ORIGINAL ARTICLE

The Neurobiological Role of the Dorsolateral Prefrontal Cortex in Recovery From Trauma

Longitudinal Brain Imaging Study Among Survivors of the South Korean Subway Disaster

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Context: A multiwave longitudinal neuroimaging study in a cohort of direct survivors of a South Korean subway disaster, most of whom recovered from posttraumatic stress disorder 5 years after trauma, provided a unique opportunity to investigate the brain correlates of recovery from a severe psychological trauma.

Objectives: To investigate region-specific brain mobilization during successful recovery from posttraumatic stress disorder by assessing cortical thickness multiple times from early after trauma to recovery, and to examine whether a brain-derived neurotrophic factor gene polymorphism was associated with this brain mobilization.

Design: Five-year follow-up case-control study conducted from 2003-2007.

Setting: Seoul National University and Hospital.

Participants: Thirty psychologically traumatized disaster survivors and 36 age- and sex-matched control group members recruited from the disaster registry and local community, respectively, who contributed 156 high-resolution brain magnetic resonance images during 3 waves of assessments.

Main Outcome Measures: Cerebral cortical thickness measured in high-resolution anatomic magnetic resonance images using a validated cortical thickness analysis tool and its prospective changes from early after trauma to recovery in trauma-exposed individuals and controls.

Results: Trauma-exposed individuals had greater dorsolateral prefrontal cortical (DLPFC) thickness 1.42 years after trauma (right DLPFC, 5.4%; left superior frontal cortex, 5.8%; and left inferior frontal cortex, 5.3% [all clusters, $P \leq .01$]) relative to controls. Thicknesses gradually normalized over time during recovery. We found a positive linear trend, with trauma-exposed individuals with a valine/valine genotype having the greatest DLPFC cortical thickness, followed by those with a methionine genotype and controls ($P < .001$ for trend). Greater DLPFC thickness was associated with greater posttraumatic stress disorder symptom reductions and better recovery.

Conclusion: The DLPFC region might play an important role in psychological recovery from a severely traumatic event in humans.

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On February 18, 2003, a metropolitan subway train was set on fire by an arsonist at the Jungangno Station in Daegu, South Korea. One hundred ninety-two people perished and hundreds more were injured. After this tragedy, a substantial number of survivors have struggled to overcome the traumatic memories and to return to their normal lives. Five years after the disaster, most survivors showed significant improvement in posttraumatic stress disorder (PTSD) symptoms, echoing our innate mechanism to promote psychological recovery from a severely traumatic event.

An increased risk of exposure to extreme traumatic events, including terrorist attacks, natural disasters, accidents, physical assaults, torture, or military combats, has become a concern of modern life.[1] A substantial number of trauma-exposed individuals develop PTSD. Core symptoms of PTSD include reexperience of trauma, avoidance of trauma-related stimuli, and hypervigilence.[2-6] In a nationwide epidemiological study, individuals with PTSD showed varying clinical courses ranging from successful recovery to chronic PTSD, with recovery in about half the persons.[6]

Studies in rats have indicated the crucial role of the amygdala, hippocampus, and ventromedial prefrontal cortex and their functional relationships in fear extinction learning.[7,8] Results of functional and structural neuroimaging studies in pa-

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tients with PTSD and studies in healthy volunteers with fear extinction paradigms reflect this model of PTSD neurocircuitry.[9-14] More recently, the dorsomedial prefrontal cortex and the dorsolateral prefrontal cortex (DLPFC) have been implicated as having a role in fear extinction learning.[7] Additional studies[13,15] have suggested that the DLPFC could be pivotal in the conscious regulation of emotion to reduce fear responses,[9] suggesting the role of the DLPFC in recovery from PTSD. However, to the best of our knowledge, no longitudinal imaging study, from trauma to recovery, has studied individuals with PTSD to identify brain correlates related to recovery.[11,16-21]

Understanding how the trauma-exposed brain responds and changes during recovery from trauma and identifying specific brain regions that are linked to efficient recovery will provide valuable information regarding the development of preventive measures for trauma-exposed individuals and more treatment options for patients with PTSD.[22,23] A longitudinal brain imaging study in which trauma-exposed individuals undergo multiple assessments from trauma to recovery would be an efficient way to accomplish this goal.

Two recent studies[24,25] in combat veterans and torture survivors retrospectively assessed trauma and head injury and evaluated current psychiatric symptoms with neuroimaging data acquisition. The findings suggested that lesions and deficits in the DLPFC of the brain may be related to unfavorable mental health outcomes, including depression and PTSD. The DLPFC has a wide array of reciprocal connections to the limbic structures, including the amygdala, hippocampus, and ventromedial prefrontal cortex,[26] allowing it to exert control over these structures. The altered structure and function of these areas have consistently been reported in individuals with PTSD.[11,16-19] Therefore, the DLPFC may cautiously be hypothesized as playing an important role in recovery from PTSD by providing cognitive control over the dysregulated fear and anxiety circuit among the ventromedial prefrontal cortex, amygdala, and hippocampus.[23,26]

More studies have shown that brain structure and function measurably change in response to external stimuli and internal requirements in adults and children.[27-30] Among trauma-exposed individuals, a potential for greater cortical plasticity of the DLPFC in response to emotional distress may be an important factor in mobilizing the DLPFC function for strong and efficient emotional regulation. This plasticity thus provides resilience to or recovery from PTSD.[23,26]

Brain-derived neurotrophic factor (BDNF) is a key molecule that mediates experience-dependent cortical plasticity[30-34] and is abundantly expressed in the prefrontal cortex.[31] Increasing evidence indicates that a single nucleotide polymorphism of the *BDNF* gene (rs6265) prodomain involving substitution of valine (Val) for methionine (Met) influences experience-dependent plasticity, with Val homozygotes having the greater plasticity. This evidence suggested that capacity for mobilizing the DLPFC in an effort to overcome trauma and subsequent PTSD potentially differs by *BDNF* polymorphism. Recent animal and human studies[35,36] have also shown that efficiency in the extinction learning is associated with *BDNF* polymorphism.

To investigate the brain regions that were mobilized during individuals' active efforts to overcome trauma and following mental health sequelae including PTSD, we followed up direct survivors of the Daegu subway disaster soon after trauma through the course of recovery using multiple waves of clinical, neuropsychological, and high-resolution brain imaging measurements with acquisition of the genetic information.

We hypothesized that there would be early increases in the cortical thickness of the DLPFC in trauma-exposed individuals corresponding with successful improvement in PTSD symptoms, with greater increases associated with later recovery as well. We also hypothesized that the extent of greater thickness of the DLPFC early after trauma would differ by the *BDNF* genotype, with greater increases in Val homozygotes than in Met carriers.

METHODS

DISASTER

On February 18, 2003, a fire was started on one subway train and spread to another that was entering the station from the opposite direction. Twelve subway coaches from both trains were burned completely. Of about 450 passengers aboard these trains, 192 died and approximately 148 had various levels of injuries.

