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Index terms:
Brain, injuries, 13.43
Brain, MR, 13.121411
Children, central nervous system, 13.43

Published online before print
10.1148/radiol.2242011439
Radiology 2002; 224:345–351

Abbreviations:
BRAID = brain image database
CHI = closed-head injury
DICA = Diagnostic Interview for Children and Adolescents
PTSD = posttraumatic stress disorder
SPGR = spoiled gradient-recalled echo

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Is the Spatial Distribution of Brain Lesions Associated with Closed-Head Injury in Children Predictive of Subsequent Development of Posttraumatic Stress Disorder?[1]

PURPOSE: To determine whether there is an association between the spatial distributions of lesions detected at magnetic resonance (MR) imaging of the brain in children, adolescents, and young adults after closed-head injury (CHI) and development of the reexperiencing symptoms of posttraumatic stress disorder (PTSD).

MATERIALS AND METHODS: Data obtained in 94 subjects without a history of PTSD as determined by parental interview were analyzed. MR images were obtained 3 months after CHI. Lesions were manually delineated and registered to the Talairach coordinate system. Mann-Whitney analysis of lesion distribution and PTSD status at 1 year (again, as determined by parental interview) was performed, consisting of an analysis of lesion distribution versus the major symptoms of PTSD: reexperiencing, hyperarousal, and avoidance.

RESULTS: Of the 94 subjects, 41 met the PTSD reexperiencing criterion and nine met all three PTSD criteria. Subjects who met the reexperiencing criterion had fewer lesions in limbic system structures (eg, the cingulum) on the right than did subjects who did not meet this criterion (Mann-Whitney, $P = .003$).

CONCLUSION: Lesions induced by CHI in the limbic system on the right may inhibit subsequent manifestation of PTSD reexperiencing symptoms in children, adolescents, and young adults.

Posttraumatic stress disorder (PTSD) is a psychiatric disorder in which specific anxiety symptoms develop after exposure to an extremely traumatic event involving actual or threatened death or serious injury. PTSD symptoms are divided into the following four criteria, symptoms from each criterion being necessary for diagnosis: *(a)* response of intense fear, helplessness, or horror to an extreme traumatic stressor; *(b)* persistent reexperience of the trauma, including recurrent intrusive memories of the event, recurrent distressing dreams of the event, and feeling as if the traumatic event were recurring; *(c)* persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness; and *(d)* persistent symptoms of increased arousal such as irritability, insomnia, and an exaggerated startle response (1). For a patient to receive the PTSD diagnosis, he or she must meet criterion *a,* criterion *b* (ie, he or she must have one of four reexperiencing symptoms), criterion *c* (he or she must have three of seven avoidance symptoms), and criterion *d* (he or she must have two of six hyperarousal symptoms). People with PTSD demonstrate alterations in memory, including flashbacks, intrusive memories, and amnesia of the traumatic event (2). The lifetime prevalence of PTSD is estimated to be 7.8% (3). Recently, Bryant et al (4) reported a prevalence of PTSD of 27%

in a series of 96 adult patients 6 months after severe closed-head injury (CHI). Similarly, Gerring et al (5) found that PTSD developed in 13% of 95 children after CHI.

A wide range of neuroradiologic experimental designs have been applied to determine anatomic correlates of PTSD. Most of these studies implicate pathologic processes in limbic system structures, including the medial frontal lobe, the cingulum, the hippocampus, the orbitofrontal lobe, the amygdala, the temporal pole, and the dorsomedial thalamus, as important determinants in the development of PTSD. These structures play pivotal roles in emotional behavior, memory, and attention.

Studies that use positron emission tomography (PET) and symptom provocation and cognitive activation paradigms in subjects have been undertaken in the hope of delineating the brain systems that mediate PTSD symptoms. Because of the constraints of activation paradigms, these studies have necessarily focused on the reexperiencing criterion, eliciting symptoms of reexperiencing by means of trauma-stimulus exposure and guided mental imagery (6–8). The responses of patients with PTSD to a stress-related auditory stimulus have also been studied with single photon emission computed tomography (SPECT) (9). Although a comprehensive review of the many PET and SPECT PTSD studies is beyond the scope of this article (see references 10–15 for excellent reviews of related work), investigations of reexperiencing symptoms have consistently demonstrated activation of anterior limbic system structures, often on the right side. In particular, investigators have demonstrated activation of the cingulum and the amygdala on the right (7,8); activation of the medial temporal cortex on the left (7); activation of the orbitofrontal cortex on the right (7); activation of the prefrontal (superior and middle frontal) cortex bilaterally; activation of the motor cortex on the left (6); absence of activation in the left middle temporal region (7) or Broca's area (8); and absence of activation of the left subcallosal cortex, right hippocampus, visual association cortex, inferior temporal gyrus, and dorsolateral prefrontal cortex (6). Functional magnetic resonance (MR) imaging examination of patients with PTSD demonstrated exaggerated bilateral amygdala activation in response to stimuli relative to that demonstrated by control subjects (16).

