ORIGINAL ARTICLE

Brain Structural Abnormalities and Mental Health Sequelae in South Vietnamese Ex–Political Detainees Who Survived Traumatic Head Injury and Torture

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Context: A pilot study of South Vietnamese ex–political detainees who had been incarcerated in Vietnamese reeducation camps and resettled in the United States disclosed significant mental health problems associated with torture and traumatic head injury (THI).

Objectives: To identify structural brain alterations associated with THI and to investigate whether these deficits are associated with posttraumatic stress disorder and depression.

Design: Cross-sectional neuroimaging study.

Setting: Massachusetts General Hospital and McLean Hospital.

Participants: A subsample of Vietnamese ex–political detainees (n=42) and comparison subjects (n=16) selected from a community study of 337 ex–political detainees and 82 comparison subjects.

Main Outcome Measures: Scores on the Vietnamese versions of the Hopkins Symptom Checklist–25 (HSCL) and Harvard Trauma Questionnaire for depression and posttraumatic stress disorder, respectively; cerebral regional cortical thickness; and manual volumetric morphometry of the amygdala, hippocampus, and thalamus.

Results: Ex–political detainees exposed to THI (n=16) showed a higher rate of depression (odds ratio, 10.2; 95% confidence interval, 1.2-90.0) than those without THI exposure (n=26). Ex–political detainees with THI had thinner prefrontotemporal cortices than those without THI exposure ($P<.001$ by the statistical difference brain map) in the left dorsolateral prefrontal and bilateral superior temporal cortices, controlling for age, handedness, and number of trauma/torture events (left superior frontal cortex [SFC], $P=.006$; left middle frontal cortex, $P=.01$; left superior temporal cortex [STC], $P=.007$; right STC, $P=.01$). Trauma/torture events were associated with bilateral amygdala volume loss (left, $P=.045$; right, $P=.003$). Cortical thinning associated with THI in the left SFC and bilateral STC was related to HSCL depression scores in THI-exposed (vs non–THI-exposed) ex–political detainees (left SFC, P for interaction=.007; left STC, P for interaction=.03; right STC, P for interaction=.02).

Conclusions: Structural deficits in prefrontotemporal brain regions are linked to THI exposures. These brain lesions are associated with the symptom severity of depression in Vietnamese ex–political detainees.

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There is growing awareness in the human rights community that traumatic head injury (THI) is a common form of torture and human degradation that occurs during war and other forms of mass violence. Thygesen et al,[1] in their study of 1000 concentration camp survivors living in Denmark, demonstrated significant neurologic and psychiatric morbidity in their study population associated with the most commonly reported torture, "blows and kicks to the head." Clinical studies have documented chronic neuropsychiatric findings, including cerebral atrophy, in torture survivors.[2] Rasmussen,[3] in a clinical examination of 200 torture survivors, found that 64% showed neurologic impairments. Two-thirds of the latter had experienced head injury. Other studies of torture survivors and survivors of mass violence have linked psychiatric symptoms, neurologic impairment, and THI.[4-13] Despite the presumptive evidence during the past 50 years that THI is a common

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form of torture[14] and occurs frequently in survivors of mass violence, little research has been conducted establishing the relationship between THI and psychiatric disorders such as depression and posttraumatic stress disorder (PTSD).[15]

Several brain imaging studies have reported brain abnormalities in subjects with mild traumatic brain injury in the prefrontal and temporal brain regions and white matter tracts.[16-21] Substantial amounts of preclinical and clinical evidence suggest that the prefrontotemporal cortical and subcortical structures including the amygdala and hippocampus play an important role in the pathophysiology of depression, anxiety, and PTSD.[22-26] Prefrontotemporolimbic regions have therefore been proposed as candidate regions for neural correlates of THI-associated depression and PTSD.[27] Recent neuroimaging studies in patients with THI have reported that reduced volumes of the prefrontal cortex and hippocampus were associated with the subsequent development of depression.[28-32] No study, to our knowledge, has investigated THI-associated brain abnormalities and their associations with psychiatric symptoms by means of neuroimaging modalities in a tortured population.

To identify the brain-mediated relationship of THI to PTSD and depression in a tortured population, we conducted a community study of Vietnamese ex–political detainees and comparison subjects to obtain a subsample for neuroimaging studies. We reasoned that THI exposure, independent of the effects of torture and traumatic events, would contribute to brain structural abnormalities and that these abnormalities would be associated with symptoms of PTSD and depression.

Prefrontotemporolimbic regions were selected a priori to be examined for the neural substrates of the relationship between THI and psychiatric morbidity. Regions of interest in this study were as follows: 6 cortical regions including the superior frontal cortex (SFC), middle frontal cortex (MFC), inferior frontal cortex, orbitofrontal cortex, anterior cingulate cortex, and superior temporal cortex (STC) and 3 subcortical regions including the amygdala, hippocampus, and thalamus.

We first assessed the effects of THI exposure, independent of those of torture or traumatic events, on the prefrontotemporolimbic brain regions. The relationship between THI-associated prefrontotemporolimbic abnormalities and the symptom severity of PTSD and depression was then examined after controlling for the frequency of torture or traumatic events. Then we examined which brain regions may be affected by the total number of trauma/torture events independent of THI and their association with psychiatric symptoms.

METHODS

PARTICIPANTS AND STUDY DESIGN

Our pilot community study of a small sample of Vietnamese ex–political detainees provided the background data for the design and implementation of this study.[33] A large-scale epidemiologic survey of South Vietnamese ex–political detainees (N=337) who had been tortured in Vietnamese reeducation camps and resettled in the United States and a non-THI, non–reeducation camp Vietnamese comparison group (N=82) was conducted from May 2002 through June 2004. Demographic and clinical characteristics of the epidemiologic survey respondents and detailed comparisons between the latter and the selected subsample for the neuroimaging study are described in a National Institutes of Health final report submitted for publication (R.F.M., unpublished manuscript, May 2002 to June 2004). Some differences existed between the larger survey and the neuroimaged sample. The neuroimaged detainees spent more time in the reeducation camps and tended to have fewer traumatic events than their survey counterparts; the neuroimaged comparison subjects had more traumatic events than their counterparts.

Ninety-seven Vietnamese ex–political detainees and comparison subjects from the community survey were randomly selected to participate in the neuroimaging study (**Figure 1**). Informed consent and neuroimaging study design procedures were approved by the human subjects committee (institutional review board) of Massachusetts General Hospital and McLean Hospital.

