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Focal brain damage protects against post-traumatic stress disorder in combat veterans

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Post-traumatic stress disorder (PTSD) is an often debilitating mental illness that is characterized by recurrent distressing memories of traumatic events. PTSD is associated with hypoactivity in the ventromedial prefrontal cortex (vmPFC), hyperactivity in the amygdala and reduced volume in the hippocampus, but it is unknown whether these neuroimaging findings reflect the underlying cause or a secondary effect of the disorder. To investigate the causal contribution of specific brain areas to PTSD symptoms, we studied a unique sample of Vietnam War veterans who suffered brain injury and emotionally traumatic events. We found a substantially reduced occurrence of PTSD among those individuals with damage to one of two regions of the brain: the vmPFC and an anterior temporal area that included the amygdala. These results suggest that the vmPFC and amygdala are critically involved in the pathogenesis of PTSD.

PTSD is characterized by re-experience of a traumatic event (for example, flashbacks), emotional numbing, avoidance of reminders of the event and hyperarousal (for example, excessive vigilance)[1]. With an estimated prevalence of over 15 million, PTSD is a major global health problem and is among the ten medical conditions most likely to cause sufferers to miss work[2,3]. Yet the biological mechanism of the disorder is unclear. Prevailing neurobiological models of PTSD focus on the interaction between the vmPFC, amygdala and hippocampus[4,5]. The role of the amygdala in fear and anxiety is well documented[6], as is the role of the hippocampus in episodic memory[7]. The vmPFC projects directly to the amygdala[8,9], and is thought to provide inhibitory input that regulates emotion[10]. PTSD patients have reduced hippocampus and vmPFC volumes[4,5,11]. When exposed to reminders of traumatic events, PTSD patients show diminished hemodynamic responses in the vmPFC[12–14], but exaggerated hemodynamic responses in the amygdala[5,15–17]. Taken together, these data suggest that PTSD is associated with overactivation of the amygdala as a result of a lack of inhibitory control by vmPFC, as well as by deficient hippocampal function. However, imaging data cannot determine whether any of these neuroanatomical findings reflect an underlying cause of the disorder (such as a pre-existing risk factor for the development of PTSD or trauma-induced neuropathology that engenders PTSD symptoms) or a secondary effect of the disorder (such as an artifact of primary dysfunction in other brain areas or the neural response to the experience of PTSD symptoms). Lesion studies could, in principle, elucidate the causal contribution of the vmPFC, amygdala and hippocampus by determining if damage to these brain areas changes the likelihood of developing PTSD. However, in an illness such as PTSD, which is not amenable to animal lesion studies, this requires the standardized clinical evaluation of a large group of people who suffered the unlikely coincidence of a localizable focal brain lesion as well as emotionally traumatic events. In addition, the lesions would need to adequately sample various areas of the brain, including the vmPFC, amygdala and hippocampus. We have this unique resource available in the Vietnam Head Injury Study (VHIS).

The VHIS (Phase 3) includes 193 Vietnam veterans with lesions distributed throughout the brain (as a result of penetrating head injuries sustained during combat) and 52 veterans with combat exposure, but no brain injury. We evaluated each of these 245 individuals for PTSD using the Structured Clinical Interview for DSM-IV-TR Axis I disorders, nonpatient edition (SCID-N/P)[18]. A psychiatrist trained to administer the SCID-N/P carried out the assessment between April 2003 and November 2006. We classified veterans as either having developed PTSD at some point in their lifetime ($PTSD^+$) or having never developed PTSD ($PTSD^-$). To identify the neural substrates of PTSD, we employed two complementary analyses: (i) an exploratory approach in which we grouped brain-injured veterans according to PTSD diagnosis (positive or negative) and then compared the distributions of lesions between groups, and (ii) a hypothesis-driven approach in which we grouped veterans by lesion location (involvement of vmPFC, amygdala or neither) and then compared the prevalence of PTSD between groups.