Results of volumetric examinations of brain structures have confirmed PET and SPECT findings in that they implicate limbic structures on the right. A controlled MR imaging study of 26 combat veterans demonstrated a statistically significant smaller average right hippocampal volume relative to that of control subjects (2). Short-term verbal memory deficits were associated with smaller right hippocampal volume only in patients with PTSD. Gurvits et al (17) reported similar findings bilaterally, whereas Stein et al (18) reported similar findings on the left. Schuff et al (19) also found decreased right hippocampal volume in war veterans with PTSD, in addition to a reduction in right hippocampal *N*-acetylaspartate.

Finally, in the past, surgical lesions in the medial ventral frontal lobe, the orbitofrontal lobe, and the cingulum were associated with the best clinical results in patients with intractable anxiety (20,21).

With the exception of the subjects in the study by Bryant et al (4), none of the subjects examined in the studies mentioned in the preceding paragraphs (several of which are summarized in Table 1) had sustained CHI; that is, the trauma to their brains was primarily psychic rather than physical. In contrast to these activation and MR volumetric studies, our research centers on the psychiatric effects of CHI, and we therefore assessed lesions induced by CHI rather than activation foci or regional volume loss after psychic trauma. In the context of lesion-deficit analysis—the basis of our research—one would expect that lesions in the previously described activated brain structures would inhibit recall of trauma or would inhibit symptomatic effects of recalling trauma; either result may inhibit satisfaction of the reexperiencing criterion. Thus, increasing lesion burden in those structures that demonstrate activation during PET and SPECT experiments should be associated with fewer PTSD-related symptoms.

We hypothesize that subjects who meet the reexperiencing criterion tend to have lower lesion burdens in the limbic system on the right and in the left hippocampus. Thus, the primary purpose of this study was to determine whether the spatial distribution of brain lesions induced by CHI, as detected at MR imaging of the brain, differs between subjects who do and subjects who do not subsequently meet the criteria for the diagnosis of PTSD, with particular attention to the three major symptom criteria: reexperiencing, avoidance, and hyperarousal.

TABLE 1
Summary of Findings in Literature Regarding Structures Associated with the Reexperiencing Symptoms of PTSD

Reference	Modality	Structure	Regional Cerebral Blood Flow*
Shin et al (8)	PET	Anterior cingulate	Increased
		Right amygdala	Increased
Rauch et al (7)	PET	Right orbitofrontal cortex	Increased
		Right anterior cingulate cortex	Increased
		Right amygdala	Increased
		Right medial temporal cortex	Increased
		Left middle temporal cortex	Decreased
		Left inferior frontal cortex	Decreased
Bremner (12)	PET	Bilateral subcallosal gyrus	Decreased
		Bilateral middle temporal gyrus	Decreased
		Left anterior cingulate	Decreased
		Left thalamus	Decreased
Shin et al (22)	PET	Orbitofrontal cortex	Increased
		Anterior temporal pole	Increased
Zubieta et al (9)	SPECT	Medial prefrontal cortex	Increased

* Radiologic findings in the indicated structure that are associated with reexperiencing.

MATERIALS AND METHODS

Determination of PTSD Status after CHI: A Behavioral Study

We obtained the data for this work from an ongoing study of personality changes after CHI conducted by Gerring et al (23) in which the researchers prospectively examine children referred from tertiary trauma centers to a university-affiliated center for treatment of children with neurologic disorders. All subjects were approved by the joint committee on clinical investigation at our institution. At least one parent or legal guardian for each subject provided written informed consent before the subject's inclusion in the study. One child's family declined participation in the

study. Exclusion criteria included previous hospitalization or emergency room visits for CHI other than the event that led to inclusion in this study, premorbid (ie, prior to CHI) mental retardation, documented child abuse, and premorbid central nervous system disease. The study cohort consisted of 97 children, adolescents, and young adults aged 4–19 years who had sustained severe CHI (Glasgow Coma Scale score, 3–8). Diagnostic Interview for Children and Adolescents (DICA) results were available for all 97 subjects, but in three subjects the MR data sets were incomplete due to transmission or storage errors; thus, 94 subjects were included in this analysis (53 boys, 41 girls).

The protocol for this study included assessment of premorbid PTSD status by administering the DICA to parents on the day of a subject's enrollment in the study (average, 20 days after CHI). Similarly, the diagnosis of PTSD 1 year after injury is determined by readministering the DICA to the parent, as described by Gerring et al (23). The DICA is a structured interview based on diagnostic criteria presented in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (1); its reliability and validity in children and adolescents aged 6–17 have been established (24). The PTSD section of the DICA has been administered in many child psychiatry studies, either alone (25) or in combination with other instruments (26), to establish the diagnosis of PTSD.

