的知性が改善されることも報告されている(Kim and Park, 2010; Park and Huh, 2010; Kotozaki, 2014)。今回の我々の園芸活動では、参加者の人たちが一緒に活動する期間が長期に渡ったので、その中で彼女たちは園芸を通して新たなコミュニケーションスキルと対人関係のスキルを向上させることができたのではないかと考える。

以上、3つの研究結果から、東日本大震災を経験したことによってみられていた軽度 PTSD 症状やストレス症状など心理状態の回復が見られ、軽度 PTSD 症状を持つ女性に対する園芸療法の効果が認められた。また、被災者のストレス症状やうつ症状など心理状態の回復が見られ、かつ、コミュニティ意識の改善が確認され、新たな地域コミュニティ再生におけるコミュニティ活性のツールとしての園芸療法の有効性が認められた。これは、東日本大震災のような大規模自然災害を経験した人々に対する中長期的な心理的支援の方法の一つの可能性としての園芸療法の有効性を示唆できるものと考えられる。

E. 結論

我々の一連の研究は，東日本大震災によって特に甚大な被害を受けた地域に在住する被災者に対する心理療法の生活介入の結果を報告した世界で初めての研究であり、地域コミュニティ再生におけるコミュニティ活性のツールとしての園芸療法の有効性の結果を報告した世界で初めての研究である。災害ストレスによる心身面への影響、および、被災者に対するメンタルケアへの理解を深め，災害後の精神症状に対する中長期的なメンタルケア、心理支援に関する基礎研究として重要な位置づけにあると考える。

研究を通して、被災者への園芸療法の効果が実証され、地域コミュニティ支援としての園芸療法の体系の確立させることで、学術研究領域への知見提供だけでなく、将来的には、自治体と協働して活動に取り組むことで、被災地の地域コミュニティ再生を加速化させるシステムを構築するなど被災地・被災者復興への貢献が可能となると期待している。

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H. 知的財産権の出願・登録状況

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3. その他

なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sekiguchi, A et. al.	Resilience after 3/11: Structural brain changes 1 year after the Japanese Earthquake	Molecular Psychiatry	20	552-554	2015
Sekiguchi, A et. al.,	Long-term effects of post-earthquake distress on brain microstructural changes.	BioMed Research International	2014	180468	2014
Sekiguchi, A et. al.,	White matter microstructural changes as vulnerability factors and acquired signs of post-earthquake distress	PLoS ONE	9 (1)	e83967	2014
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Sekiguchi, A et. al.,	Causal Relationship Between Psychological Distress After a Severe Earthquake and Brain Structural Changes	Human Science & Technology	Vol 10	31-37	2013
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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kotozaki Y et. al.	Positive effects of the victim by the growing of plants after great east japan earthquake	International Journal of Recent Scientific Research	6(2)	2850-2858	2015
Kotozaki Y	Effects of horticultural intervention on cognitive function in elderly women of mild PTSD two years after the East Japan Great Earthquake	International Journal of Recent Scientific Research	6(2)	2833-2836	2015
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雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kotozaki Y	The psychological changes of horticultural therapy intervention for elderly women of earthquake-related areas	Journal of Trauma & Treatment	3	184	2013
Kotozaki, Y et. al.,	Psychological Effects of the Great East Japan Earthquake: Posttraumatic Stress, Psychological Effects and the Cortisol Levels in Women Who Li	Human Science & Technology	Vol 10	38-45,	2013
Kotozaki Y	The Psychological Effect of Horticultural Therapy Intervention on Earthquake-Related Stress in Women of Earthquake-Related Areas	Journal of Translational Medicine & Epidemiology	1(2)	1008	2013
Kotozaki, Y et. al.,	Effects of the Higashi-Nihon Earthquake: posttraumatic stress, psychological changes, and cortisol levels of survivors	PLoS ONE	Vol 7(4)	e34612	2012

