

# Smaller Global and Regional Cortical Volume in Combat-Related Posttraumatic Stress Disorder

Steven H. Woodward, PhD; Marie Schaer, MD; Danny G. Kaloupek, PhD; Lucia Cediell, BA; Stephan Eliez, MD

**Context:** Two sets of findings predict smaller cerebral cortical gray matter volume in adult posttraumatic stress disorder (PTSD). Measures of intracranial tissue volume and cerebral tissue volume have been observed to be smaller in adolescents with maltreatment-related PTSD. Second, lower intelligence, a risk factor for PTSD, is associated with smaller cerebral tissue volumes. Nevertheless, to our knowledge, only 1 study has observed globally smaller cerebral tissue volume in adults with PTSD.

**Objectives:** To apply a recently developed method providing improved estimates of cortical volume and to estimate associations between adult PTSD and selected regional cortical volumes not yet investigated.

**Design:** Between-group comparison of global and regional cerebral cortical volumes in adult patients with combat-related PTSD and controls.

**Setting:** Two Department of Veterans Affairs medical centers with large inpatient and outpatient PTSD catchments.

**Participants:** Ninety-seven combat-exposed veterans of the Vietnam and Persian Gulf wars.

**Main Outcome Measure:** Global and regional cortical volumes determined using the FreeSurfer software program and the Desikan et al parcellation (modified).

**Results:** Cerebral cortical volume, thickness, and area were observed to be smaller in association with adult combat-related PTSD. Robust associations were observed between PTSD and smaller cortical volumes in the parahippocampal gyrus, superior temporal cortex, lateral orbital frontal cortex, and pars orbitalis of the inferior frontal gyrus.

**Conclusions:** Cerebral cortical volume, thickness, and area may be smaller in adult chronic severe PTSD; however, the extracted structural variables did not mediate relations between intelligence and PTSD. The 4 regions exhibiting especially smaller cortical volumes in this sample share involvement in mechanisms subserving “top-down” facilitation of the identification of objects and words. Compromise of these regions may result in difficulty in relearning pretrauma schemata for interpreting the civilian physical and social environments.

*Arch Gen Psychiatry.* 2009;66(12):1373-1382

## Author Affiliations:

Dissemination and Training Division, National Center for PTSD, VA Palo Alto Health Care System, Palo Alto, California (Dr Woodward); Department of Psychiatry, University of Geneva, Geneva (Drs Schaer and Eliez and Ms Cediell), and Signal Processing Laboratory, Swiss Federal Institute of Technology, Lausanne (Dr Schaer); and Behavioral Science Division, National Center for PTSD, VA Boston Healthcare System (Dr Kaloupek), and Division of Psychiatry, Boston University School of Medicine (Dr Kaloupek), Boston, Massachusetts.

**A**DULT POSTTRAUMATIC stress disorder (PTSD) has been associated with smaller hippocampal and anterior cingulate cortical (ACC) volumes,<sup>1-11</sup> but to our knowledge, only 1 study has found smaller total brain volume.<sup>12</sup> In contrast, 3 studies in children and adolescents with PTSD have found smaller intracranial (gray + white + cerebrospinal fluid) volume<sup>13,14</sup> or smaller cerebral tissue (gray + white) volume.<sup>15,16</sup> No explanation has been advanced for this discontinuity between children and adults. Analogous relationships between cerebral volumes and developmental adversity appear common to children and adults. In maltreated children, De Bellis et al<sup>13,14</sup> twice found a direct linear relationship between intracranial volume and age at abuse on-

set. In adults with PTSD, Woodward et al<sup>17</sup> found a similar relationship between a bone-based measure of cranial volume and age at first trauma, while Fennema-Notestine et al<sup>18</sup> found an inverse relationship between intracranial volume and scores on the Childhood Trauma Questionnaire. However, neither of these studies found a main effect of PTSD on a measure of intracranial or cerebral tissue volume. The absence of such an effect in adult PTSD is also surprising in light of associations between PTSD and IQ<sup>19-24</sup> and between IQ and cerebral tissue volume.<sup>25-29</sup>

There are challenges associated with comparing cerebral tissue volumes over groups. While studies of hippocampal volume routinely adjust for variation in body size by using a cerebral macrovolume as a covariate, this is not possible when that

**Table 1. Sample Characteristics: Means and Standard Deviations of Continuous Variables<sup>a</sup>**

	Mean (SD)				Effect Sizes (Partial $\eta^2$ ) Where $\alpha < .05$			
	PTSD		No PTSD		PTSD	ETOH	Cohort	Interactions
	ETOH (n = 24)	No ETOH (n = 26)	ETOH (n = 19)	No ETOH (n = 28)				
Age, y	50.3 (2.6)	48.3 (9.0)	47.1 (11.1)	45.9 (9.5)	0.063	0.862	PTSD $\times$ cohort: 0.046; PTSD $\times$ ETOH $\times$ cohort: 0.103 PTSD $\times$ ETOH: 0.050	
WAIS vocabulary subscale score	42.2 (11.2)	50.9 (11.4)	55.0 (7.2)	53.5 (8.1)	0.133			
WAIS digit symbol substitution subscale score	57.5 (13.8)	56.9 (16.1)	74.2 (11.2)	75.9 (14.8)	0.321	0.132		
Combat Exposure Scale score	27.0 (12.0)	27.4 (10.9)	18.1 (8.6)	16.2 (11.9)	0.156	0.321		
CAPS-TS	78.3 (14.9)	73.0 (21.5)	19.2 (9.5)	8.4 (10.5)	0.814			
BDI score	24.9 (7.7)	22.5 (9.0)	5.3 (3.5)	3.8 (3.9)	0.639			
Height, in	70.3 (2.3)	69.8 (3.1)	70.1 (3.0)	69.7 (3.3)		0.059		

Abbreviations: BDI, Beck Depression Inventory; CAPS-TS, Clinician-Administered PTSD Scale total severity score; ETOH, lifetime (but not current) alcohol abuse/dependence; PTSD, posttraumatic stress disorder; WAIS, Wechsler Adult Intelligence Scale.

