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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 characterized by recurrent distressing memories of traumatic events. PTSD is associated with hypoactivity in ventromedial prefrontal cortex (vmPFC), hyperactivity in amygdala, and reduced volume in hippocampus, but it is unknown whether these neuroimaging findings reflect the underlying cause of the disorder, or a secondary effect. 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 significantly 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 vmPFC and amygdala are critically involved in the pathogenesis of PTSD.

Post-traumatic Stress Disorder (PTSD) is characterized by re-experience of a traumatic event (e.g., flashbacks), emotional numbing, avoidance of reminders of the event, and hyperarousal (e.g., 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 ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus[4,5]. The role of the amygdala in fear and anxiety is well documented[6], as is the role of hippocampus in episodic memory[7]. vmPFC projects directly to 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 exhibit diminished hemodynamic responses in vmPFC[12-14], but exaggerated hemodynamic responses in amygdala[5,15-17]. Taken together, these data suggest that PTSD is associated with overactivation of the amygdala due to a lack of inhibitory control by vmPFC, as well as deficient hippocampal function. However, imaging data cannot determine whether any of these neuroanatomical findings reflect an underlying cause of the disorder (such as a preexisting 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 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 that 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 vmPFC, amygdala, and hippocampus. Remarkably, 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, Non-Patient edition (SCID-N/P)[18]. A psychiatrist trained to administer the SCID-N/P performed the assessment between April 2003 and November 2006. We classified veterans as either having developed PTSD at some point in their lifetime (PTSD-positive) or having never developed PTSD (PTSD-negative). To identify the neural substrates of PTSD, we employed two complementary analyses: 1) 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 2) a hypothesis-driven approach in which we grouped veterans based on lesion location (involvement of vmPFC, amygdala, or neither) and then compared the prevalence of PTSD between groups.

RESULTS

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Comparison of lesions in PTSD+ and PTSD– veterans

In the exploratory analysis, comparison of the distribution of lesions in the PTSD-positive (n=62) and PTSD-negative (n=131) groups generated a lesion 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 10 veterans had damage to a particular voxel, and 1 of the 10 veterans developed PTSD but 9 of the 10 did not, then that voxel had a value of 1 minus 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) vmPFC in both hemispheres. The temporal regions covered much of neocortex in anterior temporal lobe. Although the bulk of this region did not include the amygdala, the medial edge of these regions intersected the amygdala. In temporal lobe the density of negative-valued voxels was much greater in anterior areas than in more posterior areas, which contain hippocampus, but not amygdala. This analysis suggests that vmPFC and amygdala may indeed be critically involved in the development of PTSD.

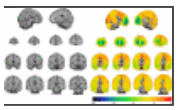

Figure 1

Lesion difference analysis

PTSD prevalence following vmPFC or amygdala damage

To test these hypotheses directly, we divided the VHIS participants into four groups based on lesion location: 1) significant damage to vmPFC in either hemisphere (vmPFC lesion group; n=40; Fig. 2), 2) damage to amygdala in either hemisphere (amygdala lesion group; n=15; Fig. 3), 3) damage not involving vmPFC or amygdala (non-vmPFC /non-amygdala lesion group; n=133), and 4) 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), nor did they differ in the age at which they arrived in Vietnam, or 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 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 ($F=2.06$; $p=.13$) and proportion of individuals with high exposure ($\chi^2=3.40$; $p=.18$), nor were there any significant differences in duration of time spent in Vietnam prior to injury ($F=0.21$; $p=.81$), or AFQT change following injury ($F=0.84$; $p=.43$). Thus differences in combat exposure, tour duration, or intellectual decline cannot account for differences in PTSD occurrence among the groups of brain-injured veterans.

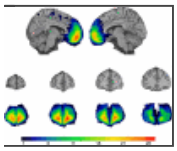

Figure 2

vmPFC group lesion overlap map

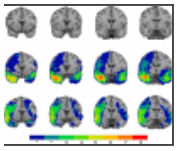

Figure 3

Lesion overlap maps for the amygdala and temporal lobe comparison groups

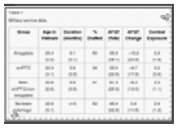

Table 1

Military service data.

We compared the proportion of veterans diagnosed with PTSD in each group (Table 2). 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=.31). These PTSD prevalences are comparable to published estimates of PTSD prevalence among Vietnam veterans exposed to intense combat[19]. By 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=.002) and the non-vmPFC/non-amygdala lesion group (p=.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=.0005) and the non-vmPFC/non-amygdala lesion group (p=.001). The difference in PTSD prevalence between vmPFC and amygdala groups was non-significant (p=.09).

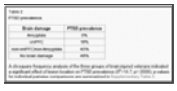

Table 2

PTSD prevalence.