III. 研究成果の刊行物・別刷

clearly distinguished from the other samples analyzed, and displayed a 1.5–2-fold greater increase in cell number, mainly at the later time points of the curve (Figure 1b, Supplementary Figure 1b), and reduced response to the antiproliferative effect of rapamycin, a specific mTOR inhibitor (Figure 1c, Supplementary Figure 1c). Curiously, whereas dual PI3K-mTOR inhibition (wortmannin+rapamycin treatment) continued to be less effective in reducing to a similar extent the proliferation of ASD1–2 and control cells, it was able to restore the enhanced proliferation of ASD3 cells (Figure 1c, Supplementary Figure 1c), suggesting a possible different regulatory mechanism in ASD3 cells. Knockout mouse models of both syndromic and nonsyndromic ASD with disinhibited mTOR signaling and dysregulated protein synthesis present dysplastic and enlarged neurons with increased spine density in several brain regions.[5,7,8] Although we did not notice increased ASD1–3 SHED volumes, it will now be important to determine and explore further whether the altered proliferative phenotype observed in these cells may also be observed in neuronal cell types, which could be a potential additional mechanism whereby disrupted mTORC1 signaling contributes to ASD neuropathology.

Conventional karyotyping and analysis of copy number variations at 15q11-q13, 16p11 and 22q13, found to occur more often in ASD, did not reveal any genomic aberrations in all patients except ASD3, who presents an inverted duplication of 15q11-q13. It is possible that genes located at this region may contribute to the aberrant molecular and cellular phenotypes observed in ASD3 cells. In addition, *TSC1/2*, *FMR1*, *PTEN*, *NF1* and *MeCP2* genes (ASD-associated genes known to be negative regulators of PI3K-mTOR signaling pathway) were screened for coding and splice-site mutations in ASD1–13 patients and no potentially deleterious variants were identified. Therefore, the causative genetic architecture underlying mTORC1 overactivity in ASD1–3 cells remains to be determined. It is also noteworthy that patients ASD1–3, who seem to some extent share overlapping pathophysiological mechanisms, show different degree of cognitive and social impairments: ASD1 was diagnosed with Asperger syndrome and ASD2–3 with low-functioning autism (Supplementary Table S1), suggesting that other genetic and environmental modifier factors may also have a role in cognitive development in these patients.

In conclusion, our results suggest that dysregulation of mTORC1 signaling has an important role in the pathogenesis of a subgroup of nonsyndromic ASD, and that mTOR pathway components might be promising therapeutic targets for these patients. Importantly, during the revision process of this manuscript, it was reported hyperactivated mTOR signaling in postmortem brain tissue from both adolescent patients with idiopathic ASD[9] and 15q11-q13 duplication patients with ASD,[10] which provide further strong support for this hypothesis. Finally, our results suggest that SHEDs are an alternative and more readily accessible source of patient material to study disease pathophysiology and to refine treatment approaches for individual patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

OPEN

Resilience after 3/11: structural brain changes 1 year after the Japanese earthquake

Molecular Psychiatry (2015) **20,** 552–554; doi:10.1038/mp.2014.28; published online 29 April 2014

Stressful events can have both short- and long-term effects on the brain.[1,2] A recent investigation by our lab identified regional grey matter volume (rGMV) changes in people in the months following the Japanese earthquake.[3] These findings indicated that smaller anterior cingulate cortex volume was a preexisting vulnerability factor for posttraumatic stress disorder (PTSD) symptoms and that decreased volume of the orbitofrontal cortex (OFC) was a result of these acquired symptoms.[3] These types of symptoms were regarded as manifestations of the short-term effects of post-earthquake stress. However, the long-lasting effects of stressful events on brain structures remain unclear. Thus, this study examined the 1-year prognoses of subjects after a stressful event to clarify the long-term effects of stress on structural brain changes.

Of the 42 subjects included in our previous study,[3] 37 subjects (male/female (M/F) = 28/9, age = 21.0 ± 1.6 years) were recruited for a third time, and their structural magnetic resonance imaging (MRI) scans were evaluated 1 year after the earthquake. The optimized voxel-based morphometry (VBM) method for a brain structural data set (for greater detail, see Sekiguchi *et al.*,[3]) was applied, and rGMVs from before (Pre), soon after (Post) and at the 1-year follow-up (Follow-up) of the earthquake were compared using conjunction analyses. In addition, we also assessed the subjects' psychological characteristics, including anxiety, depression, posttraumatic growth and self-esteem. Furthermore, we

