ORIGINAL ARTICLE

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

Richard F. Mollica, MD; In Kyoon Lyoo, MD, PhD, MMS; Miriam C. Chernoff, PhD; Hoan X. Bui; James Lavelle, LICSW; Sujung J. Yoon, MD, PhD; Jieun E. Kim, MD; Perry F. Renshaw, MD, PhD

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.

Arch Gen Psychiatry. 2009;66(11):1221-1232

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

Author Affiliations are listed at the end of this article.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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,

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

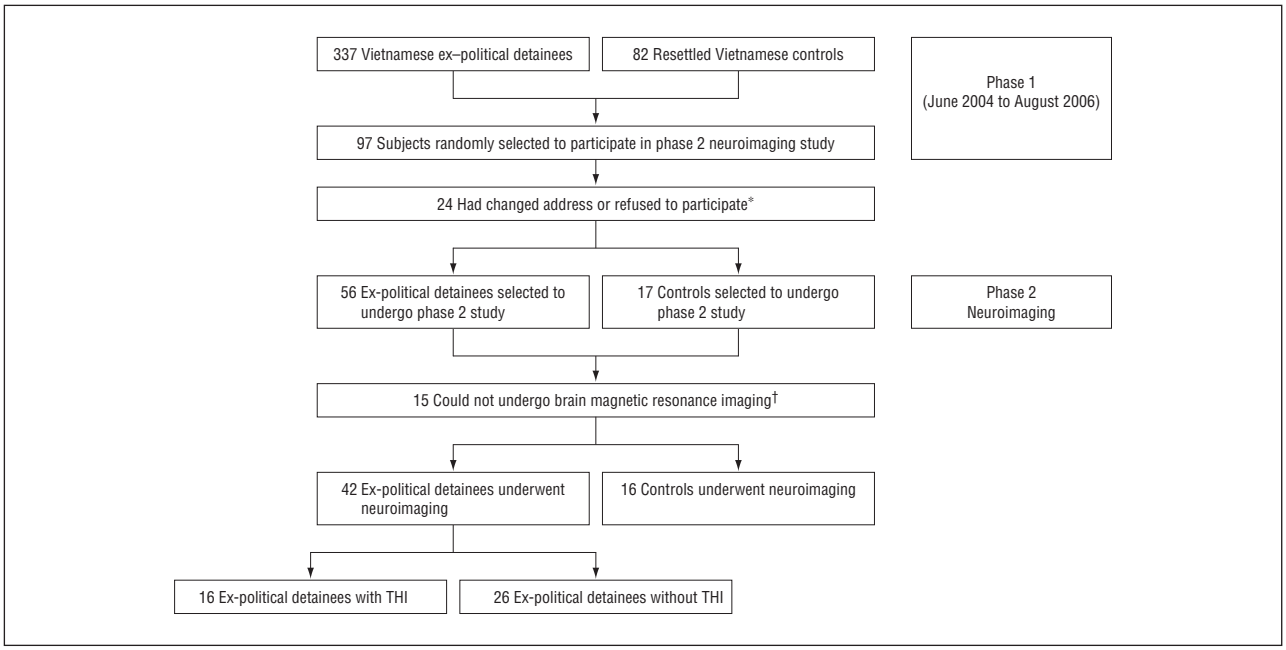

Figure 1. Participant flow through a large-scale epidemiologic survey of Vietnamese ex–political detainees and nontraumatized controls in a neuroimaging study. *After removal of these 24 subjects, 73 eligible subjects were initially screened by a nurse practitioner to determine safety and suitability 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-

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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-

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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 ($r=-0.22$, $P=.34$).

