Evidence for Acquired Pregenual Anterior Cingulate Gray Matter Loss from a Twin Study of Combat-Related Posttraumatic Stress Disorder

Kiyoto Kasai, Hidenori Yamase, Mark W. Gilbertson, Martha E. Shenton, Scott L. Rauch, and Roger K. Pitman

Background: Controversy exists over the nature and origin of reduced regional brain volumes in posttraumatic stress disorder (PTSD). At issue is whether these reductions represent preexisting vulnerability factors for developing PTSD upon traumatic exposure or acquired PTSD signs due to the traumatic stress that caused the PTSD or the chronic stress of having the disorder (or both). We employed a case–control design in monozygotic twin pairs discordant for combat exposure to address the preexisting versus acquired origin of brain morphometric abnormalities in PTSD.

Methods: We used voxel-based morphometry to search for gray matter density reductions in magnetic resonance imaging (MRI) data obtained in a previous study of combat-exposed Vietnam veteran twins with \( n = 18 \) versus without \( n = 23 \) PTSD and their “high-risk” versus “low-risk” (respectively) identical combat-unexposed cotwins.

Results: Compared with the combat-exposed twins without PTSD, the combat-exposed twins with PTSD showed significant gray matter density reductions in four predicted brain regions: right hippocampus, pregenual anterior cingulate cortex (ACC), and left and right insulae. There was a significant PTSD Diagnosis \( \times \) Combat Exposure interaction in pregenual ACC in which combat-exposed PTSD twins had lower gray matter density than their own combat-unexposed cotwins as well as than the combat-exposed twins without PTSD and their cotwins.

Conclusions: The results point to gray matter volume diminutions in limbic and paralimbic structures in PTSD. The pattern of results obtained for pregenual ACC suggests that gray matter reduction in this region represents an acquired sign of PTSD consistent with stress-induced loss.

Key Words: Anterior cingulate gyrus, brain, magnetic resonance imaging, monozygotic twins, posttraumatic stress disorder

Several structural magnetic resonance imaging (MRI) studies employing anatomic segmentation have found lower gray matter volumes in the hippocampus in posttraumatic stress disorder (PTSD) stemming from various traumatic events (1). One segmentation study found diminished gray matter volumes in pregenual anterior cingulate cortex (ACC) and subcallosal cortex but not dorsal ACC (2), whereas another did find dorsal ACC reduction (3). Decreased pregenual ACC activation in response to trauma-related stimuli is a prominent functional neuroimaging finding in PTSD (4–5).

The technique of voxel-based morphometry (VBM) allows an automated examination of structural brain differences using statistical parametric mapping (SPM) techniques. The validity of the VBM technique for assessing regional gray matter density compared with conventional region of interest measurements has been confirmed in several previous studies (6–9). Employing VBM, the first authors found reduced dorsal ACC gray matter density in victims of an urban terrorist attack with PTSD (10). Another recent study that employed VBM found gray matter density reduction in pregenual ACC but not dorsal ACC, although manual segmentation did not confirm volumetric reduction in the former structure (11). That study also found gray matter density reduction in left insula. Yet another recent PTSD VBM study found gray matter density reductions in hippocampus, pregenual ACC, and insula (12).

Controversy exists over the nature and origin of reduced regional brain volume in PTSD. Thus far the debate has focused on the hippocampus (13). At issue is whether reduced volume represents an acquired PTSD sign, for example, is due to the traumatic stress that caused the PTSD or the chronic stress of having PTSD (or both) or is a preexisting vulnerability factor for developing PTSD upon traumatic exposure. We have been employing a case–control design in monozygotic twin pairs discordant for combat exposure in Vietnam to address the preexisting versus acquired origin of biological abnormalities found in PTSD (14). In a structural MRI study that manually traced the outlines of the right and left hippocampus, we found that lower total hippocampal volume constituted a “familial” vulnerability factor for PTSD because it was found in both the combat-exposed twins with PTSD and their “high-risk” combat-unexposed cotwins whose hippocampal volumes were lower than those of the combat-exposed twins without PTSD and their “low-risk,” combat-unexposed cotwins (15). (Note that the term “familial” includes both heredity and shared environment, i.e., environmental experiences that both members of a twin pair have had in common.)

