985; **27**: 717–723.

30 Gaser C. VBM Toolbox for SPM2, VBM Toolbox for SPM5. 2007 ; Available from: http://dbm.neuro.uni-jena.de/vbm/.

31 Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001; **14**(1 Part 1): 21–36.

32 Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000; **11**(6 Part 1): 805–821.

33 Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 1996; **4**: 58–73.

34 Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L *et al.* Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 2000; **10**: 120–131.

35 Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; **19**: 1233–1239.

36 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**: 273–289.

37 van Wingen GA, Geuze E, Vermetten E, Fernandez G. Perceived threat predicts the neural sequelae of combat stress. *Mol Psychiatry* 2011; **16**: 664–671.

38 Kroes MC, Rugg MD, Whalley MG, Brewin CR. Structural brain abnormalities common to posttraumatic stress disorder and depression. *J Psychiatry Neurosci* 2011; **36**: 256–265.

39 Shin LM, Bush G, Milad MR, Lasko NB, Brohawn KH, Hughes KC *et al.* Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. *Am J Psychiatry* 2011; **168**: 979–985.

40 Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, Elzinga BM, Sjoerds Z *et al.* Increased anterior cingulate cortex and hippocampus activation in Complex PTSD during encoding of negative words. *Soc Cogn Affect Neurosci*; advance online publication, 14 December 2011; doi:10.1093/scan/nsr.084.

41 Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci* 2011; **15**: 85–93.

42 Lanius RA, Bluhm R, Lanius U, Pain C. A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J Psychiatr Res* 2006; **40**: 709–729.

43 Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry* 1993; **50**: 975–990.

44 Richman H, Frueh BC. Personality and PTSD II: personality assessment of PTSD-diagnosed Vietnam veterans using the cloninger tridimensional personality questionnaire (TPQ). *Depress Anxiety* 1997; **6**: 70–77.

45 Pujol J, Lopez A, Deus J, Cardoner N, Vallejo J, Capdevila A *et al.* Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. *Neuroimage* 2002; **15**: 847–855.

46 Frewen PA, Pain C, Dozois DJ, Lanius RA. Alexithymia in PTSD: psychometric and FMRI studies. *Ann N Y Acad Sci* 2006; **1071**: 397–400.

47 Borsci G, Boccardi M, Rossi R, Rossi G, Perez J, Bonetti M *et al.* Alexithymia in healthy women: a brain morphology study. *J Affect Disord* 2009; **114**: 208–215.

48 Butter CM, Mishkin M, Rosvold HE. Conditioning and extinction of a food-rewarded response after selective ablations of frontal cortex in rhesus monkeys. *Exp Neurol* 1963; **7**: 65–75.

49 Rolls ET, Hornak J, Wade D, McGrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J Neurol Neurosurg Psychiatry* 1994; **57**: 1518–1524.

50 Gottfried JA, Dolan RJ. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. *Nat Neurosci* 2004; **7**: 1144–1152.

51 Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005; **9**: 242–249.

52 Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. *Science* 2000; **289**: 591–594.

53 Dolcos F, McCarthy G. Brain systems mediating cognitive interference by emotional distraction. *J Neurosci* 2006; **26**: 2072–2079.

54 Bremner JD, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N *et al.* Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med* 2005; **35**: 791–806.

55 New AS, Fan J, Murrough JW, Liu X, Liebman RE, Guise KG *et al.* A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. *Biol Psychiatry* 2009; **66**: 656–664.

56 Carrion VG, Weems CF, Richert K, Hoffman BC, Reiss AL. Decreased prefrontal cortical volume associated with increased bedtime cortisol in traumatized youth. *Biol Psychiatry* 2010; **68**: 491–493.

57 Cohen RA, Grieve S, Hoth KF, Paul RH, Sweet L, Tate D *et al.* Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* 2006; **59**: 975–982.

58 Gianaros PJ, Jennings JR, Sheu LK, Greer PJ, Kuller LH, Matthews KA. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage* 2007; **35**: 795–803.