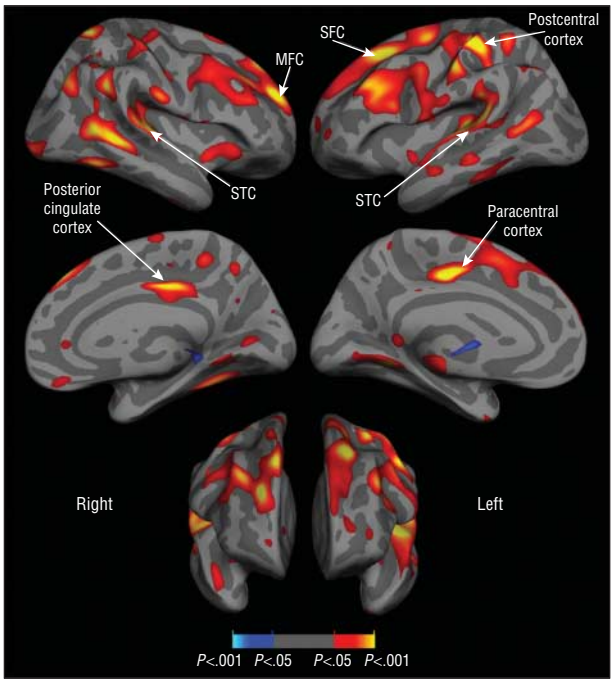

Figure 2. Statistical thickness difference maps between ex–political detainees exposed to traumatic head injury (THI) and ex–political detainees who had not experienced THI. *P* values in voxelwise statistical maps were calculated by a general linear model of cortical thickness at each voxel covarying 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]

Region	No. of Vertexes in Cluster	Cluster Size, mm²	Mean Thickness (SD) Ex–Political Detainees: Without THI (n=26)	Mean Thickness (SD) Ex–Political Detainees: With THI (n=16)	Cluster Statistics: *t* Value	Cluster Statistics: *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.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