In this study, we applied a VBM analysis to MRI data from the same twin sample to conduct a search throughout the entire brain for regional gray matter structural differences. On the basis of the published structural imaging studies just reviewed, we
predicted lower gray matter density in combat-exposed twins with PTSD compared with combat-exposed twins without PTSD in the following regions: hippocampus, dorsal ACC, pregenual ACC, subcallosal cortex, and insula. In an attempt to clarify the origin of any such differences, we used the data from the combat-unexposed cotwins. Gray matter diminution that confers familial vulnerability to PTSD would be expected in the high-risk, compared with the low-risk, combat-unexposed twins. In contrast, diminution that reflects acquired damage in PTSD would be expected to manifest in a Diagnosis × Combat Exposure interaction in which the combat-exposed twins with PTSD had lower gray matter density than their own high-risk, combat-unexposed cotwins as well as the combat-exposed twins without PTSD and their low-risk cotwins.

Methods and Materials

Subjects

The strategy for subject ascertainment and recruitment has been presented elsewhere (16). The sample was described in detail in the report of our previous hippocampus manual tracing study (15). This study reanalyzed the same MRI scans from the same subjects. In the previous study, one combat-exposed twin with PTSD and his combat-unexposed cotwin were removed from the analysis because the former was an extreme, asymmetrical outlier for manually traced hippocampal volume. This subject and his cotwin were included in the current study. (Exclusion of this pair did not alter the conclusions.) The protocol was approved by the institutional review board of the Manchester, New Hampshire, VA Medical Center. All subjects had previously given written informed consent before participation after a complete description of the procedures.

MRI Data Preanalysis

The MRI acquisition techniques were described in the previous report (15). The methods used to analyze these data in the present study were similar to those reported elsewhere (10). Image analysis was performed using ANALYZE PC3.0 (Mayo Foundation, Rochester, Minnesota) and SPM 99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom) running in MATLAB 6.1 (Mathworks, Sherborn, Massachusetts). In ANALYZE, image data were resampled using an algorithm to make them isotropic, with the sides measuring 9375 mm, and then stored. Resampled images were first spatially normalized into the standard MNI152 template (17,18). Normalized images were then segmented into gray matter, white matter, cerebrospinal fluid, and skull and scalp compartments using an automated, operator-independent process (19). The segmentation step also incorporated an image density nonuniformity correction to address image density variations caused by various positions of cranial structures within the MRI head coil (20). The spatially normalized segments of the gray matter were smoothed with a 12-mm full-width at half-maximum isotropic Gaussian kernel to accommodate individual variability in sulcal and gyral anatomy. For medial temporal regions (e.g., hippocampus), a 4-mm smoothing kernel was used instead, as has been recommended (21). By smoothing the data, the partial volume effect was used to create a spectrum of gray matter densities. Gray matter density is equivalent to the weighted average of the gray matter voxels located in the volume defined by the smoothing kernel. Because previous studies have shown a fair correlation between regional gray matter density determined by VBM and structural volumes measured by conventional, manual tracing (7,9,22), the regional gray matter density can be considered to represent the local volume of gray matter.

Statistical Analyses

Demographic and psychometric data were analyzed by means of a mixed model that treated Diagnosis (in the combat-exposed twin) as a between-pairs fixed effect, Combat Exposure as a within-pairs fixed effect (repeated measure), and pairs as a random effect (16). This model analysis yields a t statistic. Gray matter density was estimated on a voxel-by-voxel basis using SPM 99 (23). Contrasts were made between the 18 combat-exposed twins with PTSD and the 23 combat-exposed twins without PTSD, and separately between their high- and low-risk cotwins, using independent t tests, adjusted for individual intracranial volume. Diagnosis × Exposure interactions were evaluated by means of a mixed, multigroup (Diagnosis), conditions (Combat Exposure), and covariates (intracranial volume) model in which one twin pair was treated as though one subject with two conditions. In this analysis, 82 covariates were entered corresponding to 82 images ([18 + 23] × 2). For each of the foregoing analyses, a statistical parametric map (SPM) of the t statistic (SPM(t)) was created, and the SPM(t) values were transformed to the normal distribution (SPM(z)). The statistical significance threshold was set at p < .05 corrected for multiple comparisons using the False Discovery Rate (FDR) (24).