RESULTS

Comparison of lesions in $PTSD^+$ and $PTSD^-$ veterans

In the exploratory analysis, comparison of the distribution of lesions in the $PTSD^+$ ($n = 62$) and $PTSD^-$ ($n = 131$) groups generated a lesion

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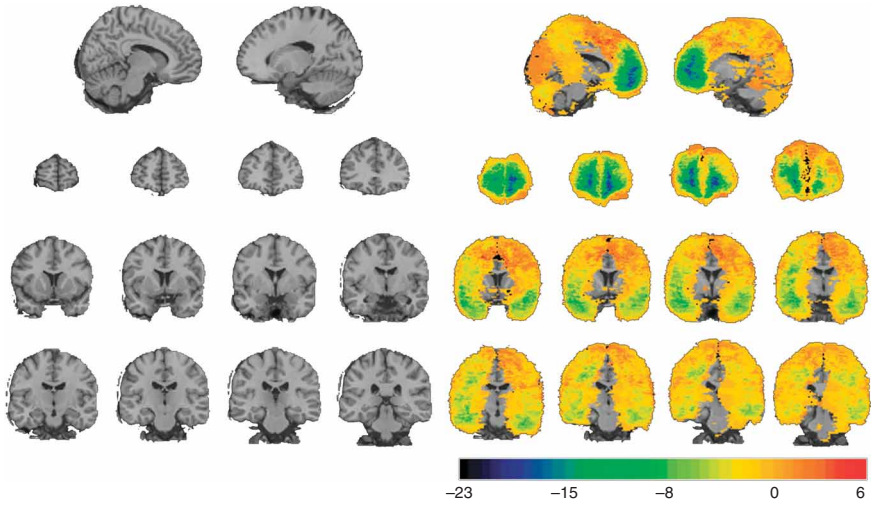

Figure 1 Lesion difference analysis. A healthy adult brain is shown on the left. The lesion difference analysis for the corresponding slices is shown on the right. The color of each voxel indicates the difference between the number of veterans with damage to that voxel that developed PTSD and the number of veterans with damage to that voxel that did not develop PTSD. The colors blue and green indicate the most negative values—areas where damage was relatively infrequently associated with PTSD. Top row, sagittal views of negative value clusters in prefrontal cortex. The left hemisphere ($x = -10$) is on the left and the right hemisphere ($x = 16$) is on the right. Second row, coronal views of negative value clusters in bilateral prefrontal cortex. Slices are arranged with the anterior-most slice on the left ($y = 66$, $y = 56$, $y = 46$, $y = 36$, respectively). In each coronal slice, the right hemisphere is on the reader's left (radiological convention). Third row, coronal views of negative value clusters in bilateral anterior temporal lobe ($y = 14$, $y = 8$, $y = 2$, $y = -4$, respectively). Fourth row, coronal views of posterior temporal lobe ($y = -10$, $y = -16$, $y = -22$, $y = -28$, respectively).

difference map (**Fig. 1**) that indicated, for each voxel, the difference between the number of veterans with damage to that voxel that did and did not develop PTSD. For example, if ten veterans had damage to a particular voxel and one of the ten veterans developed PTSD, but nine of the ten did not, then that voxel had a value of 1 – 9, or –8. Thus, large negative values indicated areas where damage was infrequently associated with the development of PTSD, whereas more positive values indicated areas where damage was more frequently associated with the development of PTSD. This analysis allowed us to identify, without any hypothesis, areas of the brain that are important for the development of PTSD. The lesion difference map (**Fig. 1**) revealed two regions with particularly dense clusters of negatively valued voxels (areas where damage was associated with a relatively small likelihood of developing PTSD): a bilateral frontal region and a bilateral anterior temporal region. The frontal region had substantial overlap with, but was not limited to, the vmPFC in both hemispheres. The temporal regions covered much of the neocortex in the anterior temporal lobe. Although the bulk of this region did not include the amygdala, the medial edge of these regions intersected the amygdala. In the temporal lobe, the density of voxels with negative values was much greater in anterior areas, which contained the amygdala, but not hippocampus, than in more posterior areas, which contained the hippocampus, but not the amygdala. This analysis suggests that the vmPFC and amygdala may indeed be critical neural substrates for the development of PTSD.