PARTICIPANTS AND TIME FRAME OF SERIAL ASSESSMENTS

A registry of the Daegu subway disaster survivors (n=83) was established to monitor their mental and physical health problems. From these survivors, a longitudinal cohort of trauma-exposed individuals was derived. A detailed flow diagram of the progress of participants from the registry through study participation is presented in Author Figure 1 (available on the authors' Web site [http://bic.snu.ac.kr/supplement/2011/AuthorContent_Trauma.pdf]).

Baseline clinical assessment (time 0) for diagnosis and symptom severity of PTSD was conducted from 1.0 to 3.5 (mean [SD], 1.65 [0.74]) months after the disaster (**Figure 1**). We included trauma-exposed individuals aged 18 to 50 years who were passengers in the fire-caught coaches; who escaped without head trauma, smoke inhalation injury, loss of consciousness, or any burns and organ damage; and who met the *DSM-IV* criteria for PTSD[37] because of this traumatic event as confirmed by the Structured Clinical Interview for the *DSM-IV*.[38] At study entry, we excluded individuals with any of the following: lifetime (before the subway disaster) Axis I psychiatric disorders, including PTSD and alcohol and other drug abuse; Axis II antisocial and borderline personality disorders; a history of or current major medical conditions, including hypertension and diabetes mellitus; clinically significant abnormal findings in physical examinations, routine laboratory tests, and electrocardiography; urinalysis findings positive for psychoactive drugs; a history of alternative and complementary medical treatments with herbal mixtures; contraindications to brain magnetic resonance imaging (MRI), including claustrophobia, pacemakers, and metal implants; and previous exposure to traumatic events that may potentially cause PTSD.

Exclusion criteria during the study period included the use of complementary and alternative medical treatments with herbal mixtures because some ingredients may exert unknown effects on brain structure and function (a detailed explanation

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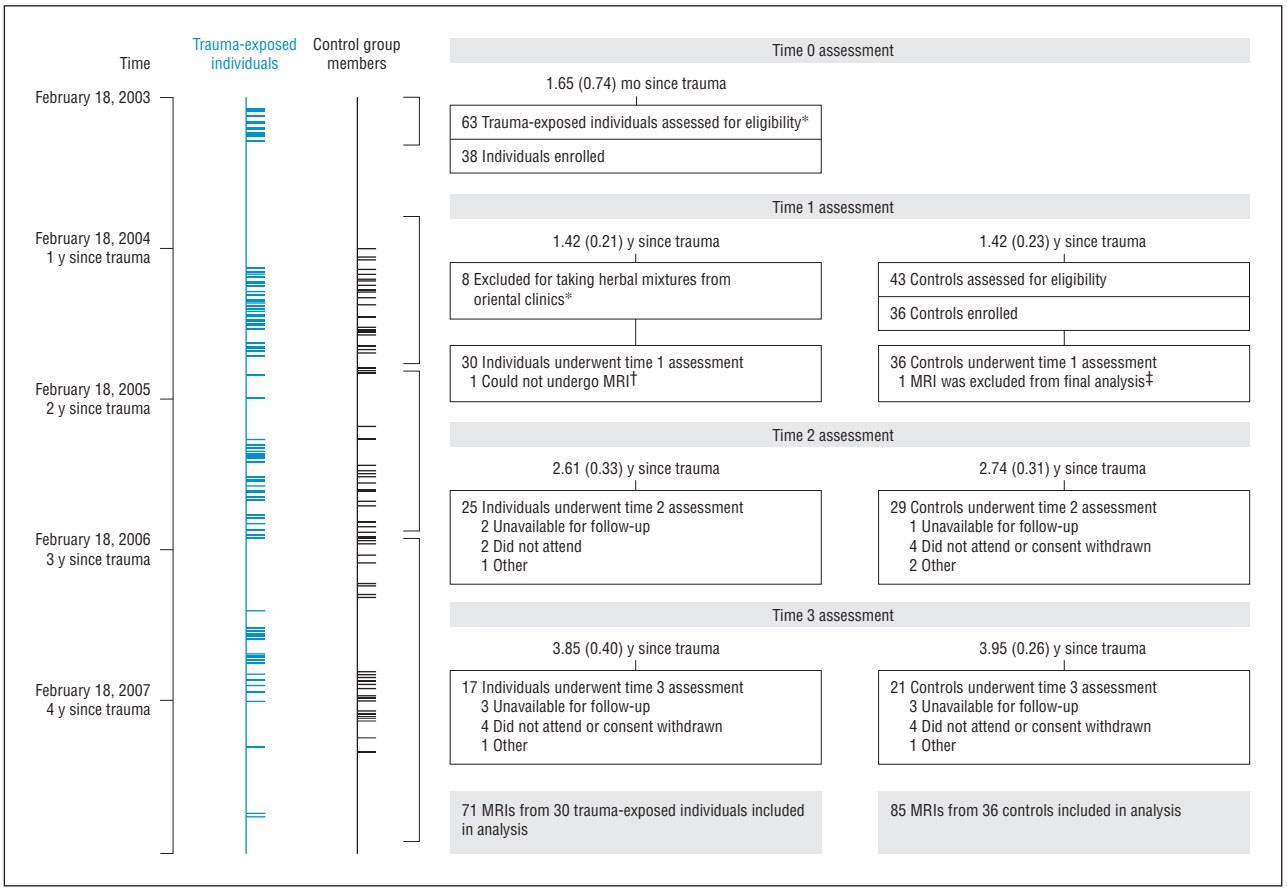

Figure 1. Flow diagram of participants through the study. *Among the 63 trauma-exposed individuals, we excluded those with a history of pituitary adenoma that had been surgically removed (n=1), loss of consciousness during escape owing to traumatic head injury or inhalation of toxic fumes or smoke (n=5), and reported history of previous admission to a psychiatric hospital for alcohol-related problems (n=1). For ethical reasons, 2 individuals who reported previous claustrophobic experiences during neck scans were also excluded. Sixteen individuals did not meet the diagnostic criteria for posttraumatic stress disorder (PTSD). We enrolled the remaining 38 trauma-exposed individuals who were diagnosed as having PTSD and were eligible for this study on the basis of inclusion and exclusion criteria. †One trauma-exposed individual could not undergo magnetic resonance imaging (MRI) at time 1 because of dental braces. Images obtained from this person at times 2 and 3 were included in the analysis. ‡One MRI of a control group member was excluded from the analysis because of inadequate image quality. Images obtained at times 2 and 3 from this person were included in the analysis. Times since trauma are expressed as mean (SD).

is available in Author Methods 1 [available on the authors' Web site]).[39-42] All trauma-exposed individuals were psychotropic naive at the time of trauma exposure. Four trauma-exposed individuals took anxiolytics and antidepressants during the early months after the trauma. Five trauma-exposed individuals were referred for treatment on the basis of predefined clinical referral criteria but did not take psychotropics or have regular psychotherapeutic sessions primarily owing to fear of being stigmatized. Consequently, 26 of 30 trauma-exposed individuals were psychotropic naive for their lifetimes, including the study period. Four trauma-exposed individuals who had taken psychotropics early after the trauma were psychotropic free for 6 months before the first wave of MRI scans and thereafter.