Two clinical subgroups of subjects who did not meet the criteria for PTSD at baseline when the DICA was administered to their parents were identified for the purposes of this study: subjects who did not subsequently develop PTSD, and subjects who had developed PTSD when the DICA was administered to their parents 1 year after CHI. On the basis of DICA results, we also identified three pairs of subgroups of subjects: those who did and those who did not meet the reexperiencing, avoidance, and hyperarousal criteria at 1 year.

MR Imaging

As we did in a similar study of attention deficit hyperactivity disorder (27), we chose 3 months as the target interval between CHI and MR imaging because of research indicating that MR images obtained immediately after CHI may not be as useful prognostically as those obtained 3 months after injury (28). Subjects underwent MR imaging an average of 104 days after injury. At the time of the MR imaging examination, all subjects were clinically stable; approximately half were outpatients, and the remainder were receiving inpatient neurorehabilitative therapy. Sixty (64%) of the 94 subjects were trained to inhibit motion through an operant-conditioning procedure (29); the remaining 24 subjects (36%) were sedated with intravenous pentobarbital (Nembutal Sodium; Wyeth Pharmaceuticals, Philadelphia, Pa). All MR imaging examinations were monitored by one of the investigators (J.P.G), and sequences were repeated as necessary to ensure absence of substantial motion degradation.

MR imaging of the brain included a T1-weighted (repetition time msec/echo time msec, 500/20; one signal acquired) sagittal localizing sequence with a section thickness of 5 mm, a section gap of 1.5 mm, a 24-cm field of view, and a 192 × 256 matrix. Midsagittal images were used to identify the anterior commissure–posterior commissure line, along which all oblique transverse images were oriented. Spin-echo spin-density-weighted (3,000/30, half signal acquired) and T2-weighted (3,000/100, half signal acquired) oblique transverse images with a section thickness of 5 mm, no section gap, a 20-cm field of view, and a 192 × 256 matrix were acquired from the vertex to the foramen magnum. T1-weighted spoiled gradient-recalled echo (SPGR) (35/7, one signal acquired, 45° flip angle) oblique transverse images with a section thickness of 1.5 mm, no section gap, a 24-cm field of view, and a 128 × 256 matrix were acquired from the vertex to the foramen magnum on 1.5-T instruments (GE Medical Systems, Milwaukee, Wis) at one site.

As in our study of attention deficit hyperactivity disorder (27), our goal in this study was to optimize demonstration of shear injury and other chronic brain lesions after CHI. In contrast to acute CHI, in which T2-weighted images are useful for demonstration of associated edema, subacute or chronic injuries are probably better delineated with images with high spatial resolution and T2* sensitivity. This is particularly true for small lesions such as those seen after axonal-shear injury (30). Given that the principal goal in obtaining the image data is to delineate chronic lesions, rather than to specify the type of injury for each lesion, and that the most common lesions in this study are axonal-shear injuries and contusions, we chose to use a T1-weighted three-dimensional SPGR sequence that has high spatial resolution and T1- and T2*-contrast sensitivity so that the CHI lesions could be delineated manually. As reported previously (27), we confirmed this choice by performing a preliminary comparison of T2-weighted MR images with T1-weighted SPGR images in two subjects; at this comparison, we found more lesions on the SPGR images.

The volumetric T1-weighted images were displayed at a 1,024 × 1,024-pixel workstation and were evaluated by two independent, trained readers (one experienced neuroradiology technologist and one physician [J.P.G.]) who were blinded to information about the subjects. Each reader manually delineated as a region of interest each intraaxial region of signal intensity abnormality, whether hypo- or hyperintensity, on each SPGR MR image. These abnormalities included hematoma, contusion, infarct, and axonal-shear injury and were generically designated as "lesions." A senior board-certified radiologist with subspecialty neuroradiology training (R.N.B.) adjudicated each of these readings. Iatrogenic lesions, such as ventriculostomy catheter tracts, were specifically excluded from the analysis by the readers and the adjudicator. After adjudication, the readers identified 1,173 lesions; interreader agreement was 72% (846 of 1,173). Regions of interest were reconstructed into three-dimensional structures. Lesion volumes were computed with proprietary software (Allegro; ISG, Toronto, Canada).

Image data were registered to the Talairach stereotaxic reference frame (31) with nonlinear elastic-deformation software (32). Because the accuracy of registration of patients' images to a common standard directly affects the quality of subsequent statistical analysis, we had previously evaluated this algorithm for registration error with images acquired with MR imaging parameters identical to those used to acquire images for this study. This analysis yielded an estimate of mean registration error of 3.4 mm (2.1 mm SD) for cortical structures and 2.5 mm (1.6 mm SD) for subcortical structures (32).