INSTRUMENTS

A detailed THI history questionnaire for this study included a checklist of 24 types of events, including vehicular accident, accidental falls, physical assaults, torture, and combat-related THI. Each of the THI events was assessed during 5 periods: (1) before the Vietnam War (before 1954), (2) during the Vietnam War (1954-1975), (3) in a reeducation camp (ex–political detainees only), (4) in Vietnam after the war or the reeducation camp, and (5) after leaving Vietnam and resettling in the United States.

In this study, THI designates concussion-associated THI, with 1 or more occasions during which all 3 postconcussive symptoms (loss of consciousness, posttraumatic transient amnesia, and any neurologic deficits) occurred.[34-36]

The trauma history was derived from the validated Vietnamese version of the Harvard Trauma Questionnaire (HTQ).[33,37,38] Measures of cumulative trauma were constructed from responses to questions about traumatic events during 3 periods: (1) during the Vietnam War (1954-1975), (2) in a reeducation camp (ex–political detainees only), and (3) other times. Affirmative responses were summed for 40 non-THI traumatic events and 27 torture events.

Two interview schedules were used to measure psychological symptoms, ie, the Hopkins Symptom Checklist–25 (HSCL)[39] and the HTQ.[37] The HSCL includes a 15-item scale of depressive symptoms, and the HTQ contains a 16-item scale for PTSD. Both instruments have been widely translated and used in a number of studies among diverse cultural groups[40-45] and validated against *DSM-IV* clinical diagnoses of depression and PTSD, respectively.[37-39,46-48] Scale cutoff points for the HSCL and HTQ for depression and PTSD have been described in previous reports[37,39] as greater than or equal to 1.75 and 2.00, respectively.[46,49-52]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed on all participants by means of a 3.0-T imager (Magnetom Trio 3T; Siemens, Erlangen, Germany). Anatomic imaging was obtained by means of a T1-weighted, sagittally oriented, 3-dimensional magnetization-prepared rapid gradient-echo sequence (repetition time [TR]/echo time [TE]/inversion time [TI], 2100/3.97/1100 milliseconds; matrix, 256×256; field of view [FOV], 256×256 mm; flip angle [FA], 12°; section thickness, 1.5 mm; and no skip). Axial proton-density and T2-weighted images using 2-dimensional double-echo T2-weighted turbo spin-echo sequence (TR, 7110 milliseconds; TE, 28/84 milliseconds; FOV,

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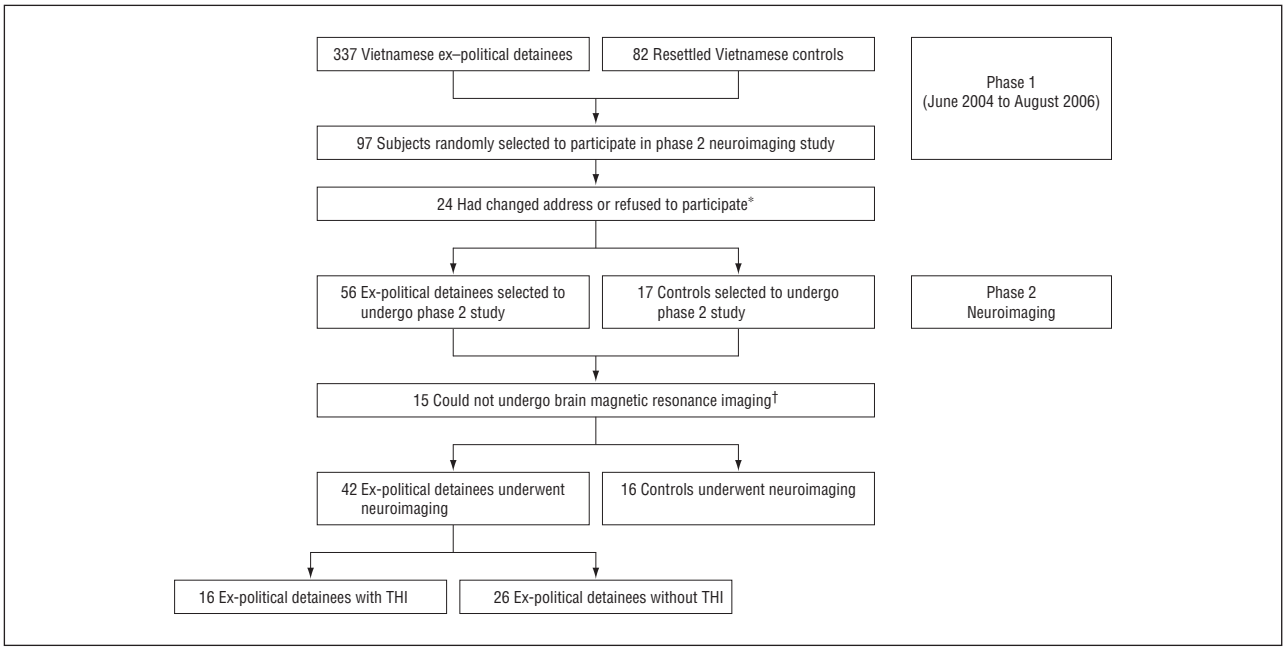

Figure 1. Participant flow through a large-scale epidemiologic survey of Vietnamese ex–political detainees and nontraumatized controls in a neuroimaging study. *After removal of these 24 subjects, 73 eligible subjects were initially screened by a nurse practitioner to determine safety and suitability for undergoing brain imaging. †Reasons were presence of shrapnel in the body, claustrophobia caused by being in a closed space, intolerance of imager noise, and history of a brain tumor and treatment. THI indicates traumatic head injury.

240 × 210 mm; FA, 150°; and section thickness, 3 mm) and axial fluid-attenuated inversion recovery sequence (TR/TE/TI, 8000/90/2500 milliseconds; FOV, 240 × 180 mm; FA, 150°; and section thickness, 5 mm) were acquired to screen for brain structural abnormalities. No qualitative structural abnormalities other than white matter hyperintensities and involutional changes in the brain images were observed as read by 2 experienced radiologists who were blind to clinical information including the group designation of the participants.