The anatomic locations of peak coordinates were initially defined using the latest version of Talairach Daemon Client (25). These localizations were then confirmed by visually inspecting the coordinates overlaid on the mean structural image of the study sample. For peaks located within predicted brain regions, small volume correction was applied using the following a priori volume approximations from the literature: hippocampus 3.5 mL each side; insula 8 mL each side; dorsal ACC 10 mL bilaterally; pregenual ACC 5 mL bilaterally; and subcallosal cortex 5 mL bilaterally (total volume of predicted brain regions = 43 mL). For peaks located outside predicted regions, correction for whole brain was employed. Because the predictions were directional, namely, lower gray matter density in combat-exposed subjects and PTSD pairs, the tests were one-tailed, and only results in the predicted direction(s) are reported.

Results

Demographics and Psychometrics. Group mean age, Combat Severity Score (26), total Clinician-Administered PTSD Scale (CAPS) score (27), number of potentially traumatic lifetime noncombat events (16), total Michigan Alcoholism Screening Test (MAST) score (28), and Symptom Check List-90-Revised (SCL-90-R) Depression scale score (29) along with statistical analyses, are presented in Table 1. It may be seen that age was similar among subject groups. Combat-exposed twins with PTSD had more severe combat exposure than combat-exposed twins without PTSD. As expected by virtue of selection, the former had greater combat-related symptom severity on the CAPS. Twin pairs with PTSD (i.e., twin pairs in which the combat-exposed twin was diagnosed with current, combat-related PTSD) reported more potentially traumatic lifetime noncombat events than non-PTSD pairs (i.e., twin pairs in which the combat-exposed twin was diagnosed with neither current nor past combat-related PTSD). Combat-exposed twins also reported more potentially traumatic lifetime noncombat events than their combat-unexposed cotwins. Combat-exposed twins with PTSD had more severe alcoholism histories than the other three groups. Combat-exposed twins with PTSD also reported more depression than
Table 1. Group Means (SD) of Combat-Exposed Vietnam Veterans with and without Posttraumatic Stress Disorder (PTSD) and Their Combat-Unexposed, Identical Cotwins

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>PTSD Pairs*</th>
<th>Non-PTSD Pairs*</th>
<th>Mixed Model</th>
<th>Independent t Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Unexposed</td>
<td>Exposure</td>
<td>Unexposed</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>(n = 18)</td>
<td>(n = 18)</td>
<td>(n = 23)</td>
<td>(n = 23)</td>
<td>t</td>
</tr>
<tr>
<td>52.8 (3.4)</td>
<td>52.8 (3.4)</td>
<td>51.8 (2.3)</td>
<td>51.8 (2.3)</td>
<td>—</td>
</tr>
<tr>
<td>73.3 (16.9)</td>
<td>—</td>
<td>6.2 (7.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7.7 (2.1)</td>
<td>—</td>
<td>3.5 (2.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8.1 (2.6)</td>
<td>5.2 (3.7)</td>
<td>5.1 (4.0)</td>
<td>4.2 (3.0)</td>
<td>2.6</td>
</tr>
<tr>
<td>19.1 (17.6)</td>
<td>6.4 (10.2)</td>
<td>2.4 (4.5)</td>
<td>2.5 (4.0)</td>
<td>4.5</td>
</tr>
<tr>
<td>2.5 (9)</td>
<td>3.5 (5)</td>
<td>6.7 (7)</td>
<td>4.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*As determined by the presence of current combat-related PTSD in the combat-exposed twin.
*As determined by the absence of current or past combat-related PTSD in the combat-exposed twin.