Data Analysis

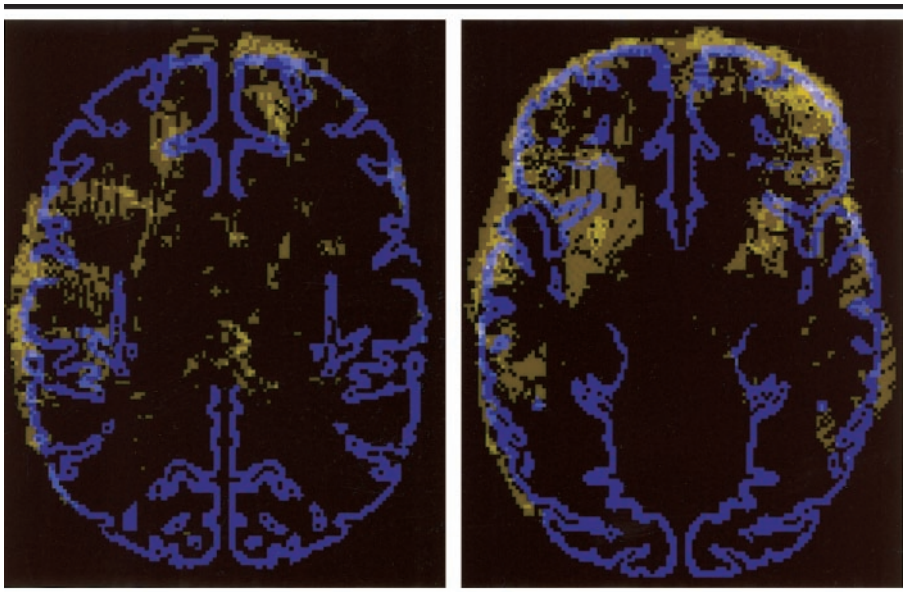
Each subject's MR imaging and clinical data were entered into our brain image database (BRAID), which integrates image-processing and statistical operators for the analysis of structural brain-image data and clinical variables such as predisposing factors or the results of neurologic examination (27,33). BRAID, which has

been designed and implemented with a commercial object-relational database management system (Illustra, Oakland, Calif), is used at a workstation (Impact; Silicon Graphics, Mountain View, Calif).

We have incorporated several digital brain atlases into BRAID, including the stereotaxic atlas of Talairach and Tournoux (31), the Brodmann atlas (34,35), and a gyral atlas, which consists of a series of 5-mm-thick cortical ribbons. The image-processing routines in BRAID are invoked via its structured query language interface (33); similarly, these atlases can be displayed with structured query language statements.

After images were registered to a common coordinate system, the image data and the corresponding clinical data (eg, PTSD criteria) were integrated into BRAID for further analysis. We then analyzed Talairach and gyral atlas structures, excluding all atlas structures that were represented as surfaces, such as the anterior commissure or claustrum, because registration error of even 1 mm could drastically affect results for these structures. For each atlas structure, we applied a statistical approach based on continuous image variables (27).

For this analysis, we started with an image of an atlas structure and intersected that structure with a particular subject's lesions. For each atlas structure, we computed the fraction of its volume that overlapped with the subject's lesions; we refer to this quantity as the *lesion fraction*. Thus, if the structure did not intersect with the subject's lesions, the lesion fraction was 0; if half of the atlas structure intersected that subject's lesions, the lesion fraction was 0.5; and so on. Because the distributions of lesion fractions are not Gaussian, we computed the independent-sample Mann-Whitney statistic to detect associations among lesion fraction and PTSD diagnosis, as well as binary variables corresponding to whether the reexperiencing, avoidance, and hyperarousal criteria were met. We computed a one-tailed statistic for structures corresponding to our hypothesis regarding an association among lesion burden for limbic system structures on the right and of the left hippocampus with satisfaction of the reexperiencing criterion; we used a two-tailed statistic for all other structure-function analyses.



a. b.

Figure 1. Transverse summary MR images obtained at the level of the genu of the corpus callosum, just above the frontal horns of **(a)** the lateral ventricles and **(b)** the hippocampi depict all lesions summed over all subjects (lesions are yellow, cortex [mapped against the Talairach stereotaxic atlas] is blue).