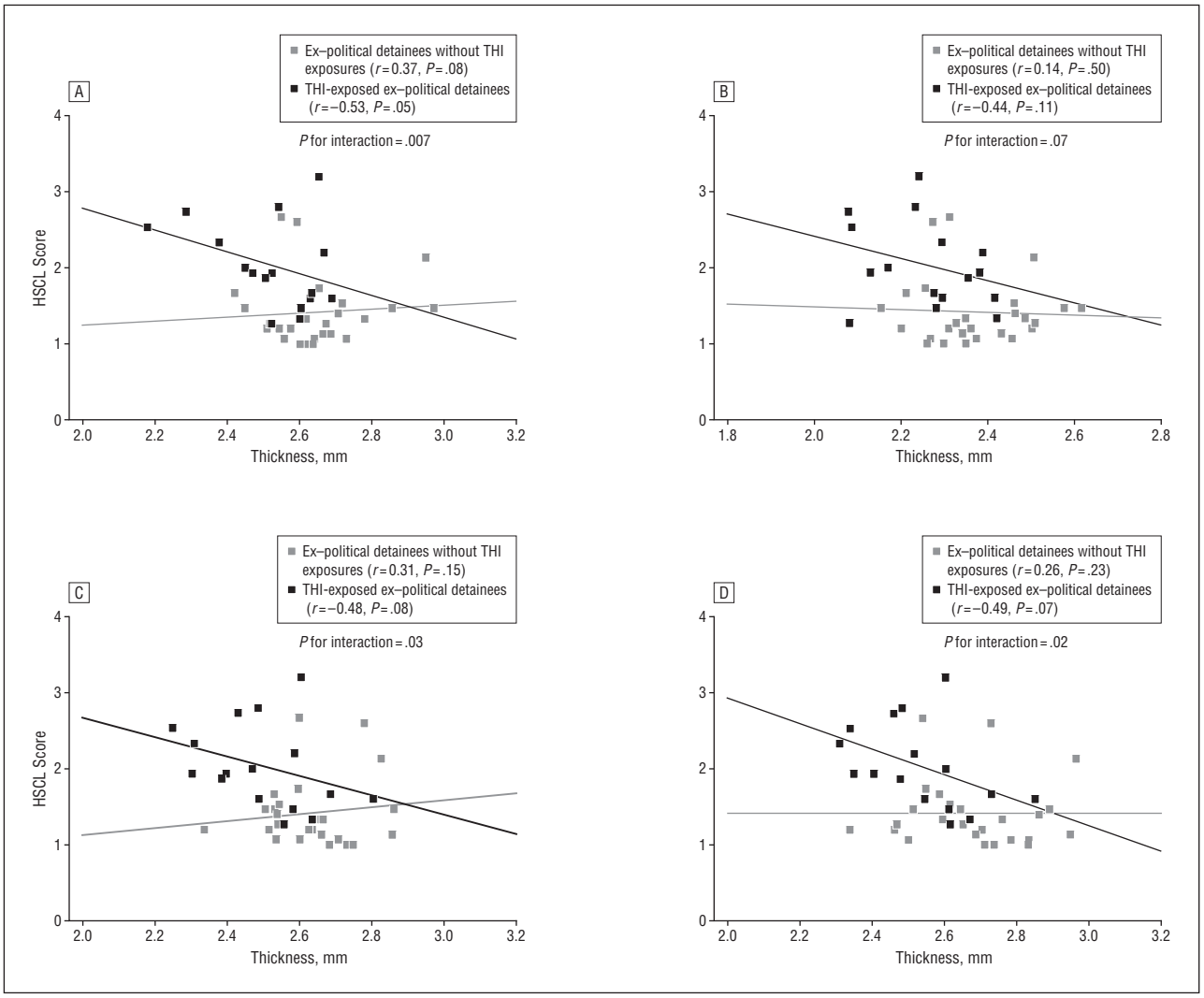

Figure 3. Relationship between severity of depression measured by the Hopkins Symptom Checklist–25 (HSCL) and cortical thickness of brain regions that were related to traumatic head injury (THI) in each ex–political detainee group. A, Left superior frontal cortex; B, left middle frontal cortex; C, left 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

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

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.

Submitted for Publication: April 18, 2008; final revision received February 6, 2009; accepted March 14, 2009.
Author Affiliations: Harvard Program in Refugee Trauma, Department of Psychiatry, Massachusetts General Hospital, Cambridge, Massachusetts (Dr Mollica and Mr Lavelle); Departments of Psychiatry (Drs Lyoo and Kim) and Neuroscience (Dr Lyoo), Seoul National University, Seoul, South Korea; McLean Hospital Brain Imaging Center and Department of Psychiatry, Harvard Medical School, Belmont, Massachusetts (Dr Lyoo); Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Massachusetts (Dr Chernoff); Vietnamese-American Civic Association, Dorchester, Massachusetts (Mr Bui); Department of Psychiatry, Catholic University Medical College, Seoul (Dr Yoon); Department of Psychiatry and The Brain Institute, University of Utah, and Department of Veterans Affairs VISN 19 Mental Illness Research, Education, and Clinical Center, Salt Lake City (Dr Renshaw).