<sup>a</sup>Subject characteristic by PTSD  $\times$  ETOH subgroup. Right-hand columns tabulate effect sizes (partial  $\eta^2$ ) for effects of PTSD, ETOH, and cohort and any interactions of these groupings in cases of nonchance effects (at  $P < .05$ ).

macrovolume is, itself, the focus of inquiry. Second, numerous studies have reported that diagnoses frequently comorbid with PTSD, such as alcoholism, are themselves associated with smaller cerebral tissue volumes.<sup>30-32</sup> Controlling such effects requires enlarged samples. A further obstacle to settling this issue may be inherent in the phenomenon itself. Bossini et al<sup>33</sup> found, in a relatively large sample of adult civilian trauma survivors meeting criteria for PTSD and free of comorbid psychopathology, that while whole-brain gray matter volume was smaller in PTSD, whole-brain white matter volume was larger. If this is the case, studies of unsegmented cortical tissue volumes in adult PTSD may be expected to produce ambiguous results.

Taking advantage of recent advances in the structural analysis of magnetic resonance images, this study revisited the status of cerebral cortical tissue volume in the same sample of 99 Vietnam and Gulf war veterans our group reported on previously.<sup>6,10,17</sup> These methodological advances enabled fully automated extraction of the 2-dimensional cortical sheet and estimation of its thickness, area, and volume.<sup>34-36</sup> A key innovation of this approach is its use of a priori knowledge of the geometry of the gray matter-white matter boundary, which is approximately planar over short distances. The validity of thickness estimates has been supported by comparisons with postmortem tissue.<sup>37</sup> The thickness estimates have also replicated well-known global and local effects of normal aging on the cerebral cortex.<sup>38</sup> Importantly, this method is relatively robust to variation in magnetic resonance manufacturer and software revision,<sup>39,40</sup> an attractive feature in a study such as this that aggregates samples across sites.

In this study, we relied on the method of Dale et al<sup>35</sup> and Fischl et al<sup>36</sup> embodied in the FreeSurfer software package (version 4.0.1; Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston). A second component of the approach of Dale et al<sup>35</sup> and Fischl et al<sup>36</sup> incorporated in FreeSurfer is the use of multiresolution deformations to construct “inflated” or spherical transformations of the cortex that expose sulci. After re-projection, cross-subject registration can proceed by ref-

erence to cortical landmarks, such as fully exposed sulci,<sup>41,42</sup> enabling the construction of more precise group average cortices than are obtainable with 3-dimensional methods.<sup>41</sup> The precision of this coregistration is also carried over into any atlas-based parcellation. The analysis of cortical structure by parcels established a priori is attractive because it enables conventional methods of type I error control.<sup>43,44</sup> This study used the “gyrographic” parcellation of Desikan et al.<sup>45</sup> Parcelwise analyses were followed by an exploratory whole-brain vertex-wise analysis of cortical thickness to mitigate the limited ability of parcelwise analysis to detect group differences not spatially correspondent to predefined regions. Lastly, using FreeSurfer-derived parameters, we tested the proposition that cortical structure mediates relations between 2 Wechsler Adult Intelligence Scale (WAIS)<sup>46</sup> subtest scores and PTSD severity.

## METHOD

### SUBJECTS

The sample for this study included 97 of 99 participants reported on in 3 previous articles describing regional brain volumes in adult combat-related PTSD.<sup>6,10,17</sup> Two participants were excluded because the cortical modeling algorithm failed to converge owing to artifact. Fifty participants with PTSD (37 Vietnam and 13 Gulf war veterans) met criteria for current PTSD as a result of experiencing 1 or more military traumas. Forty-seven subjects without PTSD (24 Vietnam and 23 Gulf war veterans) were free of diagnosable PTSD, current or lifetime. The PTSD diagnoses and severities were based on the Clinician-Administered PTSD Scale<sup>47</sup> and remaining diagnoses, on the Structured Clinical Interview for DSM-IV.<sup>48</sup> Approximately one-half of participants were classified as having lifetime (but not current) alcohol abuse/dependence. Also administered were the Combat Exposure Scale,<sup>49</sup> the Beck Depression Inventory,<sup>50</sup> and the vocabulary and digit symbol substitution subtests of the WAIS (**Table 1**).

Psychotropic medications were not discontinued. Seventy percent of the participants with PTSD were taking some form of psychotropic medication vs 10.6% of participants without

PTSD. Fifty-six percent of participants with PTSD were taking selective serotonin reuptake inhibitors vs 4 percent of participants without PTSD. Twenty-four percent of participants with PTSD were taking anticonvulsant/mood-stabilizing medications, while no participants without PTSD were taking a medication of this class.

Participants provided written informed consent in accordance with procedures of the institutional review boards of Stanford University Medical School/VA Palo Alto Health Care System or Boston VA Medical Center and the McLean Hospital.

## IMAGE ACQUISITION AND PROCESSING

Magnetic resonance images of subjects' brains were acquired with 1 of two 1.5-T GE Signa systems (GE Healthcare, Milwaukee, Wisconsin) located at the Diagnostic Radiology Center of VA Palo Alto Health Care System or the Brain Imaging Center of McLean Hospital (Belmont, Massachusetts). Coronal images were acquired with a 3-dimensional spoiled gradient recalled volumetric pulse sequence with the following parameters: repetition time=35 milliseconds, echo time=6 milliseconds, flip angle=45°, number of excitations=1, matrix size=256 × 192, field of view=24 cm<sup>2</sup>, slice thickness=1.5 to 1.7 mm, and slices=124.

Only brief summaries of the methods incorporated in FreeSurfer follow. Detailed descriptions may be found in the developers' original articles.<sup>35,36,51</sup> Image preprocessing included resampling into cubic voxels, correction of inhomogeneity artifact, and skull stripping. Constrained region growing was used to create a unitary white matter volume for each hemisphere. The surfaces of the white matter volumes were overlain with tessellations constructed by assigning 2 triangles to the square face of each surface voxel, yielding approximately 160 000 vertices per hemisphere. FreeSurfer optimized this tessellation by minimizing an energy function of intensity and both normal and tangential smoothness.<sup>35,36</sup> The pial surfaces of each hemisphere were computed by deforming the white matter surfaces toward the gray matter–cerebrospinal fluid boundary. Cortical thickness was computed as the distance between the inner and the outer cortical surfaces at each vertex.<sup>51</sup>

In FreeSurfer, cross-subject registration of hemispheric cortical surfaces was performed by projecting them onto spherical representations that minimized an energy function of concavity and cartographic distortion. This step is anchored to large-scale features of the cortex such as the central sulcus and sylvian fissure,<sup>36,41</sup> which are also used to anchor the alignment of individual subjects' hemispheric surface models with an iteratively calculated study-specific average cortex.<sup>41</sup> Following alignment, participants' cortical thickness values were resampled into a common spherical coordinate system and smoothed using a gaussian kernel with full-width at half maximum of 10 mm.