RESULTS

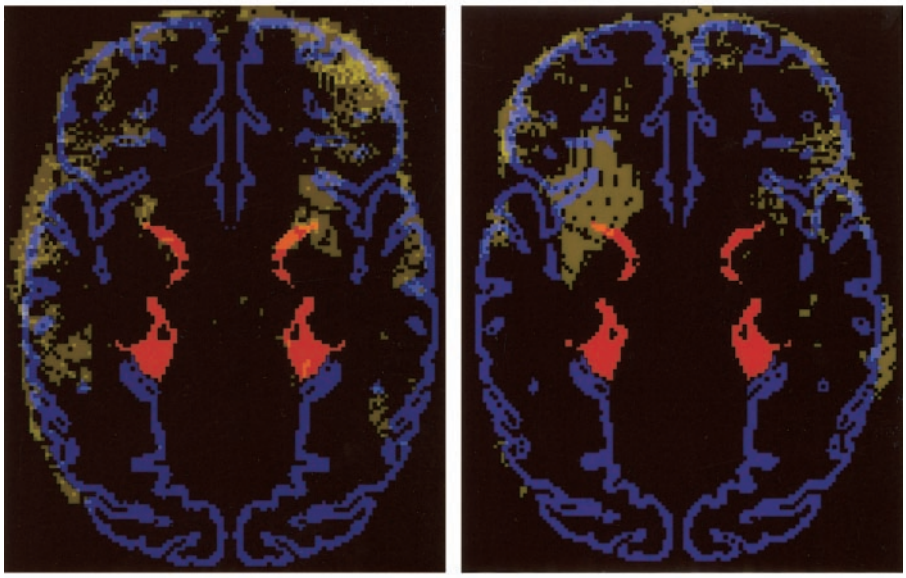
Of the 94 subjects included in this analysis, nine (10%) met all criteria for PTSD; with respect to each of the three PTSD symptom criteria, 41 subjects (44%) fulfilled the reexperiencing criterion, 12 (13%) fulfilled the avoidance criterion, and 55 (59%) fulfilled the hyperarousal criterion.

When we compared subjects who fulfilled the reexperiencing criterion or the global PTSD criterion with those who did not, we could not demonstrate significant differences with respect to Glasgow Coma Scale scores, total numbers of lesions, total lesion volumes, age, sex, or neurosurgical intervention. Only four subjects were left-handed; none of these subjects met the criteria for PTSD. After constructing the database of lesions and clinical data, we examined axially reformatted summary images of the subjects in a procedure similar to the one we previously used in visualizing data in our study of attention deficit hyperactivity disorder (27).

We submitted a query to BRAID to generate Figure 1, which shows two representative transverse images with lesions summed over all 94 subjects. By submitting more complex structured query language statements to BRAID, we can obtain equivalent images for subsets of the subjects. For example, Figure 2 shows the same transverse level through the hippocampi, with summed lesions for the 53 subjects who did not and the 41 subjects who did satisfy the reexperiencing criterion, respectively. Note that the hippocampi (outlined in red) appear to be more extensively involved in subjects who did not satisfy the reexperiencing criterion.

We confirmed the results of visualization statistically, as shown in Table 2. The one-tailed Mann-Whitney statistics that correspond to our hypothesis indicate associations between lesion fraction at 3 months and the PTSD reexperiencing criterion at 1 year. In particular, there appear to be associations between satisfaction of the PTSD reexperiencing criterion at 1 year and lesion burden in the right cingulum, the right hippocampus, the right medial frontal gyrus, and the left hippocampus. Subjects who met the reexperiencing criterion had lower lesion fractions, on average, in all of these structures than subjects who did not meet the reexperiencing criterion.

Similarly, we performed exploratory analyses of PTSD diagnosis and satisfaction of the criteria for hyperarousal and avoidance against lesion burden in Talairach and gyral atlas structures with two-tailed Mann-Whitney statistics. As shown in Table 2, lesions in the right medial frontal and left middle temporal gyri were associated with assignment to the PTSD diagnosis group; however, the association was positive for the left middle temporal gyrus, whereas there was an inverse association between lesion bur-



a. b.

Figure 2. Transverse MR images at the level of the hippocampi depict all lesions in subjects who **(a)** did not and **(b)** did develop the reexperiencing symptom complex of PTSD (lesions are yellow, cortex [mapped against the Talairach stereotaxic atlas] is blue, hippocampi are red).

TABLE 2
Structures for Which Lesion Burden is Associated with Meeting PTSD Variables

Structure	PTSD Criterion	Mann-Whitney *P* Value	Association Type*
Right cingulum†	Reexperiencing	.003‡	Negative
Right hippocampus†	Reexperiencing	.023‡	Negative
Left hippocampus†	Reexperiencing	.034‡	Negative
Right medial frontal gyrus	Reexperiencing	.035‡	Negative
Right medial frontal gyrus	PTSD status	.025	Negative
Left middle temporal gyrus	PTSD status	.026	Positive
Left subcallosal gyrus	Hyperarousal	.016	Negative
Right medial frontal gyrus	Avoidance	.010	Negative
Left inferior temporal gyrus	Avoidance	.020	Positive
Left middle temporal gyrus	Avoidance	.028	Positive

* A positive association indicates that increasing lesion burden is associated with greater probability of symptoms; a negative association indicates that increasing lesion burden is associated with lower probability of symptoms.

† As registered against the Talairach stereotaxic reference frame.