The other three groups. The Pearson Correlation Coefficient between total CAPS score and SCL-90-R Depression was large (r = .86) in the PTSD pairs but negligible (r = -.06) in the non-PTSD pairs.

Gray Matter Density

Table 2 presents the results of the contrasts between combat-exposed twins with versus without PTSD. For the sake of a complete exposition of these data, all results statistically significant at the liberal threshold of uncorrected p < .001 with spatial extent of k > 10 voxels are shown. Of the seven peaks that met this threshold, four were located in predicted brain regions, namely, right hippocampus, pregenual ACC, right midinsula, and left anterior insula (shown in Figure 1). Each of these four peaks also met the statistical significance threshold of p < .05 with small volume correction for the a priori size of the structure (as shown in the second column of Table 3). No voxels in nonpredicted brain regions met the threshold of p < .05 corrected for whole brain in these, or any other, analyses.

At the right hippocampus, pregenual ACC, left anterior insula, and right midinsula loci shown in Table 2, within the 18 PTSD combat veterans, we examined the correlations between gray matter density and total CAPS score, as well as SCL-90-R Depression score. Because these analyses involved single voxels, the significance threshold was p < .05 uncorrected. None of these correlations were significant. We also performed the same correlations for CAPS A (reexperiencing), B (avoidance/numbing), and C (hyperarousal) symptom cluster subscores; for these analyses we applied a Bonferroni correction to the significance threshold, namely, p < .017 (.05/3). The only significant correlations were between symptom cluster B (reexperiencing) and gray matter density in pregenual ACC (r = -.57, p = .008), left anterior insula (r = -.53, p = .0130), and right midinsula (r = -.59, p = .006).

The contrasts between the high-risk, combat-unexposed cotwins of the combat-exposed twins with PTSD versus the low-risk, combat-unexposed cotwins of the combat-exposed twins without PTSD did not identify any voxels that met the statistical significance threshold of p < .05, even with small volume corrections. The only statistically significant Diagnosis × Exposure interaction was found in pregenual ACC ([8 50 12], k = 3.32, k = 16, p = .02 corrected for the a priori size of this structure). The location of this cluster is shown in Figure 2. Scatterplots of individual subjects’ values at the [8 50 12] pregenual ACC locus are shown in Figure 3. There were no significant correlations between gray matter density in the 18 PTSD combat veterans minus gray matter density in their combat-unexposed cotwins, and total CAPS score, SCL-90-R Depression, or (with Bonferroni corrections) any of the CAPS symptom cluster subscores.

The mixed model and t test analyses that yielded the statistically significant results described earlier were repeated entering the following possibly confounding variables into the respective models as covariates: age, combat severity (in the exposed twin), number of potentially traumatic lifetime noncombat events, MAST score, and SCL-90-R Depression score. To control for a possibly confounding role of childhood physical or sexual abuse, the data were re-analyzed deleting pairs within which either member had such a history. All these results are shown in Table 3.

Discussion

Of the seven loci at which combat-exposed twins with PTSD had lower gray matter density than combat-exposed twins without PTSD at a liberal threshold of p < .001, four were located in predicted brain regions, namely, right hippocampus, pre-
genual ACC, and left anterior and right midinsula, even though the predicted brain regions occupy less than 10% of total gray matter volume. This regional specificity supports the validity of our results and implicates limbic and paralimbic structures as the major sites of gray matter density reductions in combat-related PTSD. Gray matter reductions in pregenual ACC and both insulae significantly correlated only with the cluster B “reexperiencing” symptoms of PTSD.

The ACC, especially its pregenual (or “affective”) division, and insula are components of the anterior “paralimbic belt,” are strongly interconnected to each other and to the amygdala, and are highly involved in emotional aspects of brain function (30–32). Impaired pregenual ACC function is one of the most robust neuroimaging findings in PTSD (4–5). A neurocircuitry model of PTSD posits that the ventromedial prefrontal cortex, including pregenual ACC, inhibits the expression of classically conditioned fear responses by the amygdala (33). Thus impairment in this brain region might be expected to most affect the DSM-IV symptoms that are putatively most closely related to conditioned fear, namely, the cluster B symptoms (especially B.4 and B.5, that is, intense psychological distress (and/or) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event). To the extent that diminished structure implies diminished function, reduced pregenual ACC gray matter density is consistent with this neurocircuitry model.