The Desikan et al<sup>45</sup> parcellation used to delineate cortical regions was based on a diverse training sample of 40 brains. These brains were first parcellated manually by a neuroanatomist using FreeSurfer-derived cortical surface representations with final sulcal delineations performed on "inflated" projections allowing full visualization of sulci. The probability of a cortical location falling into a specific cortical region was modeled by an anisotropic, nonstationary Markov random field incorporating global and local structural information and inter-regional constraints. A computational procedure determining the parcellation pattern with the highest probability given all priors ran iteratively until a stable pattern emerged. Additional details regarding the mathematic underpinnings and extensibility of this approach can be found in Fischl et al.<sup>44</sup>

These automated procedures required approximately 24 hours of computation per brain on a 2 × 3-GHz quad-core Mac-

intosh workstation. After processing, both lateral and medial surfaces of each parcellated cortical hemisphere were manually reviewed for gross artifacts. None were found.

To provide a brain tissue–based index that could be used to adjust for nuisance variance in body size, we imported estimates of cerebral white matter volume obtained from the same magnetic resonance image set using BrainImage and the protocols of the Stanford Psychiatric Neuroimaging Program (BrainImage 5.x; A. L. Reiss, Stanford University, Stanford, California). These estimates were independently derived and based on a nonoverlapping set of manual and automated procedures.<sup>6,52</sup>

## STATISTICAL PROCEDURES

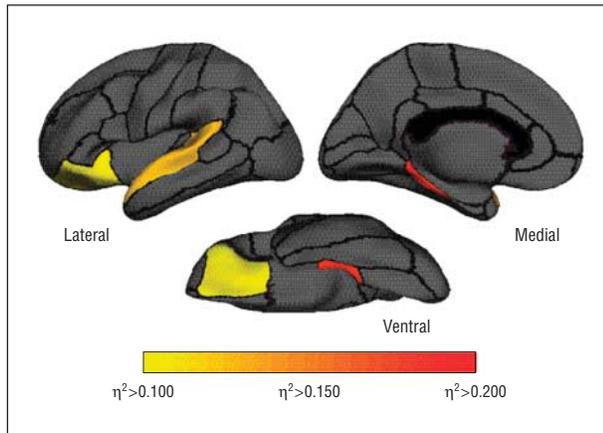
To provide robust protection against type I error, the parcellated data were reduced in dimensionality to satisfy to the assumption of multivariate analysis of variance that the number of within-subjects factors be fewer than the number of cases in the smallest cell.<sup>53</sup> Three strategies were used. Whereas prior analyses of these data used cohort (Vietnam vs Gulf war) as a factor, in this study we covaried for age. Second, homologous parcel volumes were summed across hemispheres. Third, 15 parcels were collated into a single superparcel. In the Desikan nomenclature, the constituents of this superparcel were as follows: lateral occipital cortex, inferior parietal cortex, superior parietal cortex, inferior temporal gyrus, middle temporal gyrus, banks of the superior temporal sulcus, supramarginal gyrus, postcentral gyrus, precentral gyrus, fusiform gyrus, lingual gyrus, pericalcarine cortex, cuneus cortex, precuneus cortex, and paracentral lobule. In addition, the transverse temporal cortex was merged with the surrounding superior temporal gyrus. This approach retains detailed parcellation of all cortex anterior to the motor strip and most limbic cortical regions, domains that have received the lion's share of empirical support for structural and functional cerebrocortical compromise in PTSD. In the context of a significant multivariate effect, between-subjects effects of PTSD at individual parcels were required to meet a Bonferroni-adjusted criterion of  $\alpha < .0028$  (0.05/18).<sup>53</sup> Additional planned comparisons were performed on parcels corresponding to regions that have demonstrated structural and/or functional compromise in PTSD, the ACC,<sup>7,10,54-59</sup> and the superior temporal gyrus.<sup>60</sup> (The Desikan parcellation does not include the insular cortex or separately quantify the subgenual ACC.) Tests of adjustment for stature and cerebral white matter volume were accomplished with analysis of covariance and multivariate analysis of covariance. Neither stature (with PTSD, 172.5 cm; without PTSD, 173.25 cm) nor cerebral white matter volume (with PTSD, 512 mm<sup>3</sup>; without PTSD, 518 mm<sup>3</sup>) exhibited a significant effect of PTSD diagnosis ( $F$ 's < 1).<sup>61</sup>

## RESULTS

Neither cortical volume, thickness, nor area exhibited an effect of study site (all  $F$ 's < 1).

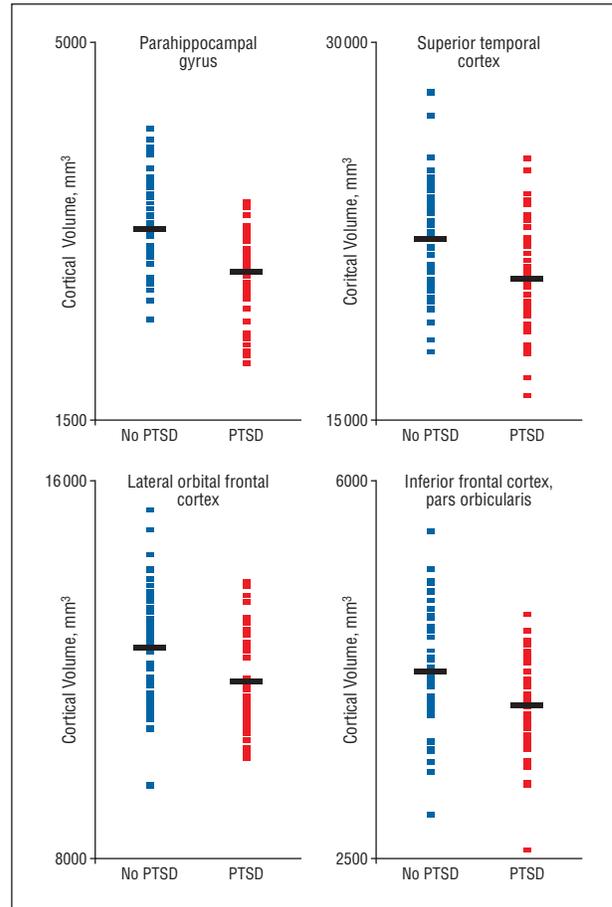
### CORTICAL VOLUME

Our analyses first considered parcellated cortical volume, which combines both thickness and area information, because volumetric indexes have been the subject of most prior research in this area. Total cortical volume summed over all parcels and analyzed with univariate analysis of variance covarying for age exhibited a significant main effect of PTSD ( $F_{1,92} = 10.66$ ;  $P < .01$ ; partial