Correspondence: Richard F. Mollica, MD, Harvard Program in Refugee Trauma, 22 Putnam Ave, Cambridge, MA 02139 (rmollica@partners.org).
Financial Disclosure: None reported.
Funding/Support: Research for this report was supported by grants MH R01-059559-04 from the National Institutes of Health and 2009K001272 from the Brain Research Center of the 21st Century Frontier Research Program, Ministry of Education, Science, and Technology of South Korea.
Additional Contributions: Melissa A. Culhane, MPH, and Daniel H. Hovelson, BA (Harvard Program in Refugee Trauma, Department of Psychiatry, Massachusetts General Hospital), and Erin Habecker, BA (McLean Brain Imaging Center), were research assistants; Donna Diamond, RN (Massachusetts General Hospital), screened all subjects prior to neuroimaging to determine safety and suitability for undergoing brain imaging; Dajung Kim, BA (Neuroscience Program, Seoul National University), Younghoon Sung, MD (McLean Brain Imaging Center and Harvard Medical School), and Namkug Kim, PhD (Seoul National University Clinical Research Institute), assisted with neuroimaging analyses; Rosemond A. Villafuerte, MA (McLean Hospital Brain Imaging Center), coordinated all neuroimaging studies; and Duy V. Pham (Vietnamese-American Civic Association) provided transportation and community support for all aspects of the study.