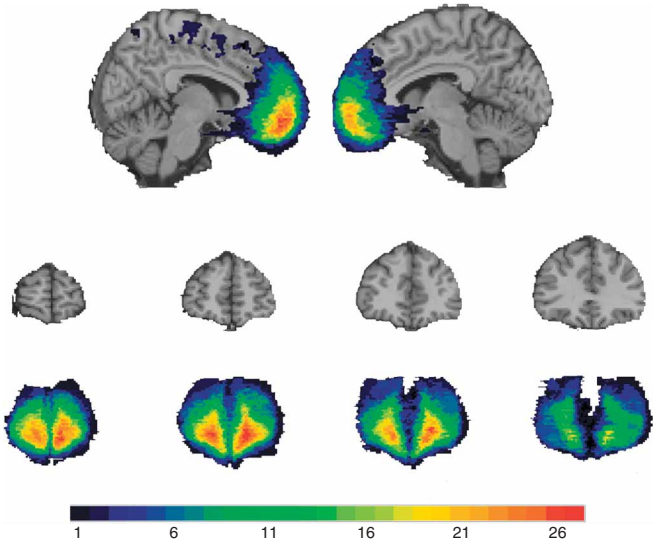

Figure 2 vmPFC group lesion overlap map. The color indicates the number of veterans in the vmPFC group ($n = 40$) with damage to a given voxel. The greatest lesion overlap (red) occurred in the anterior vmPFC bilaterally. Top row, sagittal views of the vmPFC group lesion overlap. The left hemisphere ($x = -8$) is on the left and the right hemisphere ($x = 6$) is on the right. Middle row, coronal views of a healthy adult brain. Slices are arranged with the anterior-most slice on the left (y = 66; y = 56; y = 46; y = 36; respectively). In each coronal slice, the right hemisphere is on the reader's left (radiological convention). Bottom row, coronal views of the vmPFC group lesion overlap, corresponding to the slices in the middle row. Of the 40 vmPFC patients, 14 had bilateral vmPFC lesions, 15 had exclusively or predominantly left vmPFC lesions and 11 had exclusively or predominantly right vmPFC lesions. Of the seven vmPFC patients who developed PTSD, two had bilateral vmPFC lesions, two had exclusively or predominantly left vmPFC lesions and three had exclusively or predominantly right vmPFC lesions. vmPFC lesions typically originated in the polar aspect of frontal lobe.

PTSD prevalence following vmPFC or amygdala damage

To test these hypotheses directly, we divided the VHIS participants into four groups on the basis of lesion location: (i) substantial damage to the vmPFC in either hemisphere (vmPFC lesion group, $n = 40$; **Fig. 2**), (ii) damage to the amygdala in either hemisphere (amygdala lesion group, $n = 15$; **Fig. 3**), (iii) damage not involving the vmPFC or amygdala (non-vmPFC /non-amygdala lesion group, $n = 133$) and (iv) no brain damage (non-brain-damaged group; $n = 52$). Groups did not significantly differ from each other on basic demographic variables (age, race, sex and education; **Supplementary Table 1** online), nor did they differ in the age at which they arrived in Vietnam, or in pre-combat scores on the Armed Forces Qualifying Test (AFQT, a measure of basic intellectual function; **Table 1**). As one would expect, combat exposure was greater for the brain-injured veterans than for the veterans without brain damage, and the duration of time spent on duty in Vietnam was shorter for the brain-injured veterans than for the veterans without brain damage (**Table 1**). Among the three groups of