**Figure 1.** Effect sizes of posttraumatic stress disorder (PTSD) diagnosis at parcels where statistically significant parcellated. Left lateral, medial, and inferior views of average parcellations of subjects with PTSD and subjects without PTSD with color encoding PTSD diagnosis effect sizes ( $\eta^2$ ) on cortical volume in those regions for which the probability of type I error was  $\alpha < .0028$ . The presentation of the right hemisphere is arbitrary because statistics were limited to cortical volumes summed over both hemispheres (see text). Only 3 colored regions are obvious because the latter 2 are adjacent to one another and produced nearly equivalent effect sizes.

$\eta^2=0.104$ ), being smaller in subjects with PTSD (350 744 vs 368 896  $\text{mm}^3$ ). Cortical volume also tended to be smaller in subjects with lifetime alcohol abuse/dependence ( $F_{1,92}=3.59$ ;  $P=.06$ ) but exhibited no PTSD  $\times$  lifetime alcohol abuse/dependence interaction ( $F < 1$ ). The PTSD contrast was sharpened by adjustment for stature and cerebral white matter volume ( $F_{1,90}=14.40$ ;  $P < .001$ ; partial  $\eta^2=0.138$ ), while effects of lifetime alcohol abuse/dependence ( $F_{1,90}=3.04$ ;  $P=.09$ ) and the PTSD  $\times$  lifetime alcohol abuse/dependence interaction ( $F < 1$ ) remained insignificant. Parcellated cortical volume exhibited a significant multivariate effect of PTSD (Wilks  $\lambda=0.61$ ;  $F_{18,75}=2.69$ ;  $P=.002$ ; partial  $\eta^2=0.39$ ). There were no multivariate effects of lifetime alcohol abuse/dependence (Wilks  $\lambda=0.83$ ;  $F_{18,75}=0.86$ ;  $P=.63$ ) or the PTSD  $\times$  lifetime alcohol abuse/dependence interaction (Wilks  $\lambda=0.85$ ;  $F_{18,75}=0.75$ ;  $P=.75$ ). The multivariate effect of PTSD (Wilks  $\lambda=0.58$ ;  $F_{18,73}=2.95$ ;  $P < .001$ ; partial  $\eta^2=0.42$ ), lifetime alcohol abuse/dependence (Wilks  $\lambda=0.81$ ;  $F_{18,73}=0.96$ ;  $P=.25$ ), and their interaction (Wilks  $\lambda=0.85$ ;  $F_{18,73}=0.73$ ;  $P=.33$ ) was not substantially modified by adjustment for stature and cerebral white matter volume. Parcels meeting the Bonferroni-corrected significance criterion were, in order of effect size, the parahippocampal gyrus ( $P < .001$ ; partial  $\eta^2=0.181$ ; approximating Brodmann area 36), superior temporal cortex ( $P=.001$ ; partial  $\eta^2=0.121$ ; encompassing Brodmann areas 22, 41, and 42), lateral division of the orbital frontal cortex, ( $P=.002$ ; partial  $\eta^2=0.103$ ; lateral aspect of Brodmann area 11), and pars orbitalis of the inferior frontal gyrus ( $P=.002$ ; partial  $\eta^2=0.101$ ; approximating Brodmann area 47). All effects were in the direction of smaller cortical volumes in subjects with PTSD (**Figure 1** and **Figure 2**) and (**Table 2**). The associations of PTSD with smaller volumes at the parahippocampal gyrus ( $P < .001$ ; partial  $\eta^2=0.192$ ), superior temporal cortex ( $P < .001$ ; partial  $\eta^2=0.148$ ), lateral division of the orbital frontal cortex ( $P=.001$ ; partial  $\eta^2=0.112$ ), and pars orbitalis of the



**Figure 2.** Scatterplots depicting the between-group and within-group distributions underlying findings of regionally smaller cortical volume at the parahippocampal gyrus, superior temporal cortex, lateral division of the orbital frontal cortex, and pars orbitalis of the inferior frontal gyrus. Least-squares means are indicated by vertical bars. PTSD indicates posttraumatic stress disorder.

inferior frontal gyrus ( $P=.002$ ; partial  $\eta^2=0.098$ ) all remained significant after adjustment for stature and cerebral white matter volume.

Planned comparisons at parcels corresponding to the rostral and caudal ACC (generally corresponding to pregenual and dorsal subregions of ACC, respectively) both found significant but relatively modest effects of PTSD (rostral division:  $F_{1,92}=4.83$ ;  $P=.03$ ; partial  $\eta^2=0.050$ ; caudal division:  $F_{1,92}=6.55$ ;  $P=.01$ ; partial  $\eta^2=0.066$ ). Findings at both the rostral and caudal ACC remained significant after adjustment for stature and cerebral white matter volume (rostral division:  $F_{1,90}=4.85$ ;  $P=.03$ ; partial  $\eta^2=0.051$ ; caudal division:  $F_{1,90}=6.26$ ;  $P=.01$ ; partial  $\eta^2=0.065$ ). A planned comparison of cortical volume at the superior temporal cortex was moot.