Table 3. Results Adjusted for Potentially Confounding Variables

<table>
<thead>
<tr>
<th>Unadjusted Age</th>
<th>Combat Severitya</th>
<th>Traumatic Eventsb</th>
<th>MAST Scorec</th>
<th>Childhood Abusebd</th>
<th>SCL-90-R Depressionse</th>
<th>Brain Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combat-Exposed Twins: PTSD vs. non-PTSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.50 (.001)</td>
<td>4.43 (.001)</td>
<td>3.23 (.05)</td>
<td>3.98 (.005)</td>
<td>3.39 (.02)</td>
<td>3.19 (.04)</td>
<td>2.07 (.49)</td>
</tr>
<tr>
<td>4.39 (.001)</td>
<td>4.36 (.001)</td>
<td>3.05 (.11)</td>
<td>4.11 (.004)</td>
<td>4.63 (&lt; .001)</td>
<td>3.56 (.04)</td>
<td>1.52 (.99)</td>
</tr>
<tr>
<td>3.95 (.005)</td>
<td>3.98 (.005)</td>
<td>3.32 (.03)</td>
<td>3.06 (.07)</td>
<td>3.26 (.04)</td>
<td>3.63 (.01)</td>
<td>2.15 (.44)</td>
</tr>
<tr>
<td>3.71 (.004)</td>
<td>3.59 (.009)</td>
<td>2.50 (.18)</td>
<td>2.79 (.08)</td>
<td>2.40 (.14)</td>
<td>2.92 (.03)</td>
<td>.93 (.99)</td>
</tr>
</tbody>
</table>

Diagnosis × Combat Exposure Interaction
| 3.32 (.02) | 3.39 (.02) | 3.32 (.02f) | 2.76 (.10) | 2.77 (.10) | 3.42 (.01) | 1.81 (.53) | Pregenual anterior cingulate cortex [8 50 12] |

*p SVC, significance level with small volume correction; PTSD, posttraumatic stress disorder.
a18-item measure (range 0–18).
bNumber of potentially traumatic lifetime noncombat events.
cMichigan Alcoholism Screening Test (range 0–25).
dDeleting six PTSD pairs and five non-PTSD pairs within which either twin had a history of childhood abuse.
eDepression subscale of Symptom Check List 90—Revised.
fCovariate is value in combat-exposed twin.
Functional neuroimaging studies of the hippocampus in PTSD are less common, but they, too, support impairment in this brain region (34–36). Hippocampal impairment may contribute to PTSD by reducing the ability to construct declarative narratives that bind the affect associated with the traumatic event (37), by the ability to recognize safe contexts (33), or by other unknown mechanisms. The reduced gray matter density found in bilateral insulae is paradoxical in light of studies that have generally found hyperactivity in this brain region in PTSD (38) and other anxiety conditions (39). One model of anterior insula function posits that this structure detects the difference between an observed and expected body state and generates an interoceptive prediction signal that triggers anxiety (39). A structurally compromised insula may be less inhibited in generating such signals in PTSD, but this is in the realm of speculation.

The most interesting result from our study is the significant Diagnosis × Exposure interaction in the pregenual ACC, with combat-exposed PTSD twins having lower gray matter density than their own combat-unexposed cotwins and than the combat-exposed twins without PTSD and their cotwins, supporting the inference that pregenual ACC gray matter reduction is an acquired sign of PTSD. In animals, exposure to chronic stress has been shown to damage not only the hippocampus in rodents (40) and primates (41) but also the ACC in rodents (42,43) and primates (44). It has been hypothesized that such damage may provide a basis for structural changes observed in PTSD (42,45). A recent study of mentally healthy persons that used automated segmentation found that those who reported early life stressors had smaller ACCs than those who did not (46). However, causal inferences are difficult to draw from the cross-sectional study of nontwins.