No control met clinical referral criteria or used psychotropics before or during the study period.

Among 63 candidates undergoing the initial screening, 38 trauma-exposed individuals (16 men and 22 women) were enrolled according to the inclusion and exclusion criteria and underwent assessment at time 0 (Figure 1). We excluded 8 individuals owing to the use of herbal mixtures between time 0 and time 1, leaving 30 trauma-exposed individuals at time 1.

Thirty-six age- and sex-matched healthy controls (14 men and 22 women) were recruited from the local community by time 1 for matching the time 1, 2, and 3 evaluations in the trauma-exposed individuals, with the same set of exclusion criteria as that for trauma-exposed individuals. This control cohort included 6 surplus individuals (3 men and 3 women) who were enrolled in consideration of the potential difficulties of following up healthy volunteers. Previous lifetime stressors were documented for all individuals using the Life Stressor Checklist–Revised[43] (Author Methods 2 [available on the authors' Web site]).

Three serial sets of clinical and neuropsychological assessments and brain MRI scans were performed at approximately 1.3-year intervals during the 5-year study for trauma-exposed individuals and controls. Figure 1 provides a detailed timeline of individual assessments and the number of participants.

Symptom severity for PTSD and comorbid Axis I disorders were determined using the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS)[44,45] and the Structured Clinical Interview for the *DSM-IV*, respectively. Reliability measures for all structured interviews are described in Author Methods 3 (available on the authors' Web site).

This study was approved by the Seoul National University Hospital institutional review board. All individuals provided written informed consent to participate in this longitudinal follow-up study at study entry and at each subsequent assessment.

Subject protection policies included clinical referrals for further evaluation and treatment if participants scored higher than 14 on the 17-item Hamilton Depression Rating Scale[46] or showed suicidal ideation or clinical psychiatric syndromes. These evalu-

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ations were performed at each time point by independent psychiatrists who were not involved in the research project. Clinical referral during the study was not an exclusion criterion.

MRI ACQUISITION

Brain MRI scans were obtained on the same 3-T whole-body imaging system (Signa EXCITE; General Electric Medical Systems, Milwaukee, Wisconsin). Sagittal T1-weighted images were acquired with the 3-dimensional inversion recovery spoiled gradient-echo pulse sequence (echo time [TE], 1.4 milliseconds; repetition time [TR], 5.7 milliseconds; inversion time [TI], 400 milliseconds; matrix, 256 × 256; field of view [FOV], 22 cm; flip angle, 20°; number of excitations [NEX], 1; section thickness, 0.7 mm; no skip). Axial T2-weighted images (TE, 118 milliseconds; TR, 3500 milliseconds; matrix, 256 × 192; FOV, 22 cm; flip angle, 90°; NEX, 3; section thickness, 5 mm; 1.5-mm skip) and fluid-attenuated inversion recovery axial images (TE, 145 milliseconds; TR, 9900 milliseconds; TI, 2250 milliseconds; matrix, 256 × 192; FOV, 22 cm; flip angle, 90°; NEX, 1; section thickness, 5 mm; 1.5-mm skip) were also obtained.

We used the same scanner with the same software version and initial hardware settings throughout the 5-year study period. Detailed scanner maintenance information and measures for securing consistent head positions throughout serial MRI scans are described in Author Methods 4 (available on authors' Web site).

Experienced neuroradiologists confirmed that no subject had any gross brain abnormality. Potential image acquisition errors including motion artifacts were also assessed and rated (Author Methods 4).

CORTICAL THICKNESS MEASUREMENT

We performed cortical surface reconstruction and cortical thickness measurement with cortical surface-based analysis. We used FreeSurfer tools,[47] an automated procedure involving a series of steps that consisted of intensity normalization, skull stripping, segmentation of the cortical white matter, subsequent tessellation of gray/white matter boundaries, and smoothing and inflation of the surface.[48,49] The deformable surface algorithm allows for detection of the gray/white matter boundaries and surfaces with submillimeter precision.[49,50]

At several junctures through the processing stream, data from each individual were visually inspected, manually corrected, and reinspected to ensure the accuracy by an experienced doctoral-level rater (S.J.Y.) who was blinded to the participant's identity. Each person's data were smoothed onto the surface tessellation using a kernel of 20 mm full-width at half-maximum and then resampled into a common spherical coordinate system.[48] The detailed process has been described elsewhere.[25,51]

This technique used to measure cerebral cortical thickness was validated via histological[50] and manual measurements,[52,53] establishing excellent test-retest reproducibility.[54,55] Reliability of the cortical thickness measurement was assessed in the following 2 ways: (1) interrater and intrarater reliabilities of measuring cortical thickness using the same set of brain images and (2) measuring cortical thickness of controls who underwent repeated scans at 2-week intervals (Author Methods 5 [available on the authors' Web site]).

SURFACE-BASED ANALYSIS OF CORTICAL THICKNESS

Surface-based between-group comparisons used general linear models adjusted for age and sex. Mean cerebral cortical thickness and intracranial volume were initially considered as potential covariates but were not included in the main analysis because models with or without these covariates produced similar results (eFigure 1A-C; http://www.archgenpsychiatry.com).

To correct for multiple comparisons, we used the cluster size inference by means of z Monte Carlo simulations implemented in the FreeSurfer software.[56,57] This program is based on the AFNI program AphaSim.[58] The Monte Carlo simulation creates multiple simulated z statistic maps and from them creates a distribution of cluster sizes. We tested clusters against an empirical null distribution of maximum cluster size across 10 000 iterations created using z-distributed data. For this study, the initial cluster-forming threshold was $P < .01$ (2-tailed). This determines the likelihood that a cluster of a certain size, observed for the main effects of group, would be found by chance.[56,57]

GENOTYPING OF *BDNF* GENE

All blood samples for genotyping were drawn after participants provided written informed consent for the procedure. We analyzed the *BDNF* polymorphism in duplicate. Genomic DNA was extracted from whole blood using the high-salt extraction technique. We performed polymerase chain reaction amplification of a 274–base pair fragment containing the *BDNF* Val66Met polymorphism (rs6265) using the forward primer 5′-TGATGACCATCCTTTTCCTT-3′ and the reverse primer 5′-CACTGGGAGTTCCAATGC-3′. Genotyping of the *BDNF* Val66Met polymorphism used the single base primer extension assay with a multiplex kit (PRISM SnaPShot; Applied Biosystems, Inc, Foster City, California). Analysis was performed using the identification software (GeneMapper, version 4.0; Applied Biosystems, Inc).