## CORTICAL THICKNESS

Weighted mean cortical thickness calculated over the whole brain was analyzed with univariate analysis of variance covarying for age and found to be significantly lower in subjects with PTSD than in subjects without PTSD (2.384 mm vs 2.428 mm, respectively;  $F_{1,92}=4.69$ ;  $P=.03$ ;  $\eta^2=0.049$ ). There were no effects of lifetime alcohol abuse/

**Table 2. Least Squares Mean Cortical Volumes by Parcel and Group<sup>a</sup>**

Parcel	Mean (SD), mm <sup>3</sup>		$\eta^2$
	No PTSD	PTSD	
Cingulate cortex, rostral anterior division	3480 (541)	3240 (532)	0.050
Cingulate cortex, caudal anterior division	2634 (514)	2961 (506)	0.066
Cingulate cortex, isthmus division	3715 (535)	3568 (526)	0.020
Cingulate cortex, posterior division	5497 (672)	5220 (660)	0.043
Entorhinal cortex	3156 (522)	3022 (513)	0.017
Frontal pole	1579 (242)	1451 (238)	0.069
Inferior frontal gyrus, pars opercularis	6435 (1046)	6293 (1028)	0.005
Inferior frontal gyrus, pars orbitalis	4229 (497)	3906 (489)	0.101 <sup>b</sup>
Inferior frontal gyrus, pars triangularis	6564 (944)	6329 (929)	0.016
Middle frontal gyrus, caudal division	9793 (1606)	9299 (1579)	0.024
Middle frontal gyrus, rostral division	25 603 (2886)	24 510 (2838)	0.037
Orbital frontal cortex, lateral division	12 504 (1126)	11 760 (1107)	0.103 <sup>b</sup>
Orbital frontal cortex, medial division	7782 (862)	7523 (847)	0.023
Parahippocampal gyrus	3317 (408)	2945 (401)	0.181 <sup>b</sup>
Superior frontal gyrus	35 764 (3415)	33 926 (3358)	0.071
Temporal pole	4390 (493)	4244 (484)	0.023
Superior temporal + transverse temporal cortex <sup>c</sup>	22 203 (2211)	20 599 (2174)	0.122 <sup>b</sup>
Occipital-parietal-temporal superparcel <sup>c,d</sup>	209 658 (16 821)	199 949 (16 541)	0.081

Abbreviation: PTSD, posttraumatic stress disorder.

<sup>a</sup>Least squares means of cortical volume by parcel in PTSD and no PTSD groups, controlling for lifetime (but not current) alcohol abuse/dependence and age. Nomenclature corresponds to Desikan et al.<sup>45</sup>

<sup>b</sup>Values of partial  $\eta^2$  associated with effects exceeding a chance probability of  $P < .003$ .

<sup>c</sup>Modified parcel.

<sup>d</sup>Occipital-parietal-temporal superparcel value is the sum of bilateral volumes of the lateral occipital cortex, inferior parietal cortex, superior parietal cortex, inferior temporal gyrus, middle temporal gyrus, banks of the superior temporal sulcus, supramarginal gyrus, postcentral gyrus, precentral gyrus, fusiform gyrus, lingual gyrus, pericalcarine cortex, cuneus cortex, precuneus cortex, and paracentral lobule.

dependence or the PTSD  $\times$  lifetime alcohol abuse/dependence interaction on cortical thickness ( $F$ 's  $< 1$ ). Analyses of cortical thickness by parcel found no multivariate effect of PTSD (Wilks  $\lambda = 0.71$ ;  $F_{18,75} = 1.66$ ;  $P = .07$ ; partial  $\eta^2 = 0.285$ ), lifetime alcohol abuse/dependence (Wilks  $\lambda = 0.835$ ;  $F_{18,75} = 0.82$ ;  $P = .67$ ), or their interaction (Wilks  $\lambda = 0.78$ ;  $F_{18,75} = 1.20$ ;  $P = .28$ ) (**Table 3**). Planned comparisons at the rostral and caudal divisions of the ACC found significant effects in the direction of thinner cortex in PTSD (rostral division:  $F_{1,92} = 7.72$ ;  $P = .007$ ; partial  $\eta^2 = 0.077$ ; caudal division:  $F_{1,92} = 4.97$ ;  $P = .03$ ; partial  $\eta^2 = 0.051$ ). Planned comparisons also found thinner cortex in participants with PTSD at the superior temporal cortex ( $F_{1,92} = 4.264$ ;  $P = .04$ ; partial  $\eta^2 = 0.044$ ). These results were unchanged by adjustment for stature and cerebral white matter volume.

### CORTICAL AREA

Adjusted for age, total cortical area tended to be smaller in PTSD ( $F_{1,92} = 3.79$ ;  $P = .06$ ) but exhibited no effect of lifetime alcohol abuse/dependence ( $F_{1,92} = 1.03$ ;  $P = .16$ ) and no PTSD  $\times$  lifetime alcohol abuse/dependence interaction ( $F < 1$ ). Adjustment for stature and cerebral white matter volume rendered the effect of PTSD significant ( $F_{1,90} = 7.29$ ;  $P = .34$ ; partial  $\eta^2 = 0.075$ ), but not effects of lifetime alcohol abuse/dependence or the PTSD  $\times$  lifetime alcohol abuse/dependence interaction (lifetime alcohol abuse/dependence:  $F_{1,90} = 1.72$ ;  $P = .34$ ; PTSD  $\times$  lifetime alcohol abuse/dependence:  $F < 1$ ). Cortical area exhibited no multivariate effects of PTSD (Wilks  $\lambda = 0.78$ ;  $F_{18,75} = 1.16$ ;  $P = .32$ ), lifetime alcohol abuse/dependence (Wilks  $\lambda = 0.78$ ;

$F_{18,75} = 1.15$ ;  $P = .32$ ), or the PTSD  $\times$  lifetime alcohol abuse/dependence interaction (Wilks  $\lambda = 0.78$ ;  $F_{18,75} = 1.9$ ;  $P = .29$ ), a result not modified by adjustment for body size. Among planned comparisons, only the superior temporal cortex exhibited an effect of PTSD ( $F_{1,92} = 6.14$ ;  $P = .02$ ; partial  $\eta^2 = 0.063$ ), being smaller in participants with PTSD, a result strengthened by adjustment for body size ( $F_{1,92} = 9.44$ ;  $P = .003$ ; partial  $\eta^2 = 0.095$ ).