‡ We used a one-tailed statistic for this association, as it was part of the hypothesis stated in the Introduction section; we used two-tailed statistics for associations that were not part of this hypothesis.

den in the right medial frontal gyrus and a diagnosis of PTSD. A higher lesion fraction in the left subcallosal gyrus was associated with a lower probability of satisfying the hyperarousal criterion. Finally, Table 2 lists three structures in which we found lesion burden to be associated with satisfaction of the avoidance criterion. In the right medial frontal and left inferior temporal gyri, lesion burden was inversely associated with subsequent satisfaction of the avoidance criterion, whereas a higher lesion fraction in the left middle temporal gyrus was associated with a higher probability of meeting the avoidance criterion.

DISCUSSION

In comparing children, adolescents, and young adults who develop symptoms of PTSD 1 year after CHI with those who do not, we have shown that subjects who do not satisfy the reexperiencing criterion tend to have higher lesion fractions in the limbic system on the right, in particular in the cingulum and hippocampus, than subjects who do satisfy the reexperiencing criterion. Assuming that increasing lesion burden would impair a structure's activation, these findings appear to confirm activation studies that implicate the right limbic system (6,7). This result is also consistent with results of previous studies of psychosurgery, in which leukotomy was found to benefit patients with severe anxiety (20,21). Notably, we also found an association between left hippocampal lesion burden and reexperiencing (Mann-Whitney one-tailed test, $P = .034$), which may suggest that a combination of emotion-related (ie, limbic system) and memory-related (ie, left hippocampal) structures are involved in reexperiencing.

Although other researchers have found that the right amygdala is activated during reexperiencing, we did not detect such an association (Mann-Whitney, $P > .3$). This result is probably not due to the spatial distribution of lesions induced by CHI: Seven of our 94 subjects had lesions in the right amygdala, which is similar to the findings for several structures listed in Table 2. Other potential reasons for our failure to detect an association between lesion burden in the right amygdala and satisfaction of the reexperiencing criterion include differences among studies in assessing the presence of reexperiencing symptoms and fundamental differences between activation and lesion-deficit paradigms. In particular, it could be the case that reexperiencing causes activation of the amygdala on the right, even if the amygdala were not necessary to manifest reexperiencing symptoms.

Results for the avoidance criterion implicate the right medial frontal cortex (as with the reexperiencing criterion), as well as the left middle and inferior temporal gyri. However, this criterion has not been studied or characterized as well as the reexperiencing criterion, and further evaluation, either with MR imaging examination of brain structure volumes, PET, functional MR activation studies, or lesion-deficit analysis, is indicated to confirm or refute these findings. Similarly, little is known about the pathophysiology of hyperarousal, and thus our results implicating the left subcallosal gyrus are tentative pending further studies.

Subjects who satisfied all three criteria required for the diagnosis of PTSD tended to have lower lesion fractions in the right medial frontal cortex and greater lesion fractions in the left middle temporal gyrus; both phenomena were also true of subjects meeting the avoidance criterion.

We could not demonstrate associations with other structures, such as those associated with the reexperiencing criterion, probably because only nine subjects fulfilled all three diagnostic PTSD criteria; these nine subjects represented the majority of the subjects who fulfilled the criteria for avoidance, but a minority of the subjects who fulfilled the reexperiencing and hyperarousal criteria.

All structures found to be associated with these three criteria, except for the left middle and inferior temporal gyri, demonstrated an inverse structure-function relationship in that high lesion burden was associated with decreased probability of satisfying a PTSD criterion. The results for the left middle temporal gyrus appear to confirm those reported by Rauch et al (7) and Bremner et al (36), in which regional cerebral blood flow, as measured with PET, decreased (relative to that in control subjects) with script-driven imagery; thus, lesions located in the left middle temporal gyrus may play a modulating or inhibitory role in the manifestation of reexperiencing symptoms.

As mentioned earlier, and as we have previously reported (27), the distribution of lesions in CHI is an important confounding factor in this analysis in that even if a brain structure were critical to the development of PTSD-related symptoms, we would not be able to detect this association if lesions induced by CHI were uncommon in that structure. Similarly, to the extent that CHI produces characteristic patterns of injury, several structures may spuriously be associated with PTSD through their common association with the mechanism of injury; for example, deceleration injury commonly injures frontal and temporal lobes.

Our results critically depend on our abilities to detect and accurately delineate lesions, which in turn is affected by our choice of a T2*-sensitive, T1-weighted SPGR sequence, the quality of the graphical user interface for delineating lesions, and the expertise of those who delineated the lesions. To the extent that these facets of this analysis are suboptimal, we would expect to lose statistical power, but not to introduce systematic error into our analysis. Thus, as we continue to improve our image-acquisition and lesion-delineation methods, we can expect to find more lesion-deficit associations from the same data set.