STATISTICAL ANALYSIS

We performed independent t tests and χ^2 tests to compare continuous and categorical demographic or psychometric variables, respectively. Thickness in clusters at time 1 was adjusted for age and sex for further correlational analyses. Pearson correlation analyses were used to measure associations between the CAPS score changes and adjusted cortical thickness in clusters at time 1. Associations between the *BDNF* Val66Met polymorphism and cortical thickness in clusters of group differences were examined using the test for linear trend.[59]

We evaluated changes in PTSD symptoms over time using the mixed-effects regression model to minimize the effects of missing data.[60-62] The CAPS score was the dependent variable. Fixed factors were the time effect as the predictor of interest and age, sex, and baseline CAPS scores as covariates. Subject variable was included as a random effect, meaning that the individual time trajectories could vary randomly with the subject-specific coefficients.

The main effect of time on changes in the thickness of the DLPFC cluster was evaluated in the mixed-effects regression model, which included age and sex as fixed effects and subject as a random effect. We added a group × time interaction term to test whether the slopes of the DLPFC thickness changes differed by groups.

We constructed linear and quadratic models for time effects on the CAPS scores and the DLPFC thickness and compared these using the likelihood ratio test. The best-fitting model with the smallest number of terms was selected.

Two-tailed significance of $P < .05$ was considered as statistically significant. We analyzed data using commercially available software (STATA SE, version 11.0; StataCorp LC, College Station, Texas).

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Table 1. Demographic and Clinical Characteristics of Participants

Characteristic	Trauma-Exposed Individuals (n = 30)	Control Group Members (n = 36)	*P* Value [a]
Male sex, No. (%)	11 (37)	14 (39)	.85
Age, mean (SD), y	27.0 (8.8)	26.5 (6)	.76
Education, mean (SD), y	13.6 (2.2)	14.1 (2)	.37
Right-handedness, No. (%)	28 (93)	35 (97)	.45
Marital status, No. (%)			
Married	12 (40)	12 (33)	.44
Separated/widowed/divorced	1 (3)	0	
Never married	17 (57)	24 (67)	
PTSD symptom severity, CAPS total score, mean (SD)			
Time 0 (n = 30)	87.1 (12.6)	NA	
Time 1 (n = 30)	54.0 (14.1)	NA	
Time 2 (n = 25)	45.6 (11.8)	NA	
Time 3 (n = 17)	35.1 (15.0)	NA	
PTSD diagnosis, No. (%)			
Time 0 (n = 38)	38 (100)	NA	
Time 1 (n = 30)	23 (77)	NA	
Time 2 (n = 25)	12 (48)	NA	
Time 3 (n = 17)	2 (12)	NA	
Depressive symptom severity, HDRS total score, mean (SD)			
Time 0	13.8 (5.7)	1.8 (2.0)	<.001
Time 1	11.8 (5.2)	1.6 (1.6)	<.001
Time 2	8.5 (4.5)	2.5 (2.9)	<.001
Time 3	9.3 (5.4)	1.8 (1.9)	<.001
BDNF Val66Met allele frequency, No. (%) [b]			
Val/Val	10 (33)	14 (39)	.78
Val/Met	15 (50)	18 (50)	
Met/Met	5 (17)	4 (11)	
Comorbid psychiatric diagnoses, No. (%) [c,d]			
Major depressive disorder and other depressive mood disorders	9 (30)	0	NA
Anxiety disorders	2 (7)	0	

Abbreviations: *BDNF*, brain-derived neurotrophic factor gene; CAPS, Clinician-Administered Posttraumatic Stress Disorder Scale; HDRS, Hamilton Depression Rating Scale; Met, methionine; NA, not applicable; PTSD, posttraumatic stress disorder; Val, valine.

[a] Values are calculated by χ^2 statistics for categorical measures and 2-tailed *t* statistics for continuous measures.

[b] Hardy-Weinberg expectations (*P* values) for trauma-exposed individuals and controls are .88 (χ^2 = 0.02) and .62 (χ^2 = 0.25), respectively.

[c] Numbers are not mutually exclusive.

[d] Indicates current or "since trauma" diagnoses at time 0. Persons with lifetime diagnoses of Axis I disorders at study entry were excluded from the study. Details of specific Axis I comorbid psychiatric diagnoses at times 1, 2, and 3 are given in Author Table 1 (available on the authors' Web site).

RESULTS

CHARACTERISTICS OF PARTICIPANTS

There were no significant differences in any of the baseline demographic characteristics between trauma-exposed and control groups (**Table 1**).

There were no significant differences in age, sex, handedness, or educational level between trauma-exposed and control groups at each time point or between subjects who completed all assessments and those who did part of the assessments. Details are provided in Author Table 1 (available on the authors' Web site).

Table 1 includes detailed demographic and clinical information, including CAPS scores and comorbid diagnoses at study entry. Further information on demographics and comorbidity during the study period is provided in Author Table 1 (available on the authors' Web site).

TRAJECTORIES OF PTSD SYMPTOMS

Of trauma-exposed individuals who met all the diagnostic criteria for PTSD at time 0, 23 of 30 (77%), 12 of 25 (48%), and 2 of 17 (12%) met the diagnostic criteria for PTSD at times 1, 2, and 3, respectively (Table 1). Reductions in PTSD symptoms, as assessed by changes in CAPS total scores, are shown in Table 1 and Author Figure 2 (available on the authors' Web site).

Mixed-model regression analyses showed that trauma-exposed individuals had overall and continuous reductions in CAPS scores throughout the study period. For the first model with a linear time term, the time effect was significant (linear time effect, $z=-16.8$ [$P<.001$]). For the second model with linear and quadratic time terms, the linear ($z=-13.7$ [$P<.001$]) and quadratic effects ($z=7.24$ [$P<.001$]) were significant with improvement in model fitness.

CORTICAL THICKNESS GROUP DIFFERENCES AT TIME 1 AND PTSD SYMPTOM IMPROVEMENT

Maps showing mean cortical thicknesses of the trauma-exposed and control groups are provided in **Figure 2**A. Trauma-exposed individuals had greater cortical thickness in the following 3 DLPFC clusters (Figure 2B) relative to controls (corrected $P<.01$): the right DLPFC