CORTICAL THICKNESS MEASUREMENTS AND SUBCORTICAL VOLUME ANALYSES

Brain surface reconstruction and measurements of cortical thickness were conducted by cortical surface-based analysis, an automated procedure involving segmentation of the cortical white matter.[53-55] This technique to measure the thickness of the cerebral cortex has been validated via histologic[56] as well as manual[57] measurement. Detailed methods were described elsewhere.[58]

Subcortical and intracranial volume analyses were performed with the Analyze 5.0 software (Analyze Direct, Rochester, Minnesota). Manual tracing technique and defined anatomic criteria were used to estimate volumes of the amygdala, hippocampus, and thalamus.[59-61] Anatomic boundaries for intracranial volume estimation were also defined.[62] Intraclass correlation coefficients for the intrarater and interrater reliabilities, respectively, were as follows: 0.91 and 0.89 for right amygdala, 0.93 and 0.88 for left amygdala, 0.91 and 0.93 for right hippocampus, 0.92 and 0.88 for left hippocampus, 0.93 and 0.90 for right thalamus, 0.89 and 0.94 for left thalamus, and 0.91 and 0.90 for intracranial volume.

STATISTICAL ANALYSIS

Group differences in continuous and categorical demographic variables were computed by means of independent *t* tests and χ^2 tests or Fisher exact tests, respectively.

To identify the brain-mediated relationship of THI to PTSD and depression, we conducted the following analysis. As the first step, we examined the relationship between past THI exposure and PTSD and depression by using multiple logistic regression analysis. Age, education years, marital status, and the total number of trauma/torture events were included in the model as covariates.

Second, we investigated whether THI-exposed ex–political detainees had prefrontotemporal cortical thinning or reduced volumes of the subcortical limbic structures in comparison with the ex–political detainees without previous THI exposure. Whole brain-wise statistical mapping was conducted by using a general linear model (GLM) with the difference between groups as a main effect. Age, handedness, and the total number of trauma/torture events were included in the analysis as covariates to evaluate the independent effect of THI on brain structural changes in torture survivors. An uncorrected $P < .001$ (2-tailed) was considered a significant threshold in the statistical difference maps. This threshold, when an a priori hypothesis is present, is approximately equivalent to $P < .05$ corrected for multiple comparisons.[57,58,63] The regions displayed in yellow on the statistical maps are compatible with the difference at $P < .001$. The thickness differences at a subthreshold level (uncorrected $P < .05$) are also displayed in red on the statistical maps. We identified the clusters of a significant group effect, which composed at least 58 contiguous vertexes (corresponding to a cluster size of 31.8 mm^2) at $P < .001$.[64-66]

As a region-of-interest analysis approach, a multivariate GLM analysis for each set of prefrontotemporolimbic regional variables (cortical thickness of 6 regions and subcortical volumes of 3 regions) was used to test the hypothesis that regional brain thickness or volumes would be different between groups. The multivariate GLM model posits the interdependency of the outcome variables and takes multiple comparisons into account.[67] Age, handedness, and the total number of trauma/torture events (continuous variable) were entered into the model for cortical thickness as covariates; for subcortical volumes, in-

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tracranial volume was included additionally as a covariate to control for generalized scaling effects.

Our third step in the analysis was to determine whether THI-induced deficits in the prefrontotemporolimbic regions, if present, would be correlated with the symptom severity of PTSD and depression in THI-exposed ex–political detainees (vs non–THI-exposed detainees). These associations were examined by means of partial correlation analyses including total number of trauma/torture events as a covariate. To conduct this analysis, regression lines were compared between the 2 groups, with an interaction term as an indicator.

Next, we assessed the regions associated with the severity of trauma/torture independent of THI and the association of these changes with PTSD and depression. Multivariate GLM analysis for each set of prefrontotemporolimbic regional variables was used to determine the effects of trauma/torture events on brain structural alteration. Age, handedness, intracranial volume, and THI exposures were appropriately covaried. The total number of trauma/torture events was treated as a continuous as well as a categorical variable in this exploratory analysis. When it was used as a categorical variable, the 42 ex–political detainees were divided into 2 groups according to the 50th percentile of total number of trauma/torture events. Twenty-two detainees with fewer than 19 trauma/torture events were categorized as the "mildly traumatized" group and 20 detainees with 19 or more events were categorized as the "severely traumatized" group.

Given the observed thickness difference of 0.13 mm in the SFC between ex–political detainees with and without THI, this study of 42 ex–political detainees had a statistical power of 0.88 to detect a difference of 0.1 mm between any 2 groups in mean absolute cortical thickness.

Statistical significance was defined at an α level of less than .05 by means of 2-tailed significance. STATA 5.0 (StataCorp, College Station, Texas) was used for statistical calculations.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 shows detailed demographics and clinical characteristics of the study subjects. There were significant differences in educational levels ($P<.001$) between ex–political detainees (n=42) and comparison subjects (n=16). Ex–political detainees were likely to be exposed to more trauma ($P<.001$) and torture ($P<.001$) events than were comparison subjects. Comparison subjects, by definition, had no previous THI. Although there was no difference in rate of depression between ex–political detainees and comparison subjects ($P=.63$), more ex–political detainees were diagnosed as having PTSD ($P=.01$). Other demographic characteristics were similar between the 2 groups.

The 42 ex–political detainees were categorized into 2 subgroups, ie, detainees with THI (n=16) and without THI (n=26), to assess THI effects on brain structures in this multiply traumatized population. Ex–political detainees with THI were different from those without THI both in the number of torture ($P<.001$) and trauma ($P=.009$) events, as anticipated by the grouping scheme, and in their living situation ($P=.02$).

The THI-exposed ex–political detainees were likely to have a high risk of the diagnosis of depression (odds ratio, 10.2; 95% confidence interval [CI], 1.2-90.0; $P=.04$) in comparison with detainees who had not experienced THI after controlling for age, education years, marital status, and the total number of trauma/torture events. Although THI-exposed ex–political detainees showed higher HTQ scores after controlling for age, education years, marital status, and the total number of trauma/torture events ($\beta=0.39$, $P=.02$), there was no difference in the risk of the diagnosis of PTSD between groups (odds ratio, 4.2; 95% CI, 0.7-26.8; $P=.13$). This means that THI-exposed ex–political detainees showed more severe PTSD symptoms than those without THI exposure despite a similar rate of diagnosed PTSD.