As we (27) and Letovsky et al (37) have previously reported, an important limiting factor of atlas-based analysis of brain images is the accuracy of registration, particularly for small or thin atlas structures such as the cortex. Figure 1 demonstrates, in accordance with our previous findings (27), that some cortical contusions appear to lie outside of the brain after registration, which would decrease the statistical power during analysis of frontal lobe structures. Also, even the 2.5-mm mean registration error that we reported for subcortical structures (32) would affect the registration of small or thin structures such as the anterior commissure or the caudate nucleus; however, we used a gyral atlas with 5-mm-thick cortical sections in this study, which we did not use in our evaluation of children with attention deficit hyperactivity disorder (27). This more realistic, volumetric (as opposed to surface-based) gyral atlas should increase the statistical power of lesion-deficit research; we are currently testing this hypothesis with our lesion-deficit simulator (38). The relatively large sample size (compared with those found in functional-activation PTSD studies) and the longitudinal nature of this study improve its statistical power.

In addition to biases due to CHI lesion distribution and image-processing methods, there are fundamental differences between our study and most studies of PET or volumetric MR imaging. In addition to differences between activation and lesion-deficit paradigms, these differences include study populations (usually combat veterans or adults with a childhood history of sexual abuse in activation studies), the use of scripts to provoke imagery of the traumatic event, and the small numbers of subjects in most activation studies (typically on the order of 10–20 patients and control subjects). Our data are unique in that they include the spatial distribution of brain lesions induced by CHI in addition to the psychiatric effects of trauma; our incorporation of image data may account for the differences between our results and those resulting from the evaluation of subjects who suffered trauma—whether psychic or physical—other than CHI.

Another important difficulty when comparing results among neuroimaging researchers is the absence of standard anatomic nomenclature. Of particular concern is the possibility of one term referring to several structures. An important example in the PTSD literature is the location of the medial frontal cortex. Bremner et al (6,36), Zubieta et al (9), Lucey et al (39), and Rauch et al (13) use overlapping yet different anatomic definitions of the medial frontal cortex. A move in the direction to standardize location names would include Brodmann numbers in addition to location names. Although there is not yet a current published Brodmann neuroimaging atlas, many investigators use Brodmann numbers adapted from pathology atlases in their research. Our use of advanced image-registration algorithms and electronic atlases supports the development of standards for image-based clinical trials, which should increase their reproducibility.

Although PTSD is difficult to characterize reliably, we have demonstrated associations between increasing lesion burdens in certain brain structures and decreasing probabilities of satisfying PTSD criteria. In particular, it appears that lesions in the right limbic system (ie, the right cingulum and hippocampus) are associated with the absence of these symptoms 1 year after injury, perhaps because these structures are critical for reexperiencing. Given differences in subjects, nomenclature, and data-collection paradigms, our findings provide independent confirmation of those of activation studies, as well as those discussed in the psychosurgery literature.

Several aspects of this study distinguish it from previous research in this field. First, to our knowledge, this study represents the first evaluation of PTSD in children, adolescents, and young adults after CHI. To our knowledge, our study represents the only lesion-deficit analysis of PTSD after CHI in children or adults; although Bryant et al (4) examined the prevalence of PTSD following CHI in adults, they did not analyze the spatial distribution of brain lesions induced by CHI. Our brain image database supports the management and analysis of imaging and clinical data for large numbers of subjects and was central in supporting this study, which has more subjects than most previous PTSD studies. It is our belief that our use of a brain image database with registration of image data to electronic atlases will foster standardization of nomenclature and greater reproducibility of image-based studies, in a manner similar to the way in which it has become accepted that clinical variables such as blood-pressure measurement must be standardized across study subjects.

Acknowledgment: We thank Cindy Wursta, RT, for assistance with reading MR images.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed (DSM-III-R). Washing-