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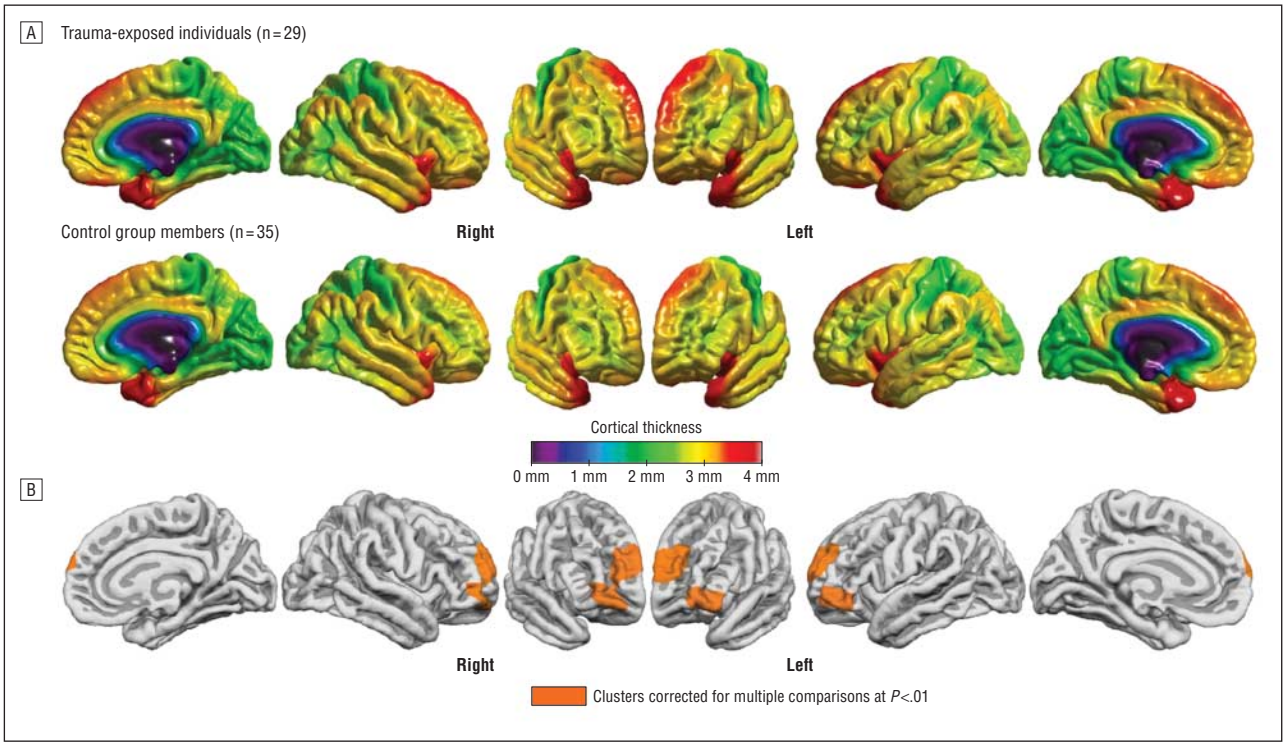

Figure 2. Cortical thickness and statistical maps. A, Mean cortical thickness maps of trauma-exposed individuals (top row) and control group members (bottom row). B, Group differences in cortical thickness. Brain regions in orange indicate clusters of significant group differences, greater in trauma-exposed individuals relative to controls, adjusting for age and sex and corrected for multiple comparisons at $P<.01$. Clusters, defined as contiguous vertices with significant group differences at corrected $P<.01$, were in the right dorsolateral prefrontal cortex, the left superior frontal cortex, and the left inferior frontal cortex. No regions were thinner in trauma-exposed individuals relative to controls.

Table 2. Detailed Information on 3 DLPFC Clusters Where Trauma-Exposed Individuals Had Greater Cortical Thickness Than Controls at Time 1

	Cluster		
	Right DLPFC (BA 9, 45-46)	Left Superior Frontal Cortex (BA 9)	Left Inferior Frontal Cortex (BA 45-46)
Cluster size, mm^2	2424.9	1284.2	1509.5
No. of vertices in cluster	2686	1509	1998
Talairach coordinate			
x	16.1	–19.2	–47.2
y	54.7	53.8	32.7
z	14.3	16.7	–7.0
Thickness, mean (SD)			
Trauma-exposed individuals	2.95 (0.14)	3.08 (0.19)	2.98 (0.14)
Control group members	2.80 (0.11)	2.91 (0.13)	2.83 (0.16)
Effect size[a]	1.01	0.93	0.91
Cluster *P* value[b]	<.001	0.001	<.001

Abbreviations: BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex.
[a] Indicates Cohen *d* effect size for trauma-exposed individuals with greater cortical thickness than controls.
[b] Indicates the likelihood that each cluster would be observed by chance based on 10 000 Monte Carlo simulations.

(5.4%; Cohen *d* effect size [ES] for group differences, 1.01), the left superior frontal cortex (5.8%; ES, 0.93), and the left inferior frontal cortex (5.3%; ES, 0.91). Information on cluster size, number of vertices, Talairach coordinates, cortical thickness, and cluster-level *P* values are shown in **Table 2**.

To ensure the robustness of our findings, we conducted 4 sensitivity analyses in reduced data sets, excluding individuals with prior sub–PTSD-level life stressors, trauma-exposed individuals who had a comorbid psychiatric diagnosis, those who had taken psychotropic medications, or individuals who were not able to complete all 3 assessments. Similar results of these analyses showed that the present results were not likely to be modulated by potential confounding factors (eFigure 1A and E-H [see also Author Results 1 on the authors' Web site]).

Functional significance of this greater DLPFC thickness was measured by testing the association between cor-

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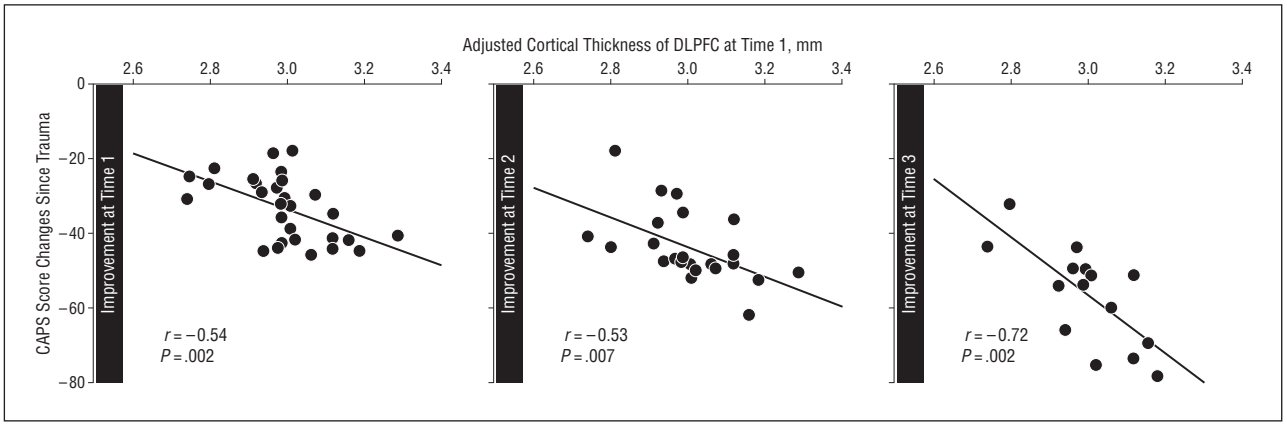

Figure 3. Relationships between adjusted cortical thickness of the dorsolateral prefrontal cortex (DLPFC) and improvement in posttraumatic stress disorder (PTSD) symptoms of trauma-exposed individuals. The 3 panels demonstrate relationships between age- and sex-adjusted cortical thickness of the DLPFC region at time 1 and improvement in Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS) scores at times 1, 2, and 3. The DLPFC region is where trauma-exposed individuals had greater cortical thickness than control group members at time 1, shown in Figure 2 and eFigure 3.

tical thickness and performance levels on a set of relevant neuropsychological tests that measure executive function (Author Results 2 and Author Table 2 [available on the authors' Web site]). In brief, correlation analysis revealed that greater thickness of the DLPFC at time 1 was associated with better performance in relevant neuropsychological tests at time 1 (greater executive function domain score) among the trauma-exposed individuals ($\rho = 0.45$ [$P = .02$]) (eFigure 2).