REFERENCES

1. Thygesen P, Hermann K, Willanger R. Concentration camp survivors in Denmark: persecution, disease, disability, compensation: a 23-year follow-up: a survey of the long-term effects of severe environmental stress. *Dan Med Bull*. 1970; 17(3):65-108.
2. Jensen TS, Genefke IK, Hyldebrandt N, Pedersen H, Petersen HD, Weile B. Cerebral atrophy in young torture victims. *N Engl J Med*. 1982;307(21): 1341.
3. Rasmussen OV. Medical aspects of torture. *Dan Med Bull*. 1990;37(suppl 1): 1-88.
4. Eitinger L. Concentration camp survivors in Norway and Israel. *Isr J Med Sci*. 1965;1(5):883-895.
5. Petersen HD, Jacobsen P. Psychical and physical symptoms after torture: a prospective controlled study. *Forensic Sci Int*. 1985;29(3-4):179-189.
6. Strom A. *Norwegian Concentration Camp Survivors*. Oslo, Norway: Oslo University Press; 1964.
7. Strom A, Refsum SB, Eitinger L, Gronvik O, Lonnum A, Engeset A, Osvik K, Rogan B. Examination of Norwegian ex–concentration-camp prisoners. *J Neuropsychiatr*. 1962;4:43-62.
8. Sulway MR, Broe GA, Creasey H, Dent OF, Jorm AF, Kos SC, Tennant CC. Are malnutrition and stress risk factors for accelerated cognitive decline? a prisoner of war study. *Neurology*. 1996;46(3):650-655.
9. Sutker PB, Vasterling JJ, Brailey K, Allain AN. Memory, attention, and executive deficits in POW survivors: contributing biological and psychological factors. *Neuropsychology*. 1995;9:118-125.
10. Sutker PB, Allain AN. Assessment of PTSD and other mental disorders in World War II and Korean conflict POW survivors and combat veterans. *Psychol Assess*. 1996;8:18-25.
11. Sutker PB, Allain AN Jr, Johnson JL, Butters NM. Memory and learning performances in POW survivors with history of malnutrition and combat veteran controls. *Arch Clin Neuropsychol*. 1992;7(5):431-444.
12. Sutker PB, Galina ZH, West JA, Allain AN. Trauma-induced weight loss and cognitive deficits among former prisoners of war. *J Consult Clin Psychol*. 1990; 58(3):323-328.
13. Sutker PB, Winstead DK, Galina ZH, Allain AN. Assessment of long-term psychosocial sequelae among POW survivors of the Korean Conflict. *J Pers Assess*. 1990;54(1-2):170-180.
14. Goldfeld AE, Mollica RF, Pesavento BH, Faraone SV. The physical and psychological sequelae of torture: symptomatology and diagnosis. *JAMA*. 1988; 259(18):2725-2729.
15. Mollica RF, Henderson DC, Tor S. Psychiatric effects of traumatic brain injury events in Cambodian survivors of mass violence. *Br J Psychiatry*. 2002; 181:339-347.
16. Belanger HG, Vanderploeg RD, Curtiss G, Warden DL. Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2007; 19(1):5-20.
17. Bigler ED. Quantitative magnetic resonance imaging in traumatic brain injury. *J Head Trauma Rehabil*. 2001;16(2):117-134.
18. McAllister TW, Sparling MB, Flashman LA, Saykin AJ. Neuroimaging findings in mild traumatic brain injury. *J Clin Exp Neuropsychol*. 2001;23(6):775-791.
19. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT, McCandliss BD. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR Am J Neuroradiol*. 2008;29(5):967-973.
20. Rutgers DR, Toulgoat F, Cazejust J, Fillard P, Lasjaunias P, Ducreux D. White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2008;29(3):514-519.
21. Yount R, Raschke KA, Biru M, Tate DF, Miller MJ, Abildskov T, Gandhi P, Ryser D, Hopkins RO, Bigler ED. Traumatic brain injury and atrophy of the cingulate gyrus. *J Neuropsychiatry Clin Neurosci*. 2002;14(4):416-423.
22. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct*. 2008;213(1-2):93-118.
23. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476-1488.
24. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry*. 2008;13(11):993-1000.
25. Steele JD, Currie J, Lawrie SM, Reid I. Prefrontal cortical functional abnormality in major depressive disorder: a stereotactic meta-analysis. *J Affect Disord*. 2007;101(1-3):1-11.
26. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry*. 2004;161(11):1957-1966.
27. Jorge RE, Starkstein SE. Pathophysiologic aspects of major depression following traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(6):475-487.
28. Chen JK, Johnston KM, Petrides M, Ptito A. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. *Arch Gen Psychiatry*. 2008;65(1):81-89.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