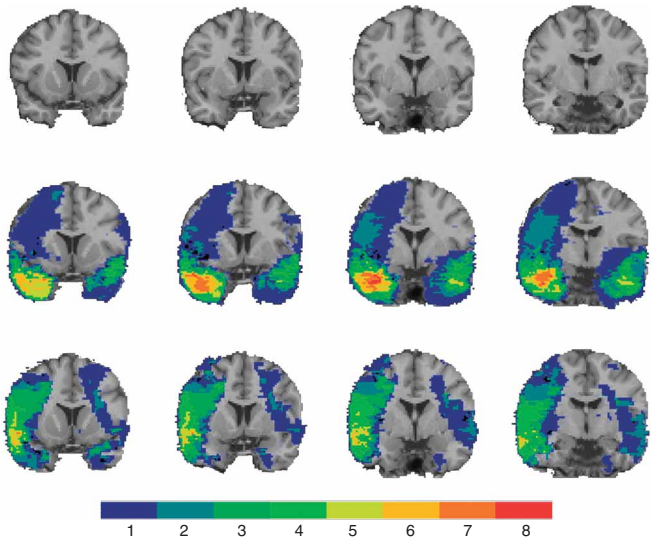

Figure 3 Lesion overlap maps for the amygdala and temporal lobe comparison groups. The color indicates the number of veterans with damage to a given voxel. Top row, coronal views of a healthy adult brain. Slices are arranged with the anterior-most slice on the left (y = 14; y = 8; y = 2; y = –4; respectively). In each coronal slice, the right hemisphere is on the reader's left (radiological convention). Middle row, coronal views of the amygdala group lesion overlap. Bottom row, coronal views of the temporal lobe comparison group lesion overlap. Slices in the middle and bottom rows correspond to the top row. The overlap maps were similar, except for the medial anterior temporal area containing the amygdala, which was damaged in the amygdala group, but intact in the temporal lobe comparison group. In both groups, damage typically originated in the lateral aspect of the temporal lobe. Of the 15 amygdala patients, seven had damage to the left amygdala and eight had damage to the right amygdala.

brain-injured veterans (amygdala, vmPFC and non-vmPFC/non-amygdala groups), there were no significant differences in combat exposure, both in terms of mean ratings ($F = 2.06$, $P = 0.13$) and proportion of individuals with high exposure ($\chi^2 = 3.40$, $P = 0.18$), nor were there any significant differences in duration of time spent in Vietnam before injury ($F = 0.21$, $P = 0.81$) or in AFQT change following injury ($F = 0.84$, $P = 0.43$). Thus, differences in combat exposure, tour duration or intellectual decline cannot account for differences in PTSD occurrence among the groups of brain-injured veterans.

We compared the proportion of veterans diagnosed with PTSD in each group (**Table 2** and **Supplementary Table 2** online). Nearly half (48%) of veterans in the non-brain-damaged group developed PTSD. There was a similar PTSD prevalence in the non-vmPFC/non-amygdala lesion group (40%; $P = 0.31$). These PTSD prevalences are comparable to published estimates of PTSD prevalence among Vietnam veterans exposed to intense combat[19]. In contrast, only 18% of the vmPFC lesion group developed PTSD. The prevalence of PTSD in the vmPFC group was significantly lower than in the non-brain-damaged group ($P = 0.002$) and the non-vmPFC/non-amygdala lesion group ($P = 0.009$). PTSD prevalence was even lower in the veterans with amygdala damage, none of whom ever developed PTSD. The prevalence of PTSD in the amygdala group (0%) was significantly lower than in the non-brain-damaged group ($P = 0.0005$) and the non-vmPFC/non-amygdala lesion group ($P = 0.001$). The difference in PTSD prevalence between vmPFC and amygdala groups was not significant ($P = 0.09$).

It is possible that the absence of PTSD in the amygdala group was a result of accompanying damage in anterior temporal cortex or medial temporal lobe structures, rather than damage to the amygdala *per se*. In fact, the lesion data clearly indicate the involvement of areas lateral to the amygdala in this group (**Fig. 3**). The nature of the brain injuries explains this result. All brain lesions were caused by penetrating wounds (for example, bullets and shrapnel). In this sample of patients, the temporal lobe damage never originated from the medial aspect, as this would require the penetrating missile to traverse midline structures such as the Circle of Willis, diencephalon or midbrain, which would probably be fatal. Thus, as all temporal lobe lesions originated laterally, and only a subset of those lesions extended to the amygdala, the overlap of temporal lesions was centered lateral to the amygdala. To address this inherent limitation in the group of amygdala patients, we selected the veterans who had anterior temporal and/or medial temporal lobe damage, but no amygdala damage ($n = 28$; **Fig. 3**). The proportion of veterans in this group who developed PTSD (32%) was significantly greater than in the amygdala group ($P = 0.01$), but was not significantly different than the rest of the non-vmPFC/non-amygdala group ($P = 0.38$) or the non-brain-damaged group ($P = 0.17$). This result indicates that damage to the temporal cortex lateral to the amygdala is not responsible for the lack of PTSD in the amygdala group.