For further analyses, the mean thickness of DLPFC clusters of significant group differences at time 1 was calculated by cluster size–weighted averaging of the thickness of 3 clusters where group differences were noted at corrected $P < .01$ (eFigure 3). This mean thickness of DLPFC clusters was then adjusted for age and sex. Auxiliary post hoc analyses were repeated with 3 individual DLPFC clusters and produced similar results (eFigure 4 and eFigure 5 [see also Author Figure 3 on the authors' Web site]). Analysis results with nonadjusted raw thickness of the DLPFC clusters are also presented in Author Figure 4 (available on the authors' Web site).

Thickness of the DLPFC region at time 1 was correlated with CAPS score decreases from time 0 to time 1 ($r = -0.54$ [$P = .002$]) (**Figure 3**) but not with CAPS scores at time 0 or at time 1 ($r = 0.24$ [$P = .22$] and $r = -0.12$ [$P = .52$], respectively) in trauma-exposed individuals.

Thickness of the DLPFC region at time 1 was also correlated with CAPS score decreases from time 0 to time 2 ($r = -0.53$ [$P = .007$]) and those from time 0 to time 3 ($r = -0.72$ [$P = .002$]) (Figure 3). Adjusted cortical thickness of the DLPFC region at time 1 was also correlated with CAPS score changes from time 1 to time 3 ($r = -0.55$ [$P = .03$]) (Author Results 3, Author Figure 5, and Author Figure 6 [available on the authors' Web site]).

RELATIONSHIP BETWEEN *BDNF* POLYMORPHISM AND DLPFC CORTICAL THICKNESS AT TIME 1

Genotype distribution for the *BDNF* Val66Met polymorphism did not deviate from the Hardy-Weinberg equilibrium in trauma-exposed individuals and controls

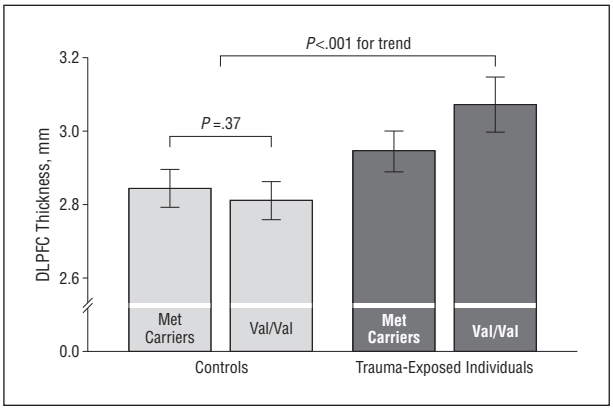

Figure 4. Cortical thickness of the dorsolateral prefrontal cortex (DLPFC) by the brain-derived neurotrophic factor (*BDNF*) genotype. We compared cortical thickness between control group members (n=35) and trauma-exposed individuals with a methionine/valine (Met/Val) or a methionine/methionine (Met/Met) genotype (n=19) or a valine/valine (Val/Val) genotype (n=10). Controls did not differ in cortical thickness in this region by the *BDNF* genotype. There was a positive linear trend ($P < .001$ for trend), with trauma-exposed individuals with a Val/Val genotype having the greatest DLPFC cortical thickness, followed by those with a Met genotype and controls. Error bars represent 95% confidence intervals. Cortical thickness is age and sex adjusted. The DLPFC region is where trauma-exposed individuals had greater cortical thickness than controls at time 1, shown in Figure 2 and eFigure 3.

(trauma-exposed individuals, $\chi^2 = 0.02$ [$P = .88$]; controls, $\chi^2 = 0.25$ [$P = .62$]).

We tested the association between the *BDNF* Val66Met polymorphism and DLPFC cortical thickness using the trend analyses. There was a significant linear trend toward greater cortical thickness at time 1; trauma-exposed individuals with a Val/Val genotype in the DLPFC region had greater thickness than those with a Met/Val or a Met/Met genotype, who had greater thickness than controls ($P < .001$ for trend) (**Figure 4**). This linear trend remained unchanged when the depressive symptom severity as measured by the Hamilton Depression Rating Scale at time 1 was included as an additional covariate ($P = .001$ for trend).

In an effort to examine potential functional significance of the *BDNF* polymorphism, we explored how changes in CAPS scores and cortical thickness of the

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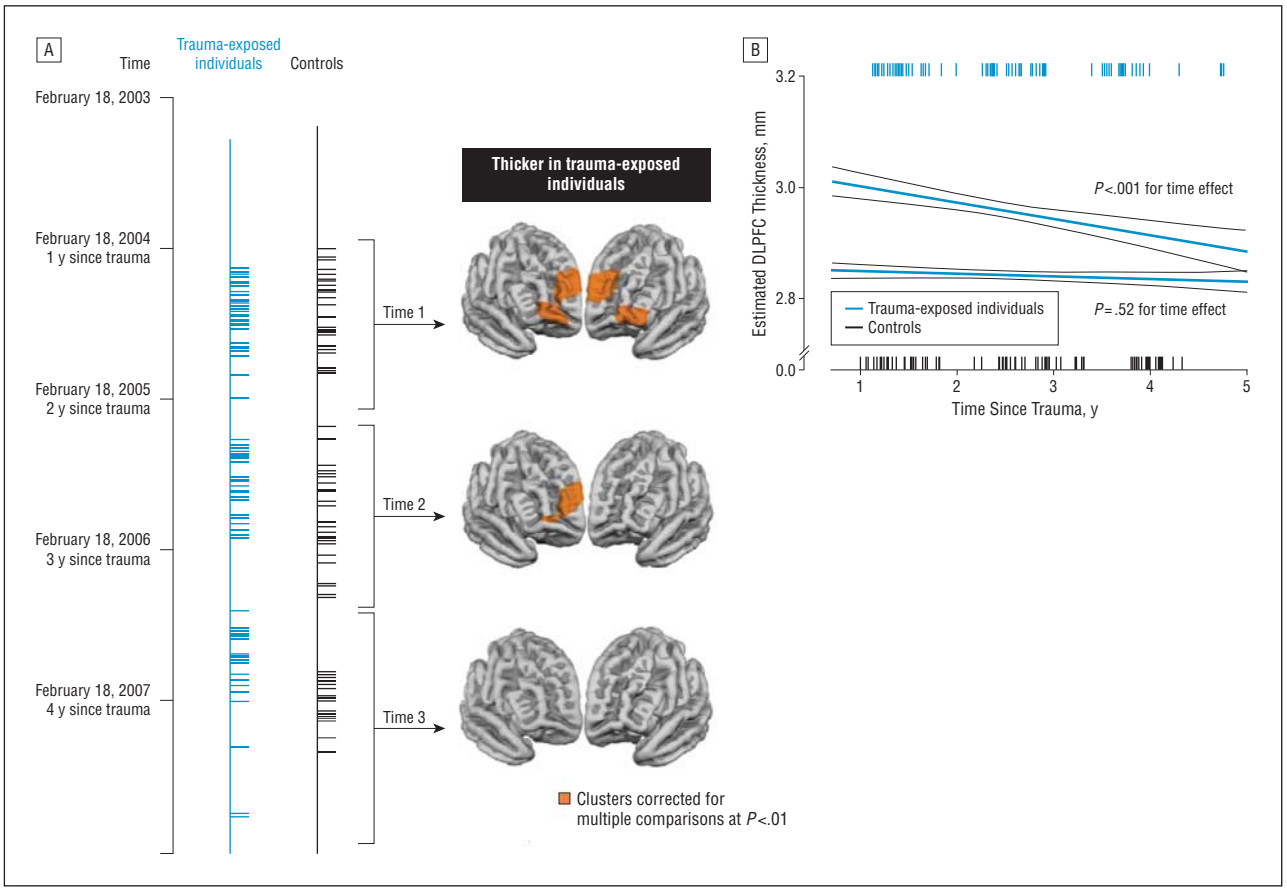