CORTICAL THICKNESS DIFFERENCE IN VIETNAMESE EX–POLITICAL DETAINEES AND COMPARISON SUBJECTS

The voxelwise statistical map of cortical thickness difference across the entire cortical surface demonstrated no significant difference between groups. When we confined our regions of interest to the prefrontotemporal and subcortical regions, where THI effect was observed in ex–political detainees, cortical thickness was lower, at a trend level, in some cortical subregions in ex–political detainees relative to comparison subjects.

PREFRONTOTEMPORAL CORTICAL AND SUBCORTICAL REGIONAL ALTERATIONS RELATED TO THI EXPOSURE

The THI-exposed ex–political detainees showed overall left and right cortical thinning by 3.0% and 2.6%, respectively, in comparison with ex–political detainees who had no exposure to THI. These differences were significant after controlling for age, handedness, and the total number of trauma/torture events (left: regression coefficient [b] = –0.09; 95% CI, –0.15 to –0.03; right: –0.09; –0.16 to –0.02).

Table 2 describes the results of analyses with the region-of-interest approach. Multivariate GLM analysis showed significantly thinner left dorsolateral prefrontal and bilateral STC regions in THI-exposed ex–political detainees than in those without THI exposure (left SFC, $P=.006$; left MFC, $P=.01$; left STC, $P=.007$; right STC, $P=.01$) (Table 2). Because this model was adjusted for the total number of trauma/torture events as well as demographic data, this finding suggests that THI dorsolateral prefrontotemporal cortical thinning is independent of the severity of trauma and torture events. In contrast, subcortical volumes were not different between groups (Table 2).

Figure 2 shows voxelwise statistical difference maps between THI-exposed ex–political detainees and those without THI exposure at a significance level of uncorrected $P<.001$ (equivalent to $P<.05$ corrected). Among a priori hypothesized regions, significant cortical thinning in THI-exposed ex–political detainees was observed in the left SFC, right MFC, and bilateral STC regions in comparison with those without any THI exposure, as shown in Figure 2 and **Table 3**. Outside of a priori regions, the right postcentral, right paracentral, and left posterior cingulate cortical regions were thinner in THI-

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Table 1. Characteristics of Male Vietnamese Ex–Political Detainees and Comparison Subjects Not Detained in Reeducation Camps

	Ex–Political Detainees				*P* Value[b]	
	With THI (n=16)[a]	Without THI (n=26)	All Detainees (n=42)	Comparison Subjects (n=16)	Between Detainee Subgroups	Between Detainees and Controls
Demographic Characteristics						
Age, mean (SD), y	62.0 (4.9)	63.4 (9.5)	62.9 (8.0)	62.6 (9.6)	.58	.35
Handedness, No. (%) right	15 (94)	26 (100)	41 (98)	16 (100)	.38	.72
Marital status, No. (%)						
Currently married	10 (63)	25 (96)	35 (83)	13 (81)	.14	.94
Separated, divorced	3 (19)	1 (4)	4 (10)	2 (13)		
Widowed	3 (19)	0	3 (7)	1 (6)		
Never married	0	0	0	0		
Religion, No. (%)						
Buddhist	8 (50)	15 (58)	23 (55)	6 (38)	.46	.23
Christian	3 (19)	7 (27)	10 (24)	3 (19)		
Other	5 (31)	4 (15)	9 (21)	7 (44)		
Living alone, No. (%)						
No	12 (75)	26 (100)	38 (90)	14 (88)	.02	.53
Yes	4 (25)	0	4 (10)	2 (13)		
Education, y, No. (%)						
1-8	1 (6)	0	1 (2)	10 (63)	.37	<.001
9-12	11 (69)	21 (81)	32 (76)	3 (19)		
≥13	4 (25)	5 (19)	9 (21)	3 (19)		
Currently employed, No. (%)						
No	11 (69)	15 (58)	26 (62)	12 (75)	.47	.27
Yes	5 (31)	11 (42)	16 (38)	4 (25)		
Trauma and Torture Characteristics						
Time in reeducation camp, mean (SD), y	8.21 (3.70)	7.69 (3.45)	7.89 (3.51)	NA	NA	.65
Trauma exposures						
No. of exposures, mean (range)	14.8 (8-24)	11.0 (4-19)	12.4 (4-24)	3.1 (0-10)	.009	<.001
No. (%) of patients	16 (100)	26 (100)	42 (100)	13 (81)	NA	.02
Torture exposures						
No. of exposures, mean (range)	10.2 (5-17)	6.4 (1-15)	7.9 (1-17)	0.9 (0-4)	<.001	<.001
No. (%) of patients	16 (100)	26 (100)	42 (100)	7 (44)	NA	<.001
Total trauma/torture exposures, mean (range)	24.9 (13-40)	17.4 (5-33)	20.3 (5-40)	3.9 (0-14)	.002	<.001
Psychiatric Characteristics						
Psychiatric morbidity, No. (%)[c]	13 (81)	4 (15)	17 (40)	6 (38)	<.001	.84
Depression, No. (%)	10 (63)	3 (12)	13 (31)	6 (38)	<.001	.63
PTSD, No. (%)	8 (50)	4 (15)	12 (29)	0	.02	.01
HSCL score, mean (SD)	2.03 (0.56)	1.41 (0.45)	1.64 (0.57)	1.56 (0.39)	<.001	.60
HTQ score, mean (SD)	2.05 (0.58)	1.48 (0.47)	1.69 (0.57)	1.20 (0.27)	.001	.002

Abbreviations: HSCL, Hopkins Symptom Checklist–25; HTQ, Harvard Trauma Questionnaire; NA, not applicable; PTSD, posttraumatic stress disorder; THI, traumatic head injury.

[a] Concussion-associated THI event was defined as THI with 1 or more occasions during which all 3 postconcussive symptoms (loss of consciousness, posttraumatic transient amnesia, and any neurologic deficits) occurred. Traumatic head injury in this study designates concussion-associated THI unless otherwise specified.

[b] Pearson χ^2 tests, Fisher exact tests, and 2-tailed *t* tests were used when appropriate.

[c] Psychiatric morbidity denotes PTSD and/or depression. Diagnosis of PTSD was defined as a mean score of 2.00 or greater on the HTQ, whereas that for depression was defined as a mean score of 1.75 or greater on the HSCL.

exposed ex–political detainees than in those without THI-exposure.