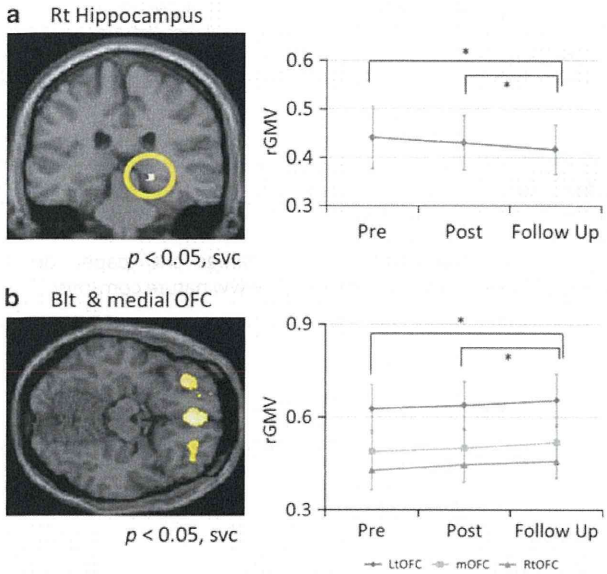

Figure 1. (**a**) Right hippocampal volumes significantly decreased from Pre to Post and from Post to Follow-up and (**b**) bilateral and medial orbitofrontal cortex (OFC) volumes significantly increased from Pre to Post and from Post to Follow-up. These regional grey matter volume (rGMV) changes are illustrated by the plots on the right side, where vertical axes represent rGMV at peak voxels in each cluster, and horizontal axes indicate time periods. Error bars represent s.d. values. Blt, biltateral; Lt, left; Rt, right.

collected longitudinal brain structural MRI data from 11 normal controls (M/F = 7/4, age = 20.2 ± 1.0 years) obtained on at least two occasions before the earthquake (see Supplementary Methods for additional details).

At 1 year after the earthquake, none of the subjects in this study had developed clinical PTSD, whereas other psychological measures did not significantly change from Post to Follow-up (see Supplementary Table S1). In terms of rGMV, bilateral and medial OFC volumes significantly increased ($P < 0.05$; small-volume correction, SVC), and right hippocampal volumes significantly decreased ($P < 0.05$, SVC) from Pre and Post to Follow-up (Figure 1; Supplementary Table S2), whereas the control subjects did not show above-mentioned rGMV changes between two time points. *Post hoc* correlation analyses revealed that the increase in the volume of the left OFC from Post to Follow-up was significantly correlated with self-esteem scores at Post ($r = 0.43$, $P = 0.007$; Supplementary Table S3).

The increase in OFC volume identified in some subjects who reported stress indicates that recovery from emotional distress is possible following a stressful event. Previous neuroimaging findings have shown that a reduction in OFC volume is a sign of emotional distress following stressor,[3] but stress-induced structural and functional alterations in the OFC are reversible.[4] Although the left OFC volume in our subjects experiencing PTSD symptoms soon after the earthquake decreased in the short term,[3] the mean OFC volumes increased during this period (Figure 1b), which is consistent with previous findings soon after a disaster.[5] Moreover, the results provide an initial indication that the increased left OFC volume was caused by higher self-esteem. Given that higher self-esteem is one of the most important traits of resilience in the context of stressful life events,[6] it is possible that self-esteem is a predictor of increased OFC volume, representing the successful regulation of emotional distress after the earthquake by healthy survivors.

In contrast, stress related to the earthquake may persist even after 1 year. Psychological evaluations at 1 year revealed that even subclinical levels of depression and anxiety levels had not improved from soon after the earthquake. Hippocampal volume reduction is a robust finding in traumatized subjects,[7] and is observed even in subjects with subclinical depression after a disaster.[5] Even if the hippocampal volume of young healthy adults were not significantly but slightly reduced as a function of aging (see Supplementary Discussion), post-earthquake stress would accelerate the hippocampal volume reduction because age-related reduction is modified by PTSD and depression.[8] Together, these findings led us to hypothesize that both prolonged stress and aging affect a reduction in hippocampal volume over time, whereas short-term stress does not reduce hippocampal volume in the period immediately following stressful events such as earthquakes[3] (see Supplementary Discussion).