Figure 5. Longitudinal mapping of cortical thickness differences between trauma-exposed individuals and control group members. A, Brain regions in orange indicate clusters of significant group differences, greater in trauma-exposed individuals relative to controls, adjusting for age and sex and corrected for multiple comparisons at $P<.01$ at times 1, 2, and 3. No regions were thinner in trauma-exposed individuals than in controls. B, Estimated cortical thickness changes in the dorsolateral prefrontal cortex (DLPFC) region (Figure 2 and eFigure 3), where significant between-group differences were present at time 1, for trauma-exposed individuals (blue line) and controls (gray line) from 156 scans of the cohort, which was followed up for 4.76 years. Regression lines for DLPFC cortical thickness changes from times 1 through 3 were fitted using mixed-effects regression modeling. Heavy blue and gray lines represent the fit of linear modeling in trauma-exposed individuals and controls, respectively; thin lines correspond to their fitted 95% confidence intervals. Blue tick marks above the fitted lines represent times since trauma of trauma-exposed individuals, whereas gray tick marks below the fitted lines represent those of controls. Estimates for cortical thickness of the DLPFC region were age and sex adjusted. Cortical thickness in the DLPFC region decreased in trauma-exposed individuals during the follow-up period of 4.76 years. This pattern was not observed in controls.

DLPFC region vary with the *BDNF* polymorphism (Author Results 4 [available on the authors' Web site]).

TRAJECTORIES OF CORTICAL THICKNESS CHANGES FROM TIMES 1 TO 3

The size of DLPFC clusters of group differences decreased over time, and there was no significant group difference in cortical thickness in the prefrontal cortical region at time 3 (**Figure 5**A). Estimated trajectories of mean cortical thickness in the DLPFC region during the study period are plotted in Figure 5B, Author Figure 3, and Author Figure 7 (available on the authors' Web site).

Linear mixed-model regression analyses have shown that trauma-exposed individuals had linear decreases in cortical thickness over time in the DLPFC region ($z=-3.92$ [$P<.001$]), whereas controls had no thickness changes in this region ($z=-0.64$ [$P=.52$]). A significant group × time interaction was noted in this DLPFC region ($z=-2.07$ [$P=.04$]). The extent of cortical thinning of the DLPFC over time was correlated with changes in CAPS scores ($r=-0.66$ [$P=.006$]).

COMMENT

This first longitudinal multiwave neuroimaging study of disaster survivors, who initially met the criteria for a PTSD diagnosis and had significant improvement in PTSD symptoms several years later, provides a unique opportunity to identify brain correlates that promote psychological recovery from severe trauma.

Our study demonstrated that disaster survivors early in the course of PTSD had greater cortical thickness in the DLPFC regions relative to controls and that, among survivors, Val homozygotes had greater DLPFC cortical thickness than Met carriers. This greater DLPFC thickness early after the trauma, which was associated with earlier improvement and later recovery, has gradually normalized to the level of controls. Taken together, greater DLPFC thickness early after the trauma in trauma-exposed individuals is likely to reflect disaster survivors' active use of DLPFC function to overcome trauma-related distress.

Although the cellular basis of changes in cortical thickness has yet to be established, increased cortical thickness

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may be attributed to the greater arborization of neurons, increased glial volume, or increased vacularization.[12,63-66] Changes in cortical thickness during adulthood may also reflect experience-dependent cortical plasticity.[27,64,67-69] The DLPFC might be the region that undergoes plastic changes during trauma-exposed individuals' active efforts to overcome the distress from the trauma.

DLPFC FUNCTION IN CONTROLLING NEGATIVE EMOTIONS

The role of the DLPFC in controlling negative emotions has been well documented in healthy individuals.[23,26,70] Emotion-regulating cognitive strategies, such as reappraisal of negative events and suppression of unpleasant memories, are associated with increased DLPFC and decreased limbic activities.[15,71-75] In nonhuman primates, mild and intermittent stress exposure helps develop resilience to severe stressors[76,77] and increase the volume and thickness of the prefrontal cortex.[78,79] In patients with PTSD, cognitive behavioral treatment and transcranial magnetic stimulations induce functional and structural changes in the prefrontal cortex.[80-82] Thus, changes in DLPFC regions in disaster survivors are likely to reflect active use of cognitive resources of the DLPFC to control the maladaptive and overactive fear circuit.

When faced with traumatic reminders or in provoked conditions, exaggerated deactivation in the superior and inferior frontal gyrus has been noted in patients with PTSD,[83-85] which is in line with our findings that greater cortical thickness in these cortical structures was associated with better control of the symptoms.