In a more narrowly focused analysis, we considered specifically whether hippocampal damage could account for the absence of PTSD in the amygdala group. Between the amygdala group and the temporal-lobe comparison group, 20 individuals had damage involving the hippocampus (11 in the amygdala group, 9 in the temporal lobe comparison group). Of the nine veterans with hippocampal damage, but intact amygdala, four (44%) were diagnosed with PTSD. This proportion was similar to the PTSD prevalences in the non-vmPFC/non-amygdala lesion group (40%) and non-brain-damaged group (48%), but significantly higher than the PTSD prevalence in the group with damage to both the hippocampus and amygdala (0%; $P = 0.03$). Furthermore, basic memory encoding and retrieval functions were intact in the amygdala group (**Supplementary Table 3**

Table 1 Military service data

Group	Age in Vietnam	Duration (months)	Percentage drafted	AFQT (percentile)	AFQT change	Combat exposure	Combat exposure (% high)
Amygdala	20.4 ± 2.2	6.1 ± 3.1	50	65.6 ± 28.1	–15.2 ± 23.9	3.9 ± 1.6	64
vmPFC	20.3 ± 3.1	5.8 ± 3.5	36	55.0 ± 22.6	–9.7 ± 17.9	3.2 ± 0.8	43
Non-vmPFC/non-amygdala	20.6 ± 2.9	5.6 ± 3.8	31	61.3 ± 25.9	–8.2 ± 19.0	3.3 ± 1.1	58
No brain damage	20.6 ± 3.1	>10	52	65.4 ± 22.9	3.9 ± 14.5	2.6 ± 1.2	33

Age in Vietnam is the age on arrival in Vietnam. Duration is the period between arrival in Vietnam and injury (in the case of the brain-injured individuals) or end of service in Vietnam (in the case of the non-brain-injured individuals). Percentage drafted indicates the percentage of individuals drafted into military service. AFQT is a measure of basic intellectual function. AFQT (percentile) is the AFQT percentile at the time of enlistment. AFQT change is the difference between AFQT score at the time of enlistment and the Phase 3 evaluation. Combat exposure indicates the frequency of exposure to enemy contact (0 = no contact (support unit), 1 = occasional mortar attack (support unit), 2 = intermittent enemy contact (support unit), 3 = intermittent enemy contact (combat unit), 4 = constant enemy contact (combat unit)). Combat exposure (% high) is the percentage of individuals who experienced constant enemy contact in a combat unit. For Age in Vietnam, Duration, AFQT (percentile), AFQT change and Combat exposure, data are presented as mean ± s.d.

Table 2 PTSD prevalence

Brain damage	PTSD prevalence
Amygdala	0%
vmPFC	18%
Non-vmPFC/non-amygdala	40%
No brain damage	48%

A χ-square frequency analysis of the three groups of brain-injured veterans indicated a significant effect of lesion location on PTSD prevalence ($\chi^2 = 14.7$, $P = 0.0006$). P values for individual pair-wise comparisons are summarized in **Supplementary Table 2**.

online). These data support the conclusion that damage to the amygdala, rather than to the hippocampus or other temporal areas, is the basis of the amygdala group's conspicuous lack of PTSD.

In summary, veterans with vmPFC or amygdala damage were significantly less likely to develop PTSD than veterans with damage to other parts of the brain or veterans with no brain damage. Particularly notable was the complete absence of a lifetime diagnosis of PTSD among veterans with amygdala damage, which could not be attributed to damage to surrounding temporal lobe regions, including hippocampus.