29. Jorge RE, Acion L, Starkstein SE, Magnotta V. Hippocampal volume and mood disorders after traumatic brain injury. *Biol Psychiatry*. 2007;62(4):332-338.
30. Jorge RE, Robinson RG, Moser D, Tateno A, Crespo-Facorro B, Arndt S. Major depression following traumatic brain injury. *Arch Gen Psychiatry*. 2004; 61(1):42-50.
31. Vasa RA, Grados M, Slomine B, Herskovits EH, Thompson RE, Salorio C, Christensen J, Wursta C, Riddle MA, Gerring JP. Neuroimaging correlates of anxiety after pediatric traumatic brain injury. *Biol Psychiatry*. 2004;55(3): 208- 216.
32. Herskovits EH, Gerring JP, Davatzikos C, Bryan RN. Is the spatial distribution of brain lesions associated with closed-head injury in children predictive of subsequent development of posttraumatic stress disorder? *Radiology*. 2002; 224(2):345-351.
33. Mollica RF, McInnes K, Pham T, Smith Fawzi MC, Murphy E, Lin L. The dose-effect relationships between torture and psychiatric symptoms in Vietnamese ex–political detainees and a comparison group. *J Nerv Ment Dis*. 1998;186 (9):543-553.
34. Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003;290(19): 2549-2555.
35. McCrea M, Guskiewicz KM, Marshall SW, Barr W, Randolph C, Cantu RC, Onate JA, Yang J, Kelly JP. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA*. 2003;290 (19):2556-2563.
36. Wilde EA, Bigler ED, Pedroza C, Ryser DK. Post-traumatic amnesia predicts long-term cerebral atrophy in traumatic brain injury. *Brain Inj*. 2006;20(7):695-699.
37. Mollica RF, Caspi-Yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard Trauma Questionnaire: validating a cross-cultural instrument for measuring torture, trauma, and posttraumatic stress disorder in Indochinese refugees. *J Nerv Ment Dis*. 1992;180(2):111-116.
38. Fawzi MC, Pham T, Lin L, Nguyen TV, Ngo D, Murphy E, Mollica RF. The validity of posttraumatic stress disorder among Vietnamese refugees. *J Trauma Stress*. 1997;10(1):101-108.
39. Mollica RF, Wyshak G, de Marneffe D, Khuon F, Lavelle J. Indochinese versions of the Hopkins Symptom Checklist–25: a screening instrument for the psychiatric care of refugees. *Am J Psychiatry*. 1987;144(4):497-500.
40. Mollica RF, Donelan K, Tor S, Lavelle J, Elias C, Frankel M, Blendon RJ. The effect of trauma and confinement on functional health and mental health status of Cambodians living in Thailand-Cambodia border camps. *JAMA*. 1993; 270(5):581-586.
41. Shrestha NM, Sharma B, Van Ommeren M, Regmi S, Makaju R, Komproe I, Shrestha GB, de Jong JT. Impact of torture on refugees displaced within the developing world: symptomatology among Bhutanese refugees in Nepal. *JAMA*. 1998;280(5):443-448.
42. Mollica RF, Caspi-Yavin Y. Measuring torture and torture-related symptoms. *Psychol Assess*. 1991;3:1-7.
43. Gorst-Unsworth C, Goldenberg E. Psychological sequelae of torture and organised violence suffered by refugees from Iraq: trauma-related factors compared with social factors in exile. *Br J Psychiatry*. 1998;172:90-94.
44. Rasekh Z, Bauer HM, Manos MM, Iacopino V. Women's health and human rights in Afghanistan. *JAMA*. 1998;280(5):449-455.
45. Sinnerbrink I, Silove D, Field A, Steel Z, Manicavasagar V. Compounding of premigration trauma and postmigration stress in asylum seekers. *J Psychol*. 1997; 131(5):463-470.
46. Mollica RFML, Massagli MP, Silove DM, eds. *Measuring Trauma, Measuring Torture*. Cambridge, MA: Harvard Program in Refugee Trauma; 2004.
47. Caspi-Yavin Y. *The Psychiatric and Functional Impact of Refugee Trauma* [thesis]. Boston, MA: Harvard School of Public Health; 1995.
48. Hollander AC, Ekblad S, Mukhamadiev D, Muminova R. The validity of screening instruments for posttraumatic stress disorder, depression, and other anxiety symptoms in Tajikistan. *J Nerv Ment Dis*. 2007;195(11):955-958.
49. Kleijn WC, Hovens JE, Rodenburg JJ. Posttraumatic stress symptoms in refugees: assessments with the Harvard Trauma Questionnaire and the Hopkins Symptom Checklist–25 in different languages. *Psychol Rep*. 2001;88(2): 527-532.
50. Smith Fawzi MC, Murphy E, Pham T, Lin L, Poole C, Mollica RF. The validity of screening for post-traumatic stress disorder and major depression among Vietnamese former political prisoners. *Acta Psychiatr Scand*. 1997;95(2):87-93.
51. Roberts B, Ocaka KF, Browne J, Oyok T, Sondorp E. Factors associated with post-traumatic stress disorder and depression amongst internally displaced persons in northern Uganda. *BMC Psychiatry*. 2008;8:38.