Recent functional neuroimaging studies have also suggested the potential role of the DLPFC in diminishing the exaggerated fear response in concert with the amygdala, hippocampus, and ventromedial prefrontal cortex, which have consistently been implicated in fear extinction learning.[9,13,15] Studies have suggested that the DLPFC has functional connections with the amygdala via the extensive connections between the ventromedial prefrontal cortex and amygdala.[86-89]

BDNF VAL66MET POLYMORPHISM AND DLPFC PLASTICITY

In general, *BDNF* modulates experience-dependent synaptic plasticity and neuronal development.[33,90-92] Homozygous Val carriers with the Val66Met *BDNF* polymorphism have greater plasticity relative to Met carriers via greater efficiency in activity-dependent BDNF release and intracellular trafficking.[93,94] This common polymorphism influences the structure and function of the prefrontal cortex and hippocampus, where BDNF is abundantly expressed.[33,93]

Our findings that Val homozygotes had greater DLPFC cortical thickness than Met carriers approximately 1 year after trauma and that greater cortical thickness was associated with greater CAPS score changes indicate that the Val66Met *BDNF* polymorphism may play an important role in mobilizing the DLPFC that controls negative emotions and facilitates extinction learning. As a result, Val homozygotes have more efficient recovery from PTSD.[35,36]

The DLPFC thickness did not differ between controls according to *BDNF* Val66Met gene polymorphism but, in trauma-exposed individuals, those with a Val/Val genotype had greater thickness than those carrying the Met allele. This finding may be understood in that this common genetic variation of *BDNF* can modulate experience-dependent synaptic plasticity and may become more important when there is a need for the cortical plasticity.[30,31,35,94-96]

GREATER DLPFC THICKNESS AND SUCCESSFUL RECOVERY FROM PTSD

Greater DLPFC thickness early after trauma strongly related to successful reductions in PTSD symptoms but was not associated with PTSD symptom severity at a specific time point. This finding indirectly supports the hypothesis that greater DLPFC thickness has an important role in the recovery of PTSD rather than demonstrating the consequences of the distress due to the disorder. This finding may also serve to help predict mental health outcomes among trauma-exposed individuals.

With gradual and substantial recovery from PTSD, trauma-exposed individuals were likely to have a gradually lessening need for DLPFC use. This finding may have been reflected in the gradual normalization of early greater DLPFC thickness. Moreover, the greater the extent of normalization of DLPFC thickness (ie, the extent of cortical thinning of the DLPFC), the greater the changes in PTSD symptoms. This finding supports the theory that active DLPFC recruitment, which normalized later in the course of recovery, may have induced greater symptom improvement.

STUDY LIMITATIONS

The present study focused on cortical structures and their association with recovery from PTSD. Thus, it does not provide information regarding the interplay between the DLPFC and subcortical structures of the amygdala and hippocampus. Functional neuroimaging data in addition to the structural neuroimaging data would have provided more comprehensive information[97-100] on the potential role of the DLPFC in facilitating extinction learning and modulating the ventromedial prefrontal cortex–amygdala dynamics over time during recovery from PTSD.[11,101-104]

This longitudinal cohort of disaster survivors can be considered unique from other PTSD samples studied in most prior brain imaging studies.[10,105] Most of the trauma survivors recovered during the 5 years after trauma in the present study compared with PTSD diagnoses confirmed in studies typically conducted many years after trauma. The interval from trauma to brain imaging (about 1 year after trauma for the first imaging session) was also shorter compared with previous studies (mostly several years after trauma). These differences can be important moderator variables that account for sources of seemingly dissimilar findings.

To our knowledge, 3 previous reports have analyzed cortical thickness in adult patients with PTSD.[106-108] In

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those studies, sample characteristics were different from ours in that more than a decade had passed since the index trauma event. In addition, some of the participants had a history of alcohol or substance abuse, and trauma types were combat-related repeated trauma or sexual abuse.[106-108] Sample heterogeneity across studies may also explain the inconsistency in findings among studies that examined cortical structures using voxel-based morphometry or volumetry,[107,109-121] in which most commonly reported findings are ventromedial prefrontal cortical alterations. Corbo and colleagues[111] raised the possibility that these observations stemmed from differences in the shape of the anterior cingulate cortex rather than from differences in gray matter volume,[9] considering the high sulcal variabilities of the anterior cingulate and paracingulate cortex that are likely to undermine the reliability of morphometric analysis, especially when automated.[122]

Brain imaging before trauma exposure or during the early weeks after trauma would have enabled us to rule out the possibility that greater thickness in the DLPFC may be a preexisting vulnerability factor for PTSD development. The time 1 neuroimaging assessment, however, was the earliest possible time for neuro imaging owing to administrative, legal, and subject protection issues in the present study. Greater cortical thickness at time 1 was correlated with earlier improvement and later recovery in PTSD symptoms and this greater cortical thickness has gradually decreased to the level of healthy controls during the recovery course from PTSD. Together, this may suggest that DLPFC thickness increased via the experience-dependent cortical plasticity during active use of DLPFC function to help overcome trauma-related distress.

Factors other than trauma exposure or subsequent PTSD may mimic some of the cortical thickness differences between the trauma-exposed and control groups. We tried to control or covary these potential confounding factors by excluding trauma-exposed individuals with head trauma, smoke inhalation injury, loss of consciousness, or any burns and organ damage (ie, potential toxic effects of fire) in addition to psychological trauma. We conducted extensive sensitivity analyses to covary out the potential confounders.[123,124]

A high attrition rate is a common and well-recognized issue in cohort studies of disaster victims.[2] Attrition may undermine the credibility of longitudinal study findings, especially when it occurs in a biased way.[125] In addition to using an appropriate statistical method to minimize the effects of the missing data,[60,61] we conducted sensitivity analyses replacing missing data with last observations and produced similar results (eFigures 1A and H) and Author Results 5 (available on the authors' Web site). These findings indicate that missing observations are likely to have randomly occurred in the present study.[61]

IMPLICATIONS AND SUMMARY

The present findings have potential implications for people who are commonly exposed to serious levels of trauma, including firefighters, emergency rescuers, and combat personnel. Preemptive strategies to bolster DLPFC function of successful cognitive mobilization over traumatic experiences, including preventive stress inoculation measures, could prove beneficial for these personnel.

A large proportion of survivors from the subway disaster in this study had recovered from PTSD 5 years after the trauma. At follow-up, we did not estimate the prevalence of PTSD among all survivors from the disaster but only examined the individuals who were diagnosed as having PTSD at baseline and enrolled in the cohort. Therefore, our sample does not include patients who later developed PTSD, which can be very common in survivors of mass disasters. The present sample does not represent individuals with chronic PTSD, in which symptoms persist for several years or for whom multiple traumatic events were linked to the development of PTSD,[126-130] but rather provided opportunities to observe changes in the brain and behavior in a situation in which most traumatized persons recovered from acute PTSD after a single traumatic event.

Fear acquisition, retention, and extinction models involving the amygdala, hippocampus, and ventromedial cortex are well established in mammals.[131-133] Humans have the most developed DLPFC, where a substantial part of higher cognitive functions, including reappraisal of negative events and suppression of unpleasant memories, arises.[134,135] The present findings concerning the role of the DLPFC in recovery from PTSD likely will provide complementary knowledge for translational research.

In summary, this 5-year study that followed up disaster survivors during the natural course of recovery from PTSD has shown that trauma-exposed individuals develop greater thickness in the DLPFC region and that this cortical plasticity reflects active mobilization of the DLPFC function during individuals' efforts to overcome trauma and predicts successful recovery. Interventions that enhance the DLPFC mobilization or increase the DLPFC cortical thickness may merit attention as potential preventive or therapeutic options in trauma-exposed individuals and PTSD patients.

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