Follow-up analysis of PTSD symptom categories

Although the PTSD diagnosis is dichotomous, the disorder entails multiple symptoms, which may be experienced in varying degrees. To receive a diagnosis, the patient must have distressing symptoms in each of three categories: re-experience, avoidance/numbing and hyperarousal. The primary analyses thus raise questions about why the vmPFC and amygdala patients were not meeting diagnostic criteria for PTSD. Were PTSD symptoms completely eliminated, or did they just occur less frequently or less intensely? Were all symptoms affected, or only a subset? In a follow-up analysis, we sought to determine the effect of vmPFC and amygdala damage on the frequency and intensity of specific categories of PTSD symptoms. The Clinician-Administered PTSD Scale–Diagnostic Version[20] (CAPS-Dx) was used to assess the frequency and intensity (distress) of 17 specific PTSD symptoms (five symptoms of re-experience, seven symptoms of avoidance/numbing and five symptoms of hyperarousal). Each participant rated the frequency and intensity of each symptom on a scale of 0–4, where greater numbers indicated greater frequency or intensity. The mean ratings of symptom frequency (**Table 3**) and intensity (**Table 4**) for each category were compared between groups with 3 × 4 ('symptom category' × 'lesion group') ANOVAs. We found a significant main effect of lesion group on the frequency ($F = 9.5$, $P < .001$) and intensity ($F = 9.8$, $P < .001$) of PTSD symptoms, with the amygdala and vmPFC groups showing less frequent and less intense symptoms than comparison groups overall. However, there was no significant interaction between lesion group and symptom category for either frequency ($F = 0.09$, $P > .99$) or intensity ($F = 0.21$, $P > .97$). These data indicate that damage to the vmPFC or amygdala does not selectively diminish the frequency or intensity of individual categories of PTSD symptoms, but rather reduces the frequency and intensity of symptoms in all three categories to a similar extent, with amygdala damage conferring a greater overall reduction in symptom frequency and intensity than vmPFC damage.

Prevalence of other anxiety disorders

We further investigated whether the observed reduction in distress following vmPFC or amygdala damage was specific to PTSD, or if it applied to anxiety disorders in general. We evaluated VHIS patients with the SCID-N/P for panic disorder, agoraphobia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, substance-induced anxiety disorder and anxiety disorder not otherwise specified. The proportion of individuals diagnosed with any of these anxiety disorders was not significantly different among the amygdala group (13%), vmPFC group (15%) or the non-vmPFC/non-amygdala lesion group (22%) ($P > 0.10$). Although the overall prevalence of nonPTSD anxiety disorders was lower than that of PTSD (meaning less power to detect differences between groups), these data nonetheless suggest that, in this sample of veterans, vmPFC and amygdala damage had a particularly important effect on PTSD, rather than on anxiety disorders in general.

Table 3 Mean PTSD symptom frequency

Group	Re-experience	Avoidance/Numbing	Hyperarousal
Amygdala	0.43	0.28	0.36
vmPFC	0.76	0.55	0.69
Non-vmPFC/Non-amygdala	0.95	0.67	0.85
No brain damage	1.02	0.84	0.95

Participants rated 17 individual PTSD symptoms belonging to one of three symptom categories (re-experience, avoidance/numbing and hyperarousal) for frequency (0 = never, 1 = once or twice, 2 = once or twice a week, 3 = several times a week, 4 = daily or almost every day). A 3 × 4 (symptom type × lesion group) ANOVA revealed a significant main effect of lesion group, but no interaction effects.

DISCUSSION

Data from a unique sample of brain-damaged and trauma-exposed individuals provide evidence that the vmPFC and amygdala are causally involved in the pathogenesis of PTSD. Lesions involving either area reduced the occurrence of PTSD. The decreased prevalence of PTSD following vmPFC or amygdala damage appears to be to the result of an overall reduction of symptom intensity, rather than a complete abolishment of all symptoms or a reduction of only a subset of symptoms.

The results reported here are broadly consistent with a previous study of diffuse brain injury following closed-head injury in children[21]. Although the pediatric study found no association between amygdala damage and PTSD symptoms, it did find a negative association between medial prefrontal lesion burden and subsequent PTSD symptoms. In our study of adults with relatively large, focal lesions, both amygdala and vmPFC lesions were associated with reduced levels of PTSD.