The limitations of this study included the absence of psychological assessments and incomplete profiles for the control subjects (see Supplementary Discussion).

Despite these limitations, the present follow-up VBM study found that stressful events had long-lasting effects on various brain structures, suggesting that such changes are influenced by prolonged stress and self-esteem characteristics. Here, it was assumed that structural changes in the brain following stressful life events are not static, but dynamic, throughout one's lifetime. Recently, altered functional and structural connectivity, including in regions adjacent to the OFC and hippocampus as well as in the insula, basal ganglia and parietal lobe,[9,10] have been reported soon after a disaster. Therefore, further longitudinal investigations using multimodal approaches are necessary to examine whether the stress-induced alterations in brain structure are reversible (see Supplementary Discussion).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the study. AS, YK, MS, TA, SH, SN, and CMM contributed to data acquisition. AS, MS, YK, RN, HT, TA, YT and RK contributed to the data analysis and interpretation. AS, MS, RN, HT, TA, YT and RK provided statistical expertise. AS wrote the manuscript. MS, RN, HT, YT and RK reviewed/revised the manuscript. All authors discussed the results and commented on the manuscript. All authors gave their final approval for the manuscript to be submitted.

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Research Article

Long-Term Effects of Postearthquake Distress on Brain Microstructural Changes

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Stressful events can have both short- and long-term effects on the brain. Our recent investigation identified short-term white matter integrity (WMI) changes in 30 subjects soon after the Japanese earthquake. Our findings suggested that lower WMI in the right anterior cingulum (Cg) was a pre-existing vulnerability factor and increased WMI in the left anterior Cg and uncinate fasciculus (Uf) after the earthquake was an acquired sign of postearthquake distress. However, the long-term effects on WMI remained unclear. Here, we examined the 1-year WMI changes in 25 subjects to clarify long-term effects on the WMI. We found differential FAs in the right anterior Cg, bilateral Uf, left superior longitudinal fasciculus (SLF), and left thalamus, suggesting that synaptic enhancement and shrinkage were long-term effects. Additionally, the correlation between psychological measures related to postearthquake distress and the degree of WMI alternation in the right anterior Cg and the left Uf led us to speculate that temporal WMI changes in some subjects with emotional distress occurred soon after the disaster. We hypothesized that dynamic WMI changes predict a better prognosis, whereas persistently lower WMI is a marker of cognitive dysfunction, implying the development of anxiety disorders.

1. Introduction

Stressful events have both short- and long-term effects on the brain [1, 2]. Acute and chronic stress-induced brain microstructural changes have been observed in prefrontal areas in rodents [3]. Recent human studies identified white matter microstructural changes due to stress using diffusion tensor imaging (DTI) methods [4] in subjects with post-traumatic stress disorder (PTSD) [5–8] as well as healthy survivors of a disaster [9]. These studies revealed lower white matter integrity (WMI) in several brain regions, including the cingulum (Cg) and uncinate fasciculus (Uf), in subjects who developed PTSD [5–8] (i.e., long-term effect) and in individuals soon after a disaster [9] (i.e., short term effect).