### VERTEX-WISE ANALYSES OF CORTICAL THICKNESS

Though the analysis of a priori parcels permitted a conventional approach to type I error control, type II-like errors may have resulted when regional differences between groups did not correspond closely to parcels because of spatial restriction, spanning parcel boundaries, or both. **Figure 3** presents cortical thickness difference maps contrasting participants with and without PTSD (at  $P < .01$  uncorrected). Foci of cortical thinning were apparent within the boundaries of the parahippocampal and lateral orbital frontal parcels and dorsal anterior cingulate, bilaterally, within the superior temporal gyrus on the left and within the pars orbitalis of the inferior frontal gyrus on the right. These locations were generally correspondent with the parcelwise effects on volume and thickness. It is also apparent, however, that the superparcel spanned multiple regions of thinning in the parietal cortex on the right and in the lateral occipital/posterior temporal cortex bilaterally. As well, parcels containing foci of apparent thinning in the left lateral frontal cortex were summed with homologous parcels in the right hemisphere absent thinning.

**Table 3. Least Squares Mean Cortical Thicknesses by Parcel and Group<sup>a</sup>**

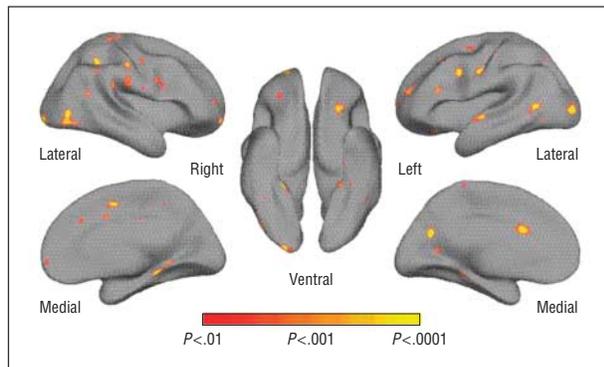
Parcel	Mean (SD), mm <sup>3</sup>		$\eta^2$
	No PTSD	PTSD	
Cingulate cortex, rostral anterior division	2.77 (0.16)	2.67 (0.16)	0.077
Cingulate cortex, caudal anterior division	2.50 (0.19)	2.42 (0.19)	0.051
Cingulate cortex, isthmus division	2.42 (0.18)	2.38 (0.18)	0.002
Cingulate cortex, posterior division	2.38 (0.13)	2.33 (0.13)	0.032
Entorhinal cortex	3.20 (0.26)	3.22 (0.25)	0.002
Frontal pole	2.72 (0.24)	2.67 (0.23)	0.009
Inferior frontal gyrus, pars opercularis	2.38 (0.13)	2.33 (0.12)	0.036
Inferior frontal gyrus, pars orbitalis	2.60 (0.17)	2.59 (0.17)	0.001
Inferior frontal gyrus, pars triangularis	2.30 (0.15)	2.28 (0.15)	0.004
Middle frontal gyrus, caudal division	2.29 (0.14)	2.24 (0.14)	0.008
Middle frontal gyrus, rostral division	2.26 (0.13)	2.20 (0.12)	0.036
Orbital frontal cortex, lateral division	2.52 (0.14)	2.47 (0.14)	0.044
Orbital frontal cortex, medial division	2.26 (0.17)	2.25 (0.17)	0.002
Parahippocampal gyrus	2.51 (0.25)	2.36 (0.24)	0.083
Superior frontal gyrus	2.54 (0.15)	2.50 (0.15)	0.016
Temporal pole	3.68 (0.24)	3.63 (0.24)	0.015
Superior temporal + transverse temporal cortex <sup>b</sup>	2.57 (0.13)	2.51 (0.13)	0.044
Occipital-parietal-temporal superparcel <sup>b,c</sup>	2.16 (0.09)	2.12 (0.09)	0.038

Abbreviation: PTSD, posttraumatic stress disorder.

<sup>a</sup>Least squares means of cortical thickness by parcel in PTSD and no PTSD groups, controlling for lifetime (but not current) alcohol abuse/dependence and age. Nomenclature corresponds to Desikan et al.<sup>45</sup>

<sup>b</sup>Modified parcel.

<sup>c</sup>Occipital-parietal-temporal superparcel value is the mean of thicknesses of the lateral occipital cortex, inferior parietal cortex, superior parietal cortex, inferior temporal gyrus, middle temporal gyrus, banks of the superior temporal sulcus, supramarginal gyrus, postcentral gyrus, precentral gyrus, fusiform gyrus, lingual gyrus, pericalcarine cortex, cuneus cortex, precuneus cortex, and paracentral lobule, bilaterally, weighted by bilateral parcel areas.



**Figure 3.** Cortical thickness: effect of posttraumatic stress disorder (PTSD). Statistical difference maps of PTSD contrast on cortical thickness at  $P < .01$  (uncorrected).

### MEDIATION ANALYSES

In light of data relating intelligence to both PTSD and brain volume, we examined whether parameters extracted with FreeSurfer were compatible with the possibility that cortical structure mediates relations between intelligence and PTSD severity. Linear regression was first used to establish the direct path between WAIS subtest scores and PTSD severity. Here, as in prior studies, estimators of intelligence accounted for additional variance in PTSD ( $F_{\text{change}2,92} = 17.42$ ;  $P < .001$ ) after entry of combat exposure. In the final model, all predictors were significant (Combat Exposure Scale score:  $\beta = 0.346$ ;  $t = 4.01$ ;  $P < .001$ ; WAIS vocabulary score:  $\beta = -0.311$ ;  $t = 3.75$ ;  $P < .001$ ; WAIS digit symbol substitution score:  $\beta = -0.279$ ;  $t = 3.07$ ;  $P = .003$ ;  $F_{\text{regression}4,91} = 18.03$ ;  $P < .001$ ; adjusted  $R^2 = 0.418$ ). Second, we

examined correlations between predictors and proposed mediators, finding that cortical volume correlated with both vocabulary ( $r = 0.220$ ;  $P = .03$ ) and digit symbol substitution ( $r = 0.351$ ;  $P < .001$ ) score. Next, we performed a Sobel test<sup>62</sup> of the reduction in predictive strength resulting from entry of cortical volume into the model separately for WAIS vocabulary and digit symbol substitution scores. In both cases, results of the test were negative (vocabulary score: Sobel test statistic = 1.72;  $P = .09$ ; digit symbol substitution score: Sobel test statistic = 1.67;  $P = .10$ ). Noting that the correlation between mean cortical thickness (weighted by parcel area) and total cortical area was mildly negative in this sample ( $r_{95} = -0.21$ ;  $P = .04$ ), we reconsidered these parameters separately. Examination of correlations between these predictors and proposed mediators disclosed that cortical thickness correlated with digit symbol substitution score ( $r = 0.276$ ;  $P = .006$ ), but not vocabulary score ( $r = -0.008$ ;  $P = .94$ ), while total area correlated with vocabulary score ( $r = 0.257$ ;  $P = .01$ ), but not digit symbol substitution score ( $r = 0.192$ ;  $P = .06$ ). Results were comparable with those obtained with volume (vocabulary score  $\rightarrow$  cortical area  $\rightarrow$  PTSD severity: Sobel test statistic = 0.204;  $P = .84$ ; digit symbol substitution score  $\rightarrow$  cortical thickness  $\rightarrow$  PTSD severity: Sobel test statistic = 1.73;  $P = .79$ ).