It is noteworthy that unilateral amygdala lesions resulted in the observed reduction in PTSD. Both animal and human studies indicate that bilateral amygdala lesions yield substantially more severe effects on emotional processing than do unilateral lesions[13]. The fact that unilateral amygdala lesions were associated with such a marked reduction in PTSD symptoms highlights the importance of the amygdala in the disorder. One possibility is that although one intact amygdala may be sufficient to mediate normal levels of fear/anxiety (for example, in fear-conditioning procedures), perhaps both amygdala are necessary to

Table 4 Mean PTSD symptom intensity

Group	Re-experience	Avoidance/Numbing	Hyperarousal
Amygdala	0.45	0.28	0.41
vmPFC	0.84	0.58	0.83
Non-vmPFC/non-amygdala	0.95	0.67	1.02
No brain damage	1.02	0.84	1.16

Participants rated 17 individual PTSD symptoms belonging to one of three symptom categories (re-experience, avoidance/numbing, and hyperarousal) for intensity (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme). A 3 × 4 (symptom type × lesion group) ANOVA revealed a significant main effect of lesion group, but no interaction effects.

mediate the 'super-normal' levels of fear/anxiety that define PTSD. Although humans with bilateral amygdala lesions are exceedingly rare, we speculate that such individuals may have an extraordinary resistance to trauma-related distress.

Conventional neurobiological models propose that deficient modulation of the amygdala by the vmPFC and hippocampus is the underlying mechanism of PTSD[5,6]. We found no evidence that hippocampal damage affected the development of PTSD. The finding that amygdala damage eliminated the occurrence of PTSD supports one aspect of the model: that amygdala hyperactivity is a critical element. However, the finding that vmPFC damage independently reduced the occurrence of PTSD argues against the theory that decreased vmPFC inhibition is the basis of the amygdala hyperactivity. If a loss of vmPFC inhibition of the amygdala were the neuroanatomical basis of PTSD, then one would expect vmPFC damage to increase the occurrence of PTSD. The fact that vmPFC damage decreased the occurrence of PTSD indicates that vmPFC has a role in the expression of PTSD; perhaps vmPFC's interaction with the amygdala is not uniformly inhibitory.

The neurobiological basis of the complex interaction between vmPFC and amygdala may lie in distinct circuits for excitation or inhibition. Animal studies indicate that vmPFC inputs may have different effects depending on the target nucleus and the particular vmPFC subfield from which the input originates. For example, projections from the vmPFC may excite neurons in the basolateral amygdala[22], but ultimately inhibit neurons in the central amygdala[23]. Further research will be necessary to specify the nature of the interaction between the vmPFC and amygdala and how dysfunction in this circuit contributes to PTSD. One specific topic for further research is the effect of damage to the pathway between the vmPFC and amygdala (for example, the uncinate fasciculus) on emotional processing.

It has been proposed that the vmPFC is critical for the reactivation of emotional states associated with past experiences[24,25]. Our results are consistent with this account of vmPFC function. Moreover, our results indicate that damage to the vmPFC or amygdala can protect against the pathological reactivation of traumatic memories that is central to PTSD. These findings suggest that treatments aimed at selectively inhibiting vmPFC and/or amygdala function[26–32] could be effective for treating PTSD.

METHODS

Subjects. We drew subjects from the W.F. Caveness Vietnam Head Injury Study (VHIS) registry, which originally included 1,221 American soldiers who survived penetrating brain wounds suffered in Vietnam. The VHIS has been organized in three phases. Phase 1 was the initial enrollment, which occurred between 1967 and 1970. For Phase 2 the 1,118 veterans still alive were invited to participate in an extensive follow-up clinical study at the Walter Reed Army Medical Center between August 1981 and August 1984. Of the 1,118 survivors, 520 participated in the Phase 2 study. Comparison subjects ($n = 85$) were recruited from Veterans Administration records of non-head-injured soldiers who had served in Vietnam during the same years and were in the same age range as soldiers on the Caveness registry. 193 head-injured and 52 nonhead-injured subjects from Phase 2 participated in Phase 3, which included a psychiatric evaluation by a neuropsychiatrist (V.R.). We conducted Phase 3 between April 2003 and November 2006 at the Bethesda National Naval Medical Center. Pre-injury characteristics of the participants were available from military and Veterans Administration records. All subjects gave informed written consent.