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

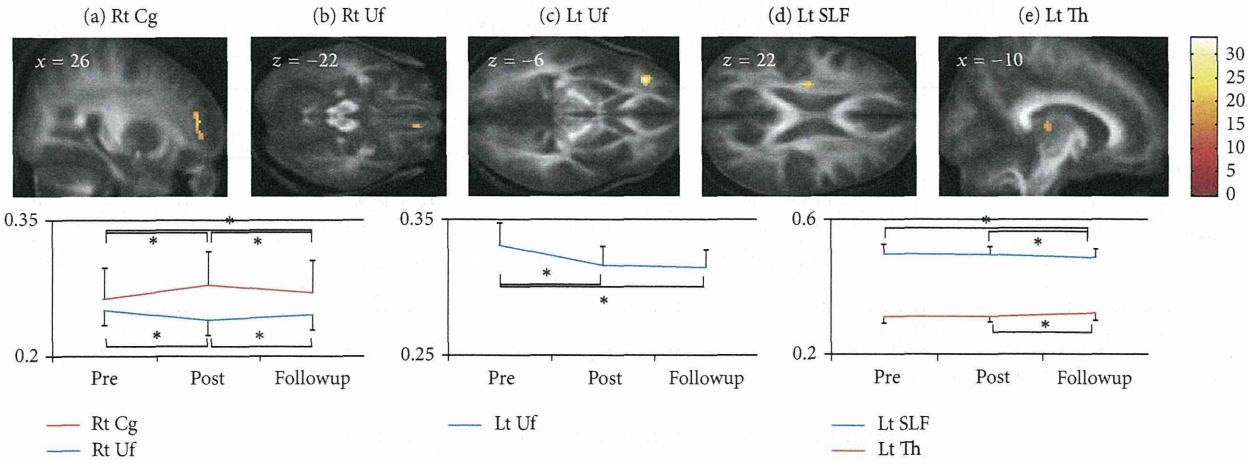

FIGURE 1: (a) FA in the right anterior Cg was significantly increased from pre to post ($P < 0.05$, paired t-test) and from pre to followup ($P < 0.05$, paired t-test), but it was significantly decreased from post to followup ($P < 0.05$, paired t-test). (b) FA in the right Uf was significantly decreased 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 SLE 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; SLE: 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

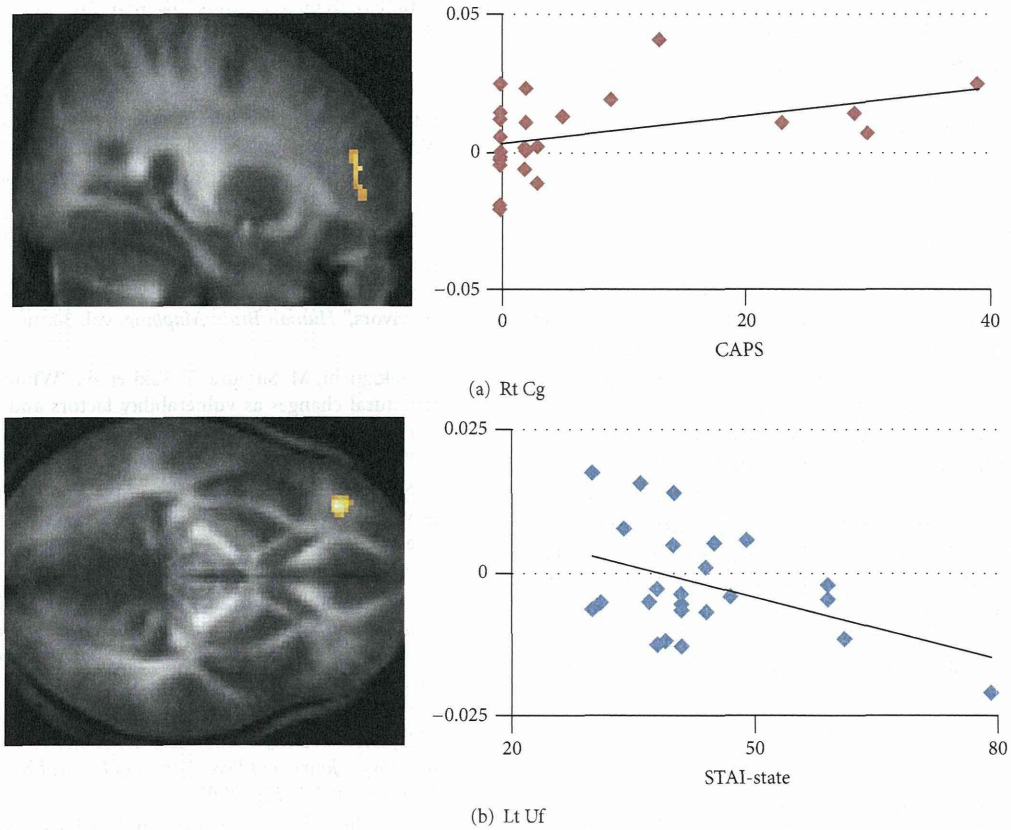

FIGURE 2: (a) CAPS scores were positively associated with FA changes from pre to followup in the right anterior Cg (Spearman's Rho = 0.414, $P = 0.039$), and (b) STAI-state scores were positively associated with FA changes from post to followup in the left Uf ($r = -0.440$, $P = 0.028$), as illustrated 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.

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