59 Lui S, Huang X, Chen L, Tang H, Zhang T, Li X *et al.* High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China. *Proc Natl Acad Sci USA* 2009; **106**: 15412–15417.

60 McCurry J. Anxiety over radiation exposure remains high in Japan. *Lancet* 2011; **378**: 1061–1062.

61 Wright IC, Ellison ZR, Sharma T, Friston KJ, Murray RM, McGuire PK. Mapping of grey matter changes in schizophrenia. *Schizophr Res* 1999; **35**: 1–14.

震災後精神症状の脆弱性・獲得因子の神経基盤の解明

関口　敦[*1,2]・杉浦　元亮[*2,3]・事崎　由佳[*4]
佐久間　篤[*2,5]・瀧　靖之[*1,6]・川島　隆太[*2,4,6]

　災害ストレスに起因する精神症状と脳形態変化について多数報告はあるが，災害ストレス暴露後の横断研究が主であり，災害後精神症状の脆弱性／獲得因子としての脳形態変化は未解明であった．本稿では，我々が発表した脳形態変化と震災後精神症状の脆弱性因子／獲得因子を解明した最新の研究を紹介し，複数の脳画像データが示唆する生物学的背景について文献的考察を加え，今後の災害ストレスに関わる脳画像研究の方向性を探る．

Key Words　東日本大震災，震災後精神症状，脳形態変化，脆弱性因子，獲得因子

背　景

　東日本大震災による家屋の倒壊や津波の被害などは，仙台市中心部に位置する東北大学の周辺では沿岸部と比してはるかに少なかった．しかし，多くの被災者はライフラインの寸断，たび重なる余震，原発事故などの多大なストレスに晒され，心的外傷後ストレス障害（PTSD）に至らずとも，幅広い心理的ケアが必要であった[7,13]．

　ストレス暴露に関連する脳形態の変化は，海馬，扁桃体，前帯状皮質，眼窩前頭皮質などの灰白質の減少や，帯状束での白質統合性の低下が指摘されている．これら変化はPTSD患者[19]のみならず，ストレス暴露後の健常者[3,18]にも認められる．しかし，前向き研究の困難さから[20]ストレス暴露後の脳画像評価が主であり，ストレス暴露と脳

形態変化の因果関係は未解明であった．

　我々の研究室では，主に東北大学の健常学生を対象とした脳画像研究を行っており，震災前の脳画像のデータを多数保有しており，これらデータベースを活用して，震災前後の縦断的な脳画像研究を行うことができた．本稿では，最近発表した脳灰白質／白質の形態変化と震災後精神症状の脆弱性因子／獲得因子に関する研究[22,23]を紹介し，脳灰白質変化と脳白質変化の一致点・不一致点および，複数の脳画像データセットから得られる生理学的背景について文献的考察を加える．

方　法

　我々の研究室では，主に健常大学生を対象とし，MRIを用いた脳画像研究を行っており，震災前の脳画像を多数保有している．今回，震災前の脳形態画像（T1強調画像）が存在する被験者に連絡をとり，42名（男／女：33／9人，年齢，21.7 ± 1.7歳）を再募集することができた．これら被験者に対して，震災後3〜4カ月の時点でT1強調像を撮像した．また42名のうち，震災前の拡散強調画像が存在した30名（男／女：24／6人，年齢，21.0 ± 1.6歳）に対して，拡散強調

＊1　東北大学　東北メディカル・メガバンク機構　地域医療支援部門　脳画像解析医学分野
〒980-8575　宮城県仙台市青葉区星陵町4-1
＊2　東北大学　加齢医学研究所　脳機能開発研究分野
＊3　東北大学　災害科学国際研究所　災害情報認知研究分野
＊4　東北大学　加齢医学研究所　スマートエイジング国際共同研究センター　応用脳科学研究分野
＊5　東北大学　大学院医学系研究科　精神神経学分野
＊6　東北大学　加齢医学研究所　認知機能発達寄附研究部門