RELATIONSHIPS BETWEEN PREFRONTOTEMPORAL CORTICAL THINNING AND DEPRESSION AMONG EX–POLITICAL DETAINEES

Because exposure to THI was associated with the diagnosis of depression and not with the diagnosis of PTSD in our ex–political detainees, HSCL depression scores were selected for the correlation analysis.

After controlling for age and the total number of trauma/torture events, right overall cerebral cortical thickness was negatively correlated with HSCL scores ($r=-0.60$, $P=.02$), whereas there was no correlation between left overall cortical thickness and HSCL scores ($r=-0.55$, $P=.05$) in the THI-exposed detainee group. However, neither right ($r=0.28$, $P=.18$) nor left ($r=0.29$, $P=.17$) overall cortical thickness was correlated with HSCL scores in ex–political detainees who had no history of THI.

Partial correlation analyses showed only trend-level associations between thicknesses in the left SFC ($r=-0.53$, $P=.05$), left MFC ($r=-0.44$, $P=.11$), left STC ($r=-0.48$, $P=.08$), and right STC ($r=-0.49$, $P=.07$) and HSCL scores in the THI-exposed group (n=16), respectively. When 1 subject with HSCL scores 2 standard deviations higher than the mean level was excluded, cortical thicknesses

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Table 2. Brain Regions Associated With Previous THI Exposures Among 42 Ex–Political Detainees

Region of Interest	Mean (SD) Thickness or Volume[a]			Adjusted[b]		Additionally Adjusted for Total No. of Trauma/Torture Events[c]	
	Ex–Political Detainees						
	Without THI	With THI	Difference, %	Regression Coefficients (95% CI)	*P* Value	Regression Coefficients (95% CI)	*P* Value
Cortical Regions of Interest[d]							
Prefrontal cortex							
Superior frontal (BA 9/10)							
Right	2.65 (0.14)	2.55 (0.15)	–3.6	–0.09 (–0.19 to 0.00)	.07	–0.09 (–0.20 to 0.01)	.09
Left	2.65 (0.13)	2.52 (0.14)	–4.7	–0.13 (–0.21 to –0.04)	.005	–0.14 (–0.24 to –0.04)	.006
Middle frontal (BA 46)							
Right	2.34 (0.13)	2.25 (0.14)	–3.7	–0.09 (–0.18 to 0.00)	.06	–0.10 (–0.20 to 0.01)	.07
Left	2.37 (0.12)	2.26 (0.12)	–4.8	–0.12 (–0.20 to –0.04)	.003	–0.12 (–0.21 to –0.03)	.01
Inferior frontal (BA 44/45/47)							
Right	2.49 (0.12)	2.45 (0.13)	–1.9	–0.05 (–0.13 to 0.04)	.28	–0.06 (–0.16 to 0.03)	.19
Left	2.45 (0.11)	2.41 (0.15)	–1.7	–0.04 (–0.13 to 0.04)	.29	–0.05 (–0.14 to 0.05)	.32
Orbitofrontal (BA 11/12)							
Right	2.57 (0.13)	2.49 (0.16)	–3.2	–0.07 (–0.16 to 0.02)	.14	–0.06 (–0.17 to 0.05)	.26
Left	2.56 (0.15)	2.50 (0.17)	–2.5	–0.06 (–0.16 to 0.04)	.22	–0.07 (–0.18 to 0.05)	.25
Cingulate (BA 32)							
Right	2.95 (0.19)	2.78 (0.19)	–5.8	–0.15 (–0.28 to –0.02)	.02	–0.10 (–0.24 to 0.04)	.17
Left	2.93 (0.24)	2.86 (0.28)	–2.3	–0.04 (–0.21 to 0.13)	.63	0.01 (–0.18 to 0.20)	.91
Temporal cortex							
Superior temporal (BA 22/41/42)							
Right	2.67 (0.16)	2.53 (0.15)	–5.0	–0.13 (–0.23 to –0.03)	.007	–0.15 (–0.26 to –0.03)	.01
Left	2.63 (0.12)	2.50 (0.15)	–5.0	–0.12 (–0.21 to –0.04)	.01	–0.14 (–0.24 to –0.04)	.007
Subcortical Regions of Interest[e]							
Amygdala							
Right	1.62 (0.14)	1.60 (0.18)	–1.0	–0.00 (–0.11 to 0.10)	.91	0.05 (–0.06 to 0.16)	.38
Left	1.65 (0.14)	1.59 (0.14)	–4.1	–0.09 (–0.18 to 0.00)	.06	–0.05 (–0.15 to 0.05)	.18
Hippocampus							
Right	4.16 (0.35)	4.12 (0.43)	–1.2	–0.08 (–0.30 to 0.13)	.44	–0.01 (–0.24 to 0.24)	.97
Left	4.04 (0.37)	3.92 (0.35)	–2.8	–0.15 (–0.37 to 0.06)	.16	–0.10 (–0.35 to 0.15)	.42
Thalamus							
Right	7.07 (0.80)	6.76 (0.76)	–4.3	–0.36 (–0.83 to 0.11)	.13	–0.12 (–0.62 to 0.37)	.62
Left	6.73 (0.72)	6.41 (0.75)	–4.8	–0.33 (–0.77 to 0.12)	.14	–0.18 (–0.72 to 0.35)	.49

Abbreviations: BA, Brodmann area; CI, confidence interval; THI, traumatic head injury.

[a] Values are thickness (in millimeters) for the cortical regions and volume (in cubic centimeters) for the subcortical regions.

[b] Regression coefficients were calculated by multivariate general linear model (GLM) analyses for cortical thickness and for volumes of subcortical structures in a priori hypothesized regions of interest. Models tested the effects of THI on the brain structural changes.

[c] Adjustment was performed by using multivariate GLM analysis controlling for age and handedness. The model for subcortical volumes included intracranial volume as an additional covariate.

[d] Adjustment was performed by using multivariate GLM analysis additionally controlling for the total number of trauma/torture events.