Lesion analysis. We acquired computed tomography (CT) data during the Phase 3 testing period. We acquired axial CT scans without contrast at the Bethesda Naval Hospital on a General Electric Medical Systems Light Speed Plus CT scanner in helical mode. We reconstructed the images with an in-plane voxel size of 0.4 × 0.4 mm, an overlapping slice thickness of 2.5 mm and a 1-mm slice interval. We determined lesion location and volume from CT images using the Analysis of Brain Lesion (ABLe) software[33,34] contained in MEDx v3.44 (Medical Numerics) with enhancements to support the Automated Anatomical Labeling (AAL) atlas[35]. For the hypotheses about specific brain areas (vmPFC and amygdala), we defined regions of interest (ROIs) in terms of AAL structures[35] and Talairach coordinates[36]. As part of this process, we spatially normalized the CT image of each subject's brain to a CT template brain image in Montreal Neurological Institute space[37]. We determined the percentage of AAL structures that were intersected by the lesion by analyzing the overlap of the spatially normalized lesion image with the AAL atlas image. We calculated lesion volume by manually tracing the lesion in all relevant slices of the CT image, and then summing the traced areas and multiplying by slice thickness. A trained neuropsychiatrist (V.R.) carried out the manual tracing, which was then reviewed by an observer that was blind to the results of the clinical evaluation and neuropsychological testing (J.G.).

The vmPFC ROI included portions of the following AAL structures: superior frontal gyrus (medial), superior frontal gyrus (orbital part), superior frontal gyrus (medial orbital), middle frontal gyrus (orbital part), inferior frontal gyrus (orbital part), gyrus rectus, olfactory cortex, anterior cingulate and paracingulate gyri. The portions of these structures included in the vmPFC ROI were those areas that were inferior to the anterior commissure (z value less than zero) and between 0 and 20 mm left and right from the anterior commissure (x value between –20 and 0 for the left vmPFC and x value between 0 and 20 for right vmPFC). These criteria outlined an area comprising the ventral portion of the medial prefrontal cortex (below the level of the genu of the corpus callosum) and the medial portion of the orbital surface (approximately the medial one-third of the orbitofrontal cortex in each hemisphere), as well as the subjacent white matter. A subject was included in the vmPFC group if his lesion occupied at least 15% of the right or left vmPFC ROI. We used 15% damage as a threshold for inclusion in the vmPFC group because it has been demonstrated that damage to approximately 15% of the vmPFC in one hemisphere can be sufficient to yield clear impairments in emotional processing[38]. As the amygdala and hippocampus are predefined in the AAL atlas, it was not necessary to specify criteria for those structures. A subject was included in the amygdala group if his lesion involved any portion of the amygdala in either hemisphere. The amygdala is a much smaller and discrete area than the vmPFC, and there is no evidence to suggest a threshold for the effect of partial damage, so any damage to the amygdala was presumed to be potentially significant.

Statistical analysis. The between-group comparisons of military service and demographic data (**Table 1** and **Supplementary Table 1**) were conducted with either a one-way ANOVA (for data reported as a mean ± s.d.), a χ-square frequency analysis or Fisher's exact test (for data reported as a proportion or percentage). The between-group comparisons of PTSD prevalence (**Table 2**, **Supplementary Table 2** and **Supplementary Data** online) were conducted using χ-square frequency analysis or Fisher's exact test. For each comparison, if there were at least five individuals with (or without) PTSD diagnosis in each group, χ-square was used; if not, Fisher's exact test was used. The mean ratings of symptom frequency (**Table 3**) and intensity (**Table 4**) for each PTSD symptom category were compared with 3 × 4 ("symptom category" × "lesion group") ANOVA. The between-group comparisons of nonPTSD anxiety disorder prevalence were conducted using χ-square frequency analysis or Fisher's exact test, depending on sample sizes.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

M.K., E.D.H. and J.G. planned the study. V.R. conducted the psychiatric assessments and carried out the lesion tracing with J.G. B.C. performed

additional data collection and organization. J.S. designed and implemented the lesion analysis software. M.K. and E.D.H. analyzed the psychiatric data. M.K. and J.S. analyzed the lesion data. M.K. prepared the figures and wrote the manuscript in consultation with E.D.H., E.M.W. and J.G. All authors reviewed and edited the manuscript. J.G. supervised the project.

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