### COMMENT

This study of cerebral cortical structure in combat veterans using the method of Dale et al<sup>35</sup> and Fischl et al<sup>36</sup> embodied in FreeSurfer combined with the Desikan parcellation found evidence that cerebral cortical volume is smaller in adults with PTSD. The cerebral cortex of par-

ticipants with PTSD was also significantly thinner, the estimated difference of 0.041 mm being similar to that found in a comparison of subjects with animal phobia with controls.<sup>63</sup> Total cortical area was also smaller in the subjects with PTSD after adjustment for stature and cerebral white matter volume. These results are in general agreement with studies of adolescents with PTSD that have found smaller macrostructural brain volumes compared with matched controls.<sup>13-15</sup> Their divergence from our prior findings of a trend only in favor of smaller cerebral tissue volume in PTSD<sup>6,10</sup> is likely related to the current focus on cortical gray matter exclusively. A similar argument might apply to the absence of effects of comorbid alcoholism when PTSD and age were controlled. The finding of a smaller cortex is also broadly compatible with studies implicating lower intelligence as a risk factor for PTSD; however, the parameters and psychometrics assessed herein did not support the proposition that cortical structure mediates the relationship between intelligence and PTSD as part of a causative scenario.

This study found evidence that the association of PTSD with smaller cortical volume is not uniform across the brain. Especially strong effects of PTSD were observed at the parahippocampal gyrus, superior temporal cortex, pars orbitalis of the inferior frontal gyrus, and adjacent orbital frontal cortex. This pattern is an intriguing one. The parahippocampal gyrus is juxtaposed to the hippocampus, the region of the brain first identified as abnormal in adult PTSD.<sup>1</sup> In humans, functional imaging studies have linked the parahippocampal gyrus to the representation of space,<sup>64</sup> a role it may have taken over from the hippocampus, in which “place” cells were first identified in rodents.<sup>64</sup> Recent results suggest that in humans the hippocampus and parahippocampal gyrus collaborate in encoding the interrelations of salient objects within space<sup>65</sup> and in contextualization more generally.<sup>66,67</sup> Misperception of safe vs threatening contexts has been proposed to contribute to PTSD.<sup>68-71</sup> Relevant rodent models have also invoked the concept of context as represented in the hippocampus proper.<sup>72-74</sup>

These observations may be translatable into concrete predictions regarding the performance of persons with PTSD on a set of cognitive tasks not previously used in this area. In a rich series of studies, Bar and Aminoff<sup>75,76</sup> developed the proposition that the representation of context, that is, of regularities in object co-occurrence and location in the environment, contributes to facilitated visual object identification in a “top-down” fashion. Bar<sup>77</sup> also identified a second substrate for facilitated object identification in the ventrolateral and orbital frontal cortex, regions also observed herein to be smaller in subjects with PTSD. Bar et al<sup>78</sup> suggest this second substrate generates an “initial guess” as to object identity that is based on a low-spatial-frequency version of the stimulus transmitted rapidly to the ventrolateral orbitofrontal cortex over the dorsal visual pathway. These “guesses” are then projected back to the inferotemporal cortex where they converge with “bottom-up” information resulting in facilitated identification. These 2 mechanisms appear to cooperate,<sup>67,79</sup> and the parahippocampal gyrus and orbital frontal cortex are known to be heavily interconnected.<sup>80-83</sup> In summary, the current results are sugges-

tive of structural compromise in PTSD of multiple components—hippocampal, parahippocampal, and orbital frontal—of a distributed system subserving facilitated object identification. Behavioral tasks assessing facilitated object identification may therefore be sensitive to PTSD. The cognitive psychology literature contains a number of tasks, such as the primed object/nonobject discrimination of Gronau et al,<sup>79</sup> that may be used in testing this hypothesis.<sup>84-86</sup>

Superior temporal cortical volume was also found to be smaller in participants with PTSD in this study. Tests of associations between PTSD and cortical structure in this region were planned a priori because De Bellis et al<sup>60,87</sup> reported larger cortical volumes in this region in adolescents with maltreatment-related PTSD. These 2 results are not necessarily incompatible, as the cortex exhibits both linear and quadratic trends during maturation such that a specific region could be initially larger and ultimately smaller than normal in a group undergoing atypical development.<sup>88</sup> Moreover, the superior temporal parcel overlaps temporal cortical regions that have exhibited inverse correlations between IQ and cortical thickness during childhood.<sup>88</sup> It is especially relevant, here, that the superior temporal cortex has also been implicated in top-down facilitation of stimulus identification, in this case, of words. Lexical decision, the discrimination of words from nonwords, a verbal analog of the Gronau et al task, is facilitated on trials preceded by primes semantically related to the words. Both functional magnetic resonance imaging and electroencephalographic studies have implicated the superior temporal cortex, especially in the left hemisphere, in such effects.<sup>89,90</sup> The obverse of semantic priming, what might be termed *semantic interference*, has been repeatedly demonstrated in PTSD in studies using the emotional Stroop task.<sup>91</sup> These studies have found evidence that, in participants with PTSD, trauma-related semantic content interferes with the performance of a cover task. Vythilingam et al<sup>92</sup> recently extended this literature by demonstrating that exaggerated Stroop interference is accompanied, in PTSD, by facilitated lexical decisions when prime and test words share negative or trauma-relevant content. How might we rationalize the co-occurrence of facilitated semantic priming of trauma-related content in PTSD despite structural compromise of a brain region subserving this function? One possibility is that structural compromise results in reduced plasticity impeding the recovery of non-trauma-related semantic contextualizations. By analogy, structural/functional compromise of the hippocampus, parahippocampal gyrus, and ventrolateral orbital frontal cortex could impede the recovery of pretrauma function of top-down mechanisms facilitating object identification. One result would be the persistence of trauma-conditioned top-down influences on the identification of objects and words in non-trauma-related settings, a phenomenologically and clinically salient feature of PTSD.