[e] The following 9 regions of interest in the prefrontolimbic areas, where we hypothesized possible differences between ex–political detainees with and without THI, were selected. Five anatomic regions in the prefrontal cortices were dorsolateral prefrontal cortices (superior and middle frontal cortex; approximate BAs 9 and 10), inferior frontal cortex (approximate BAs 44-46), orbitofrontal cortex (approximate BAs 11 and 12), and anterior cingulate cortex (approximate BA 32). Four anatomic regions in the temporal cortex and subcortical regions included superior temporal cortex (approximate BAs 22, 41, and 42), amygdala, hippocampus, and thalamus.

in the left SFC ($r=-0.74$, $P=.004$) and bilateral STC (left, $r=-0.65$, $P=.02$; right, $r=-0.65$, $P=.02$) were negatively correlated with HSCL scores in the THI-exposed group (n=15). In contrast, there were no significant associations between thickness in the left SFC ($r=0.37$, $P=.08$), left MFC ($r=0.14$, $P=.50$), left STC ($r=0.31$, $P=.15$), and right STC ($r=0.26$, $P=.23$) and HSCL scores in ex–political detainees who had not been exposed to THI (n=26).

The pattern of relationships between cortical thickness in the left SFC (*P* for interaction=.007), left STC (*P* for interaction=.03), and right STC (*P* for interaction=.02) and HSCL scores was significantly different between the 2 groups (**Figure 3**).

PREFRONTOTEMPORAL CORTICAL AND SUBCORTICAL REGIONAL ALTERATIONS RELATED TO TRAUMA/TORTURE EXPOSURE

Multivariate GLM analysis showed no significant difference between severe and mild trauma groups in 6 cortical regional thicknesses selected a priori after controlling for age, handedness, and exposure to THI. However, left and right amygdala volumes were smaller by 4.9% and 7.8%, respectively, in the severe trauma group than in the mild group (left: b=–0.09; 95% CI, –0.19 to –0.002; *P*=.045; right: –0.16; 95% CI, –0.26 to –0.06; *P*=.003) after controlling for age, handedness, intracranial volume, and exposure to THI. When

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the number of trauma/torture events was entered as a continuous variable, the model showed that it was associated with smaller right amygdala volume (b=–0.01; 95% CI, –0.01 to –0.0001; $P=.04$). Left amygdala volume was negatively associated with HSCL scores in the severe trauma/torture group ($r=-0.46$, $P=.047$) but not in the mild group ($r=-0.22$, $P=.34$).

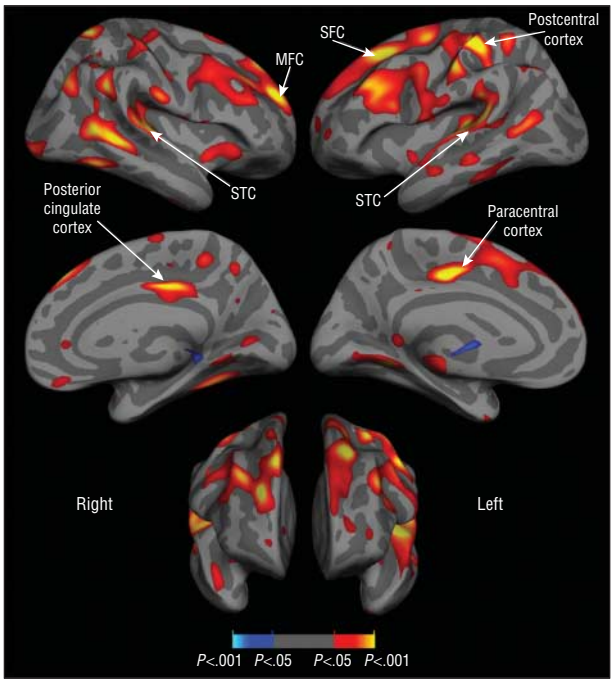

Figure 2. Statistical thickness difference maps between ex–political detainees exposed to traumatic head injury (THI) and ex–political detainees who had not experienced THI. *P* values in voxelwise statistical maps were calculated by a general linear model of cortical thickness at each voxel covarying for age, handedness, and the total number of trauma/torture events. Indicated regions in yellow illustrate where the cortices of THI-exposed detainees are thinner than those of subjects without THI exposures at uncorrected $P<.001$ (equivalent to $P<.05$ corrected). MFC indicates middle frontal cortex; SFC, superior frontal cortex; and STC, superior temporal cortex.

COMMENT

This study has replicated the findings that THI exposures are commonly reported in South Vietnamese ex–political detainees who survived torture in communist reeducation camps and that THI is highly associated with major mental health sequelae, specifically depression.[33] To the best of our knowledge, our neuroimaging study constitutes the first quantitative brain magnetic resonance imaging study in a tortured population that examines the deleterious brain effects of THI.[2,4,14,15,68] Our most notable finding is that THI was associated with cortical thinning in prefrontotemporal regions that were then correlated with symptoms of depression after controlling for potential confounders, such as severity of trauma/torture events and aging.

The present data suggest a potential neuropathological role of THI in the development of subsequent psychiatric morbidity in a multiply traumatized population.

Poorer mental health outcome in torture victims with THI has repeatedly been reported.[4,7,15,68-74] However, except for indirect evidence of brain damage obtained with measurements for neuropsychological and neurologic impairment or headache symptoms,[75] there have been no reports of studies that investigated THI-associated brain structural alterations and related mental health sequelae in torture survivors. Our findings of THI-related prefrontotemporal cortical thinning replicate previous brain imaging studies on THI.[17,18] The most prevalent type of THI in our neuroimaging study was blunt head trauma by explosion or beating on the head. These types of head trauma are more likely to damage outer areas of the brain because the brain collides with the walls and edges of the skull.[76]

In our study, we found an association between left dorsolateral prefrontal cortical thinning and depression in the THI-exposed ex–political detainee group. Given the pathophysiologic role of prefrontotemporolimbic areas in depression, the link between the selective THI-related brain regional changes and depression

Table 3. Mean Cortical Thickness for Clusters Where Significant Cortical Thinning Was Observed in Ex–Political Detainees Exposed to Traumatic Head Injury (THI) Relative to Those Without THI Exposures[a]