When the Diagnosis × Exposure interaction at [8 50 12] was adjusted for MAST score, its statistical significance level was reduced to corrected \( p = .10 \), which falls short of statistical significance. We did not obtain data regarding recent alcohol consumption. This is a limitation considering that imaging findings related to alcohol may be more sensitive to recent as opposed to more remote intake. On the other hand, the likelihood that increased alcohol use by the PTSD subjects accounts for the gray matter density reduction in their ACCs is diminished by the consideration that if the PTSD subjects studied here had consumed enough alcohol to damage their brains, evidence for this should have been found in other brain regions known to be affected by alcohol, including superior, motor, and other areas of the frontal cortex and cerebellum (47,48), none of which (except for a small cluster in left inferior frontal cortex) showed volumetric reduction in the PTSD compared with the non-PTSD combat veterans at even the liberal threshold of uncorrected \( p < .001 \). Thus the specificity of volumetric diminution to our predicted brain regions argues against a global effect such as alcohol-induced brain damage. Finally, a recent manual tracing study found comparably (and significantly) reduced ACC volume in subgroups of PTSD veterans with and without a history of lifetime alcohol abuse or dependence, in comparison to non-PTSD veterans (49).

When the Diagnosis × Exposure interaction in pregenual ACC was adjusted for number of potentially traumatic lifetime noncombat events, its statistical significance level was also reduced to corrected \( p = .10 \). This means we cannot be fully confident that stressful events other than military combat do not account for the reduced ACC gray matter density in the PTSD veterans. However, even if such events did contribute, this would still not be inconsistent with stress-induced diminution of this structure. When the Diagnosis × Exposure interaction in pregenual ACC was adjusted for depression, it was no longer significant. This is not surprising given the high association between depression and PTSD in our sample, in which self-reported depression appears to have been acquired along with
Diagnosis would support a pretrauma vulnerability factor) or a significant reduction in the combat-exposed twins with PTSD, because they failed to yield either a significant difference between high- and low-risk combat-unexposed cotwins (which would support a pretrauma vulnerability factor) or a significant Diagnosis × Exposure interaction (which would support an acquired abnormality). Finally, these results were unable to replicate previously reported segmentation and voxel-based morphometric findings of gray matter reduction in subcallosal cortex and dorsal ACC.

In the same twin sample studied here, we previously found manual tracing evidence that diminished hippocampal volume represents a pretrauma vulnerability factor for PTSD, rather than an acquired PTSD sign (15). In contrast, our VBM results suggest that diminished volume in pregenual ACC is acquired as a result of the combat exposure that led to PTSD, the PTSD itself, or both. We have no ready explanation as to why diminutions in these two structures should have different origins. As noted earlier, however, the origin of gray matter density reduction in the pregenual ACC site other than the one that showed the significant interaction could not be explained by our data; it is possible that it represents a PTSD vulnerability factor. Additional techniques that may help to clarify this uncertainty in future studies include cortical parcellation (segmentation) and magnetic resonance spectroscopy.

It has been suggested that VBM may not detect very small, localized gray matter volume reductions because false-negative VBM findings may arise from the changes in the shape or displacement of structures in the course of spatial normalization (7). Additionally, VBM may be biased against finding group differences in areas that are spatially complex (50). Inversely, we cannot rule out the possibility that the abnormalities detected by VBM in our study reflected group differences in the shape of brain structures rather than their volume (11), although even shape differences may have functional consequences. The failure of VBM to find a significant hippocampal gray matter reduction in the high- versus low-risk, combat-unexposed cotwins contrasts with our positive result in the same sample using manual segmentation of hippocampus (15) suggests that the latter technique may be more sensitive to reduced volume in this structure than the voxel-based approach. Similarly, we are unable to rule out the possibility that subtle group differences in other brain regions in this study remained below the sensitivity of VBM or the detection power conferred by our sample.

KK and HY contributed equally to this work.

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