It is possible that the absence of PTSD in the amygdala group was due to 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 involvement of areas lateral to the amygdala (Fig. 3). The nature of the brain injuries explains this result. All brain lesions were caused by penetrating wounds (e.g. bullets, shrapnel). In this sample of patients the temporal lobe damage never originated from the medial aspect, because this would require the penetrating missile to traverse midline structures such as the Circle of Willis, diencephalon, or midbrain, which would likely be fatal. Thus, since 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 the amygdala group (p=.01), but not significantly different than the rest of the non-vmPFC/non-amygdala group (p=.38) or the non-brain damaged group (p=.17). This result indicates that damage to the temporal cortex lateral to amygdala is not responsible for the lack of PTSD in the amygdala group. In a more narrowly focused analysis, we considered specifically whether hippocampus damage could account for the absence of PTSD in the amygdala group. Between the amygdala group and the temporal lobe comparison group, twenty individuals had damage involving hippocampus (eleven in the amygdala group, nine in the temporal lobe comparison group). Of the nine veterans with hippocampus damage but intact amygdala, four (44%) were diagnosed with PTSD. This proportion is 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 hippocampus and amygdala (0%; p=.03). Furthermore, basic memory encoding and retrieval functions were intact in the amygdala group (Supplementary Table 3). These data support the conclusion that damage to the amygdala, rather than 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 striking 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. In order 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 (5 symptoms of re-experience, 7 symptoms of avoidance/numbing, and 5 symptoms of hyperarousal). Each participant rated the frequency and intensity of each symptom on a scale of 0−4, where greater numbers indicate 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 exhibiting less frequent and less intense symptoms overall than comparison groups. 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 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.

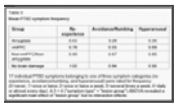

Table 3

Mean PTSD symptom frequency

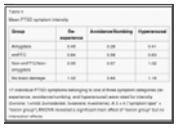

Table 4

Mean PTSD symptom intensity

Prevalence of other anxiety disorders

We further investigated whether the reduction in PTSD 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%), and the non-vmPFC /non-amygdala lesion group (22%) (p>.10). Although the overall prevalence of non-PTSD 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 has a particularly important effect on PTSD, rather than on anxiety disorders in general.

DISCUSSION

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Data from a unique sample of brain-damaged and trauma-exposed individuals provide evidence that 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 due to 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 study of diffuse brain injury following closed-head injury in children[21]. Although the pediatric study reports no association between amygdala damage and PTSD symptoms, it does report 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 much more severe effects on emotional processing than do unilateral lesions[13]. The fact that unilateral amygdala lesions were associated with such a dramatic reduction in PTSD symptoms highlights the importance of the amygdala in the disorder. One possibility is that whereas one intact amygdala may be sufficient to mediate "normal" levels of fear/anxiety (e.g. in fear conditioning paradigms), perhaps both amygdala are necessary to 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 amygdala by vmPFC and hippocampus is the underlying mechanism of the PTSD[5,6]. We found no evidence that hippocampus damage affected the development of PTSD. The finding that amygdala damage eliminated the occurrence of PTSD supports one aspect of the model, i.e., 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 opposite effects depending on the target nucleus and the particular vmPFC subfield from where the input originates. For example, projections from 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 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 vmPFC and amygdala (e.g. the uncinate fasciculus) on emotional processing.

It has been proposed that vmPFC is critical for the re-activation 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 vmPFC or amygdala can protect against the pathological re-activation of traumatic memories central to PTSD. These findings suggest that treatments aimed at selectively inhibiting vmPFC and/or amygdala function[26-32] could have efficacy to treat PTSD.

METHODS

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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 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 VA files of non-head-injured soldiers who had served in Vietnam the same years and were within the same age range as soldiers on the Caveness registry. 193 head-injured and 52 non-head-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 Bethesda National Naval Medical Center. Preinjury characteristics of the participants were available from military and VA records. All subjects gave informed written consent.

Lesion Analysis

We acquired CT data during the Phase 3 testing period. We acquired Axial CT scans without contrast at Bethesda Naval Hospital on a GE Medical Systems Light Speed Plus CT scanner in helical mode. We reconstructed the images with an in-plane voxel size of 0.4mm × 0.4mm, overlapping slice thickness of 2.5mm and a 1mm 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, Germantown, MD) 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 MNI space[37]. We determined the percentage of AAL structures intersected by the lesion by analyzing the overlap of the spatially normalized lesion image with the AAL atlas image. We calculated lesion volume by manual tracing of the lesion in all relevant slices of the CT image then summing the traced areas and multiplying by slice thickness. A trained neuropsychiatrist (V.R.) performed the manual tracing, which was then reviewed by J.G., who was blind to the results of the clinical evaluation and neuropsychological testing. 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 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, respectively). 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 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]. Since the amygdala and hippocampus are pre-defined 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 vmPFC, and there is no evidence to suggest a threshold for the effect of partial damage, so any damage to 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 analysis of variance (for data reported as a mean with standard deviation) or a chi-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 and Supplementary Table 2) were conducted using Chi-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 groups, Chi-square was used; if not, Fisher's exact test is 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”) analyses of variance. The between-group comparisons of non-PTSD anxiety disorder prevalence were conducted using Chi square frequency analysis or Fisher's exact test depending on sample sizes.

Supplementary Material

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Supp

Click here to view. (69K, doc)

ACKNOWLEDGEMENTS

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Footnotes

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Supplementary information is available on the Nature Neuroscience website

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