			Mean Thickness (SD)		Cluster Statistics	
			Ex–Political Detainees			
Region	No. of Vertexes in Cluster	Cluster Size, mm²	Without THI (n=26)	With THI (n=16)	*t* Value	*P* Value
Left						
Superior frontal sulcus	163	139.0	2.58 (0.17)	2.39 (0.19)	–3.75	.001
Superior planum temporale gyrus	148	100.7	2.29 (0.15)	2.10 (0.17)	–3.78	.001
Superior temporal gyrus	386	203.7	2.27 (0.21)	1.98 (0.22)	–3.86	<.001
Postcentral gyrus	247	145.2	2.08 (0.16)	1.86 (0.18)	–4.42	<.001
Cingulate gyrus, posterior	314	138.0	2.20 (0.16)	1.99 (0.14)	–4.18	<.001
Right						
Middle frontal gyrus	93	94.3	2.48 (0.17)	2.26 (0.16)	–3.56	.001
Middle temporal gyrus	139	116.7	2.67 (0.18)	2.53 (0.18)	–3.52	.001
Cingulate gyrus, posterior	88	55.4	2.55 (0.15)	2.37 (0.14)	–3.53	.001

[a] Clusters were determined if they were composed of at least 58 contiguous vertexes, which showed group differences at uncorrected $P<.001$ (equivalent to $P<.05$ corrected). Test statistics show the group effect after controlling for age, handedness, and the total number of trauma/torture events.

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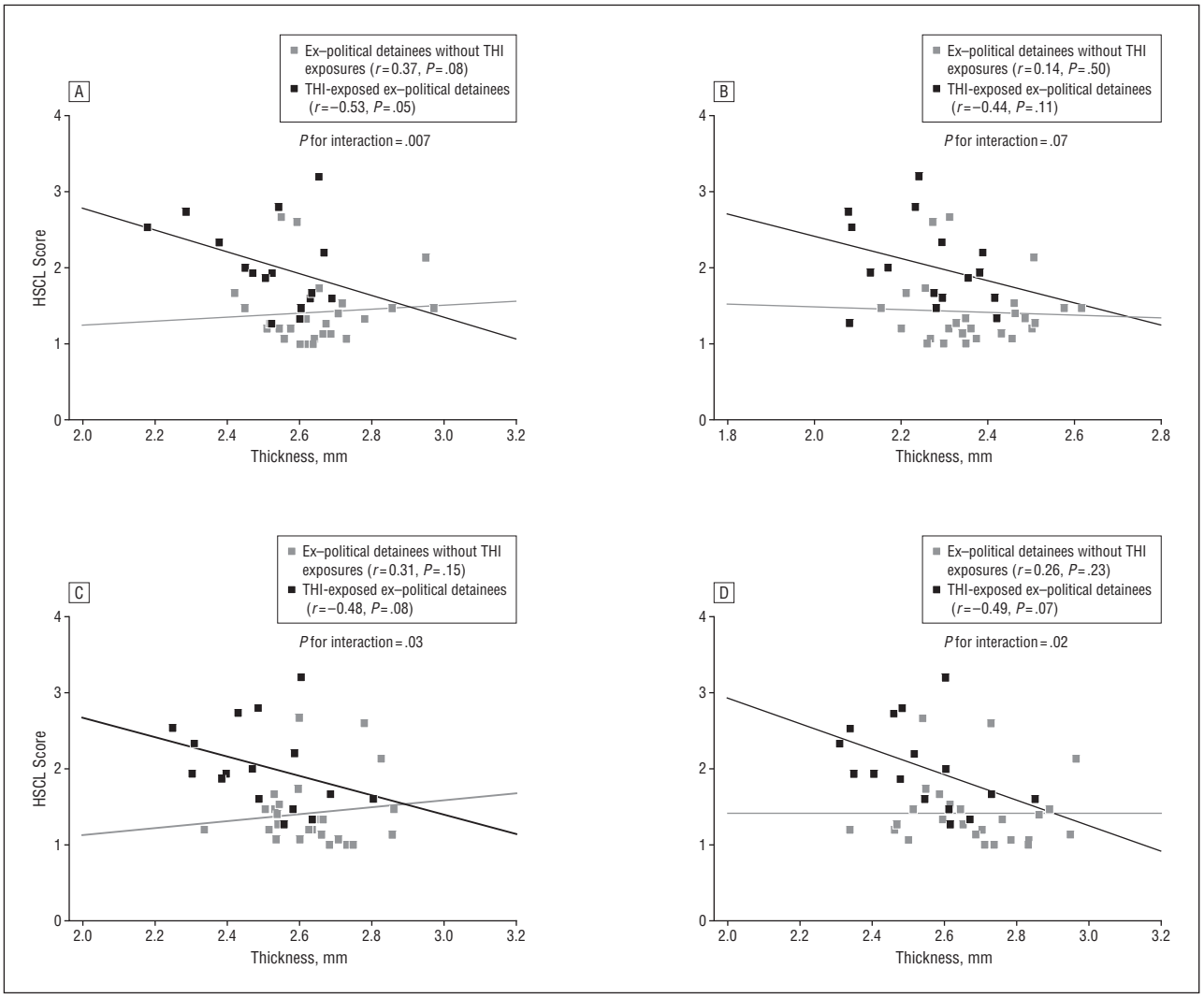

Figure 3. Relationship between severity of depression measured by the Hopkins Symptom Checklist–25 (HSCL) and cortical thickness of brain regions that were related to traumatic head injury (THI) in each ex–political detainee group. A, Left superior frontal cortex; B, left middle frontal cortex; C, left superior temporal cortex; D, right superior temporal cortex. Black and gray lines represent the regression lines of thickness in prefrontotemporal cortical regions and HSCL scores in THI-exposed ex–political detainees and those who had no history of THI, respectively. Regression lines of left superior frontal ($P = .007$ [A]) and bilateral temporal (left, $P = .03$ [C]; right, $P = .02$ [D]) cortices for the 2 groups differed significantly.

after THI has consistently been suggested.[27] Recent longitudinal and cross-sectional brain imaging studies[28,30] support that THI exposure may be associated with left prefrontal regional changes and that these regional alterations may cause subsequent depressive symptoms. Cerebral lesions in the prefrontal areas, especially on the left side, have been consistently reported to cause mood and anxiety symptoms.[30,77,78] The prefrontal cortex has been shown to play an important role in higher cortical function, including executive control over cognitive processing, social cognition, and emotional decision making.[79-82] It is not surprising, therefore, that THI-related prefrontal deficit was associated with the severity of depressive symptoms in the current study even when THI events were not combined with other psychological trauma.[27]