ton, DC: American Psychiatric Association, 1987.
2. Bremner JD, Randall P, Scott TM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 1995; 152:973–981.
3. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1995; 52:1048–1060.
4. Bryant RA, Marosszeky JE, Crooks J, Gurka JA. Posttraumatic stress disorder after severe traumatic brain injury. Am J Psychiatry 2000; 157:629–631.
5. Gerring JP, Slomine B, Vasa R, et al. Development of posttraumatic stress disorder after severe closed-head injury in children. J Am Acad Child Adolesc Psychiatry 2002; 41:157–165.
6. Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry 1999; 156:1787–1795.
7. Rauch SL, van der Kolk BA, Fisler RE, et al. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 1996; 53: 380–387.
8. Shin LM, Kosslyn SM, McNally RJ, et al. Visual imagery and perception in posttraumatic stress disorder: a positron emission tomographic investigation. Arch Gen Psychiatry 1997; 54:233–241.
9. Zubieta JK, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I. Medial frontal cortex involvement in PTSD symptoms: a SPECT study. J Psychiatr Res 1999; 33:259–264.
10. Villarreal G, King CY. Brain imaging in posttraumatic stress disorder. Semin Clin Neuropsychiatry 2001; 6:131–145.
11. Newport DJ, Nemeroff CB. Neurobiology of posttraumatic stress disorder. Curr Opin Neurobiol 2000; 10:211–218.
12. Bremner JD. Alterations in brain structure and function associated with post-traumatic stress disorder. Semin Clin Neuropsychiatry 1999; 4:249–255.
13. Rauch SL, Shin LM, Whalen PJ, Pitman RK. Neuroimaging and the neuroanatomy of posttraumatic stress disorder. CNS Spectrums 1998; 3(suppl 2):30–41.
14. Rauch SL, Shin LM. Functional neuroimaging studies in posttraumatic stress disorder. Ann N Y Acad Sci 1997; 821:83–98.
15. Stein MB, Hanna C, Koverola C, Torchia MG, McClarty B. Structural brain changes in PTSD: does trauma alter neuroanatomy? Ann N Y Acad Sci 1997; 821:76–82.
16. Rauch SL, Whalen PJ, Shin LM, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry 2000; 47:769–776.
17. Gurvits TV, Shenton ME, Hokama H, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996; 40:1091–1099.
18. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 1997; 27:951–959.
19. Schuff N, Marmar CR, Weiss DS, et al. Reduced hippocampal volume and n-acetyl aspartate in posttraumatic stress disorder. Ann N Y Acad Sci 1997; 821: 516–520.
20. Kelly D, Richardson A, Mitchell-Heggs N. Stereotactic limbic leucotomy: neurophysiological aspects and operative technique. Br J Psychiatry 1973; 123:133–140.
21. Weingarten SM. Psychosurgery. New York, NY: Guilford, 1999.
22. Shin LM, McNally RJ, Kosslyn SM, et al. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. Am J Psychiatry 1999; 156:575–584.
23. Gerring JP, Brady KD, Chen A, et al. Premorbid prevalence of attention-deficit hyperactivity disorder and development of secondary attention-deficit hyperactivity disorder after closed-head injury. J Am Acad Child Adolesc Psychiatry 1998; 37: 647–654.
24. Reich W. Diagnostic interview for children and adolescents (DICA). J Am Acad Child Adolesc Psychiatry 2000; 39: 59–66.
25. Sack WH, Clarke G, Him C, et al. A 6-year follow-up study of Cambodian refugee adolescents traumatized as children. J Am Acad Child Adolesc Psychiatry 1993; 32: 431–437.
26. Lipschitz DS, Winegar RK, Hartnick E, Foote B, Southwick SM. Posttraumatic stress disorder in hospitalized adolescents: psychiatric comorbidity and clinical correlates. J Am Acad Child Adolesc Psychiatry 1999; 38:385–392.
27. Herskovits EH, Megalooikonomou V, Davatzikos C, Chen A, Bryan RN, Gerring JP. Is the spatial distribution of brain lesions associated with closed-head injury predictive of subsequent development of attention-deficit hyperactivity disorder? analysis with a brain-image database. Radiology 1999; 213:389–394.
28. Wilson JT. The relationship between neuropsychological function and brain damage detected by neuroimaging after closed head injury. Brain Inj 1990; 4:349–363.
29. Slifer KJ, Cataldo MF, Cataldo MD, Llorente AM, Gerson AC. Behavior analysis of motion control for pediatric neuroimaging. J Appl Behav Anal 1993; 26: 469–470.
30. Gentry LR. Imaging of closed head injury. Radiology 1994; 191:1–17.
31. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart, Germany: Thieme, 1988.
32. Davatzikos C. Spatial transformation and registration of brain images using elastically deformable models. Comput Vis Image Underst 1997; 66:207–222.
33. Herskovits EH. An architecture for a brain-image database. Methods Inf Med 2000; 39:291–297.
34. Brodmann K. Vergleichende lokalisationslehre der grosshirnrinde. Leipzig, Germany: Barth, 1909.
35. Nowinski WL, Bryan RN, Raghavan RE. The electronic clinical brain atlas on CD-ROM. Stuttgart, Germany: Thieme, 1997.
36. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry 1999; 45:806–816.
37. Letovsky SI, Whitehead SHJ, Paik CH, et al. A brain image database for structure/function analysis. AJNR Am J Neuroradiol 1998; 19:1869–1877.
38. Megalooikonomou V, Herskovits EH, Davatzikos C. A simulator for evaluating methods for the detection of lesion-deficit associations. Hum Brain Mapp 2000; 10:61–73.
39. Lucey JV, Costa DC, Adshead G, et al. Brain blood flow in anxiety disorders: OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99m TcHMPAO single photon emission tomography (SPET). Br J Psychiatry 1997; 171:346–350.