52. Oruc L, Kapetanovic A, Culhane M, Lavelle J, Miley K, Forstbauer S, Mollica RF, Henderson D. Screening for PTSD and depression in Bosnia and Herzegovina: validating the Harvard Trauma Questionnaire and the Hopkins Symptom Checklist. *Int J Culture Ment Health*. 2008;1(2):117-133.
53. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis, I: segmentation and surface reconstruction. *Neuroimage*. 1999;9(2):179-194.
54. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97(20):11050-11055.
55. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis, II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9(2): 195-207.
56. Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology*. 2002;58(5):695-701.
57. Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry*. 2003; 60(9):878-888.
58. Lyoo IK, Sung YH, Dager SR, Friedman SD, Lee JY, Kim SJ, Kim N, Dunner DL, Renshaw PF. Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disord*. 2006;8(1):65-74.
59. Convit A, McHugh P, Wolf OT, de Leon MJ, Bobinski M, De Santi S, Roche A, Tsui W. MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. *Psychiatry Res*. 1999;90(2):113-123.
60. Kemether EM, Buchsbaum MS, Byne W, Hazlett EA, Haznedar M, Brickman AM, Platholi J, Bloom R. Magnetic resonance imaging of mediodorsal, pulvinar, and centromedian nuclei of the thalamus in patients with schizophrenia. *Arch Gen Psychiatry*. 2003;60(10):983-991.
61. Pruessner JC, Collins DL, Pruessner M, Evans AC. Age and gender predict volume decline in the anterior and posterior hippocampus in early adulthood. *J Neurosci*. 2001;21(1):194-200.
62. Eritaia J, Wood SJ, Stuart GW, Bridle N, Dudgeon P, Maruff P, Velakoulis D, Pantelis C. An optimized method for estimating intracranial volume from magnetic resonance images. *Magn Reson Med*. 2000;44(6):973-977.
63. Ashburner J, Csernansky JG, Davatzikos C, Fox NC, Frisoni GB, Thompson PM. Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol*. 2003;2(2):79-88.
64. Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC. Beautiful faces have variable reward value: fMRI and behavioral evidence. *Neuron*. 2001; 32(3):537-551.
65. Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE. Acute effects of cocaine on human brain activity and emotion. *Neuron*. 1997;19(3):591-611.
66. Makris N, Gasic GP, Kennedy DN, Hodge SM, Kaiser JR, Lee MJ, Kim BW, Blood AJ, Evins AE, Seidman LJ, Iosifescu DV, Lee S, Baxter C, Perlis RH, Smoller JW, Fava M, Breiter HC. Cortical thickness abnormalities in cocaine addiction: a reflection of both drug use and a pre-existing disposition to drug abuse? *Neuron*. 2008; 60(1):174-188.
67. Affifi A, Clark V, May S. *Computer-Aided Multivariate Analysis*. 4th ed. Boca Raton, FL: Chapman & Hall/CRC; 2004.
68. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med*. 2008;358 (5):453-463.
69. Chemtob CM, Muraoka MY, Wu-Holt P, Fairbank JA, Hamada RS, Keane TM. Head injury and combat-related posttraumatic stress disorder. *J Nerv Ment Dis*. 1998;186(11):701-708.
70. Eitinger L, Strøm A. *Mortality and Morbidity After Excessive Stress: A Follow-up Investigation of Norwegian Concentration Camp Survivors*. Oslo, Norway: Universitetsforlaget; 1973.
71. Vasterling JJ, Constans JI, Hanna-Pladdy B. Head injury as a predictor of psychological outcome in combat veterans. *J Trauma Stress*. 2000;13(3):441-451.
72. Jacobs U, Iacopino V. Torture and its consequences: a challenge to clinical neuropsychology. *Prof Psychol Res Pr*. 2001;32(5):458-464.
73. Moreno A, Grodin MA. Torture and its neurological sequelae. *Spinal Cord*. 2002; 40(5):213-223.
74. Quiroga J, Jaranson J. Politically-motivated torture and its survivors: a desk study review of the literature. *Torture*. 2006;15(2-3):1-111.
75. Carlsson JM, Mortensen EL, Kastrup M. Predictors of mental health and quality of life in male tortured refugees. *Nord J Psychiatry*. 2006;60(1):51-57.
76. Courville CB. *Pathology of the Central Nervous System*. Mountain View, CA: Pacific Press Publishing Assoc; 1937.
77. Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. Mood change following bilateral hemisphere brain injury. *Br J Psychiatry*. 1983;143:266-273.
78. Robinson RG, Szetela B. Mood change following left hemispheric brain injury. *Ann Neurol*. 1981;9(5):447-453.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016

79. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24:167-202.
80. Bechara A, Damasio H, Damasio AR. Role of the amygdala in decision-making. *Ann N Y Acad Sci*. 2003;985:356-369.
81. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci*. 1999;19(13):5473-5481.
82. Flannelly KJ, Koenig HG, Galek K, Ellison CG. Beliefs, mental health, and evolutionary threat assessment systems in the brain. *J Nerv Ment Dis*. 2007; 195(12):996-1003.
83. Beck JG, Coffey SF. Assessment and treatment of PTSD after a motor vehicle collision: empirical findings and clinical observations. *Prof Psychol Res Pr*. 2007; 38(6):629-639.
84. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci*. 2006;1071:67-79.
85. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biol Psychiatry*. 2006;60(4):376-382.
86. Clark CR, McFarlane AC, Morris P, Weber DL, Sonkkilla C, Shaw M, Marcina J, Tochon-Danguy HJ, Egan GF. Cerebral function in posttraumatic stress disorder during verbal working memory updating: a positron emission tomography study. *Biol Psychiatry*. 2003;53(6):474-481.
87. Kay T, Newman B, Cavallo M, Ezrachi O, Resnick M. Toward a neuropsychological model of functional disability after mild traumatic brain injury. *Neuropsychology*. 1992;6(4):371-384.
88. Başoğlu M, Livanou M, Crnobarić C. Torture vs other cruel, inhuman, and degrading treatment: is the distinction real or apparent? *Arch Gen Psychiatry*. 2007; 64(3):277-285.
89. Başoğlu M, Livanou M, Crnobarić C, Francisković T, Suljić E, Durić D, Vranesić M. Psychiatric and cognitive effects of war in former Yugoslavia: association of lack of redress for trauma and posttraumatic stress reactions. *JAMA*. 2005; 294(5):580-590.
90. Başoğlu M, Mineka S, Paker M, Aker T, Livanou M, Gök S. Psychological preparedness for trauma as a protective factor in survivors of torture. *Psychol Med*. 1997;27(6):1421-1433.
91. Joseph S, Masterson J. Posttraumatic stress disorder and traumatic brain injury: are they mutually exclusive? *J Trauma Stress*. 1999;12(3):437-453.
92. Bryant RA. Posttraumatic stress disorder and traumatic brain injury: can they co-exist? *Clin Psychol Rev*. 2001;21(6):931-948.
93. Koponen S, Taiminen T, Portin R, Himanen L, Isoniemi H, Heinonen H, Hinkka S, Tenovuo O. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. *Am J Psychiatry*. 2002;159(8):1315-1321.
94. Weinstein CS, Fucetola R, Mollica R. Neuropsychological issues in the assessment of refugees and victims of mass violence. *Neuropsychol Rev*. 2001; 11(3):131-141.
95. Ashman TA, Gordon WA, Cantor JB, Hibbard MR. Neurobehavioral consequences of traumatic brain injury. *Mt Sinai J Med*. 2006;73(7):999-1005.
96. Cicerone KD, Dahlberg C, Kalmar K, Langenbahn DM, Malec JF, Bergquist TF, Felicetti T, Giacino JT, Harley JP, Harrington DE, Herzog J, Kneipp S, Laatsch L, Morse PA. Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Arch Phys Med Rehabil*. 2000;81(12):1596-1615.
97. Gordon WA, Zafonte R, Cicerone K, Cantor J, Brown M, Lombard L, Goldsmith R, Chandna T. Traumatic brain injury rehabilitation: state of the science. *Am J Phys Med Rehabil*. 2006;85(4):343-382.
98. Gordon WA, Cantor J, Ashman T, Brown M. Treatment of post-TBI executive dysfunction: application of theory to clinical practice. *J Head Trauma Rehabil*. 2006;21(2):156-167.
99. McAllister TW. Evaluation of brain injury related behavioral disturbances in community mental health centers. *Community Ment Health J*. 1997;33(4):341-358, discussion 359-364.
100. Olver J. Traumatic brain injury—the need for support and follow-up. *Aust Fam Physician*. 2005;34(4):269-271.
101. Patterson CM. The role of the primary care physician in maximizing cognitive and behavioral recovery from moderate to severe pediatric traumatic brain injury. *J Ark Med Soc*. 1998;95(3):109-113.
102. Alderfer BS, Arciniegas DB, Silver JM. Treatment of depression following traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(6):544-562.
103. Roemer L, Litz BT, Orsillo SM, Ehlich PJ, Friedman MJ. Increases in retrospective accounts of war-zone exposure over time: the role of PTSD symptom severity. *J Trauma Stress*. 1998;11(3):597-605.
104. Southwick SM, Morgan CA III, Nicolaou AL, Charney DS. Consistency of memory for combat-related traumatic events in veterans of Operation Desert Storm. *Am J Psychiatry*. 1997;154(2):173-177.
105. Mollica RF, Caridad KR, Massagli MP. Longitudinal study of posttraumatic stress disorder, depression, and changes in traumatic memories over time in Bosnian refugees. *J Nerv Ment Dis*. 2007;195(7):572-579.
106. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev*. 2006; 30(7):1004-1031.
107. Gullen WH. A danger in matched-control studies. *JAMA*. 1980;244(20):2279-2280.
108. Macklin ML, Metzger LJ, Litz BT, McNally RJ, Lasko NB, Orr SP, Pitman RK. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol*. 1998;66(2):323-326.
109. Vasterling JJ, Brailey K, Constans JI, Borges A, Sutker PB. Assessment of intellectual resources in Gulf War veterans: relationship to PTSD. *Assessment*. 1997;4:51-59.
110. Steel Z, Silove D, Phan T, Bauman A. Long-term effect of psychological trauma on the mental health of Vietnamese refugees resettled in Australia: a population-based study. *Lancet*. 2002;360(9339):1056-1062.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 02/14/2016