Traumatic head injury–related PTSD in traumatized war veterans and refugees[15,68,71] has also been identified in nontraumatized mainstream populations that experienced major vehicle crashes, sport injuries, and other common THI events.[34,35,83] Three regions of the brain, including the amygdala, prefrontal cortex, and hippocampus, have been of interest related to PTSD. Our study shows that THI exposure in ex–political detainees was associated with PTSD symptoms. Despite this correlation, our neuroimaging findings did not show a clear association between THI-related prefrontal cortex thinning and/or trauma/torture–related thinning of the amygdala and PTSD. Our findings for the hippocampus were also negative. These results are consistent with many research studies that have not demonstrated clear evidence of the decrease in volume in the amygdala and medial prefrontal cortex volumes related to PTSD. Volume change for the hippocampus and PTSD is a mixed picture.[84]

Functional deficits of the prefrontal cortex, hippocampus, and amygdala have been shown to be associated with pathological stress responses leading to PTSD. These brain areas involve the logical processing of traumatic experiences and the modulating or inhibiting of traumatic memories.[85,86] Flannelly et al[82] provided a

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theoretical model for understanding the relationship between adverse threatening life events and brain function. Profound changes in cognitive processing after THI have been associated with emotional dysregulation.[27] A THI-related prefrontotemporal deficit may affect higher cortical functions including judgment, memory, and emotional regulations.[27,87] Brain alteration related to THI may hinder victims' resilience to these disorders. It should be noted that uncontrolled and unpredictable severe traumatic events can precipitate psychiatric complications independent of THI, as explained by learning theory.[88-90]

Recent arguments as to whether THI and PTSD can coexist[68,91,92] do not seem to be relevant to the torture situation, in which survivors have been exposed to extreme violence and human rights violations. The THI can cause lasting psychiatric illness decades later in some individuals.[93] The clinician is challenged to differentiate the possible neuropsychological impact of THI from PTSD, depression, and stress. The risk of misdiagnosing refugees and torture survivors is high, especially because treaters may be drawn to solely consider the dramatic emotional sequelae of horrific torture and traumatic events.[94] Consistent screening for THI in groups at risk[91] is important because it can lead to neuropsychological assessment,[94] evidence-based cognitive remediation,[95-98] and patient and family education.[99-102] Treatment of associated psychiatric disorders such as PTSD and depression is also important.[102] These clinical considerations in the care of torture survivors still need to be validated through scientifically and culturally valid outcome studies.

There are a number of limitations to this study. First, this cross-sectional retrospective study does not allow for the direct assessment of causal relationships over time. Vietnamese ex–political detainees had experienced THI and psychological trauma in young adulthood. Mental health problems and brain structure alterations were assessed decades after exposure to THI and psychological trauma. Consequently, the effects of THI on the brain structural alterations cannot efficiently be delineated from those of PTSD or depression. The possibility that THI-related prefrontotemporal cortical thinning may partly be affected by the disease process of PTSD or depression should be considered in interpreting the results.

Recall bias related to THI and other trauma/torture events has been a perceived limitation of all studies using retrospective memories of traumatic life events. We have addressed this recall bias critique in our longitudinal study of Bosnian refugees that used measurements also applied in this study.[103-105] Our Bosnian results clearly showed that reporting of traumatic events decreased at 3-year follow-up for all respondents, whether those individuals were asymptomatic but had depression or had PTSD and depression. Only 1 group, those with PTSD alone, displayed increases in reporting of traumatic events over time. In this study we had no respondents with PTSD alone, making it unlikely that the ex–political detainees were exaggerating their THI and/or trauma/torture event history.

The self-reporting of THI in our survey may not be totally accurate. There is the possibility that amnesia associated with THI may be contributing to poor memory of THI events. Objective history of the nature and severity of THI events and possible sequelae does not exist because Vietnamese reeducation camps did not keep records on the health status of their inmates and the medical records of the South Vietnamese Army were also not available. What is most clarifying as to the accuracy of our THI and trauma/torture self-reports is that these events are independently associated with brain changes on our neuroimaging studies. Our ex–political detainees with more trauma/torture events had the smaller amygdala volumes; the amygdala has been shown to be vulnerable to damage through experiences of psychological trauma.[106]

Considering THI and trauma/torture–related effects on the brain changes in our ex–political detainees, we expected that there would be an "ex–political detainee effect." However, there were no differences in cortical thickness between the ex–political detainees and the comparison subjects. This may stem mainly from the problems inherent in an "overmatched" comparison group.[107] Because there are no Vietnamese immigrants in the United States in the ex–political detainee age group other than those who were traumatized in the Vietnam War and migrated, our comparison subjects had experienced trauma/torture events. Also, given that higher education is associated with lesser brain atrophy or neuroprotection,[108,109] substantially higher education levels in ex–political detainees relative to comparison subjects may have partly contributed to the absence of the ex–political detainee effect. To some extent, our comparison group might not be perfectly suited to detect any "actual" differences between multiply traumatized populations and healthy subjects.

Several studies on the tortured populations clearly suggest that the psychiatric outcomes, such as PTSD, in torture survivors are associated with the perceived severity of torture events.[88-90] Furthermore, the subjective uncontrollability of traumatic stressors has been known to play an important role in observing psychiatric outcomes.[82] Although the frequency of severe traumatic events, measured by the HTQ and validated by extensive field work, is believed to have a significant effect on the prevalence of mental disorders,[33,51,110] absence of information on the subjective self-reporting of the severity of torture or trauma would be an additional limitation of this study.

Although prefrontotemporolimbic areas were an a priori hypothesized set of regions of interest and statistical modeling was minimized in number on the basis of predefined sets of hypotheses, type I error should be considered in interpreting the results. Our relatively small sample size limits the generalizability of the results. However, our neuroimaging sample is a representative subsample of the larger survey cohort and consisted of the largest group of subjects we could obtain for this neuroimaging study.

CONCLUSIONS

For the first time since the original work of Eitinger and Strøm,[4,70] which was done soon after World War II and prior to the diagnosis of PTSD, THI has been demonstrated to be strongly related to psychiatric morbidity in survivors of extreme violence. Our findings show that

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THI can have a deleterious influence on a set of specific brain structures. These THI-related lesions may have a potential role in chronic, unremitting psychiatric illness even decades after the exposure to THI. Health care professionals and human rights workers need to consider the potential mental health impact of THI in torture survivors.

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