A limitation of a priori parcellation is its insensitivity to regional findings not corresponding to parcel boundaries. Herein, an exploratory vertex-wise analysis disclosed “missed” foci of cortical thinning in the left frontal, right parietal, and bilateral occipital/posterior temporal cortex. These regions may deserve future consideration. A second limitation of a priori parcellation is that

different regions of the cortex are characterized by more or less consistent landmarks. The sulcal determinants of ACC are notably variable<sup>93,94</sup> and may represent a special challenge to automated parcellation. Our inspection of ACC parcels confirmed such variability, especially in anterior-posterior extents. The coefficients of variation of the areas of the right and left rostral ACC were the highest and third highest in their respective hemispheres. The absence of larger effects of PTSD at parcels corresponding to ACC should be considered in this light. Another important limitation of this study is the fact that the PTSD and non-PTSD groups differed in their rates of psychotropic medication use. Studies have not yet addressed the effects of the medications (principally selective serotonin reuptake inhibitors) administered to these participants with PTSD on cortical structure. In schizophrenia, results of 3 studies of the effects of antipsychotic use on cortical thickness have been negative<sup>95</sup>; however, some earlier studies quantifying volume have found reductions attributable to drug use.<sup>96</sup>

**Submitted for Publication:** March 17, 2008; final revision received May 29, 2008; accepted May 30, 2008.

**Correspondence:** Steven H. Woodward, PhD, Dissemination and Training Division, National Center for PTSD, Mail Code 334 PTSD, VA Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304 (steve.woodward@va.gov).

**Financial Disclosure:** None reported.

**Funding/Support:** Major funding for this work was provided under a Department of Veterans Affairs/Department of Defense assistance agreement to Drs Woodward and Kaloupek from the US Army Medical Research and Materiel Command (Department of Defense) administered through the Institute for Medical Research (Department of Veterans Affairs). Additional support was provided by Swiss National Research Funds grants 323500-111165 (Dr Schaer) and 3200-063135, 3232-063134, and PPO0B-102864 (Dr Eliez).

**Additional Contributions:** Stephen Grate and Lori Moll facilitated the necessary arrangements at the Department of Veterans Affairs/Department of Defense. Allan L. Reiss, MD, Perry K. Renshaw, MD, Wendy Stegman, BA, Lorraine Leskin, PhD, Kelly Teresi, MA, Catherine Kutter, PhD, Rebecca Prestel, BA, Rosemond Villafuerte, MA, Ann Smith, Eileen Connolly, and Michael A. Dove, MBA, provided institutional and technical support. We thank the Research Services of the VA Palo Alto and VA Boston health care systems for their support.

## REFERENCES

- Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry*. 1995;152(7):973-981.
- Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry*. 1996;40(11):1091-1099.
- Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med*. 1997;27(4):951-959.
- Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse— preliminary report. *Biol Psychiatry*. 1997;41(1):23-32.
- Bremner JD. Alterations in brain structure and function associated with posttraumatic stress disorder. *Semin Clin Neuropsychiatry*. 1999;4(4):249-255.
- Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ. Hippocampal volume, PTSD, and alcoholism in combat veterans. *Am J Psychiatry*. 2006;163(4):674-681.
- Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, McMullin K, Whalen PJ, Makris N. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport*. 2003;14(7):913-916.
- Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O, Kuroki N, Fukuda R, Tochigi M, Furukawa S, Sadamatsu M, Sasaki T, Aoki S, Ohtomo K, Asukai N, Kato N. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci U S A*. 2003;100(15):9039-9043.
- Kitayama N, Quinn S, Bremner JD. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord*. 2006;90(2-3):171-174.
- Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry*. 2006;59(7):582-587.
- Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev*. 2006;30(7):1004-1031.
- Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, Woodruff PW. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biol Psychiatry*. 2004;56(11):832-836.
- De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. A.E. Bennett Research Award: developmental traumatology, part II. brain development. *Biol Psychiatry*. 1999;45(10):1271-1284.
- De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry*. 2002;52(11):1066-1078.
- Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, Reiss AL. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry*. 2001;50(12):943-951.
- Tupler LA, De Bellis MD. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. *Biol Psychiatry*. 2006;59(6):523-529.
- Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ. Brain, skull, and cerebrospinal fluid volumes in adult posttraumatic stress disorder. *J Trauma Stress*. 2007;20(5):763-774.
- Fennema-Notestine C, Stein MB, Kennedy CM, Archibald SL, Jernigan TL. Brain morphology in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry*. 2002;52(11):1089-1101.
- Breslau N, Lucia VC, Alvarado GF. Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder: a follow-up study at age 17 years. *Arch Gen Psychiatry*. 2006;63(11):1238-1245.
- Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A. Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort. *Psychol Med*. 2007;37(2):181-192.
- Saltzman KM, Weems CF, Carrion VG. IQ and posttraumatic stress symptoms in children exposed to interpersonal violence. *Child Psychiatry Hum Dev*. 2006;36(3):261-272.
- Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: a review of the empirical literature. *Clin Psychol Rev*. 2000;20(8):1041-1065.
- Macklin ML, Metzger LJ, Litz BT, McNally RJ, Lasko NB, Orr SP, Pitman RK. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. *J Consult Clin Psychol*. 1998;66(2):323-326.
- McNally RJ, Shin LM. Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam Combat veterans. *Am J Psychiatry*. 1995;152(6):936-938.
- Andreassen NC, Flaum M, Swayze V II, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WT. Intelligence and brain structure in normal individuals. *Am J Psychiatry*. 1993;150(1):130-134.
- McDaniel MA. Big-brained people are smarter: a meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence*. 2005;33(4):337-346.

27. Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, Gurbani M, Toga AW, Bilder RM. Relationships between IQ and regional cortical gray matter thickness in healthy adults. *Cereb Cortex*. 2007;17(9):2163-2171.
28. Wilke M, Sohn JH, Byars AW, Holland SK. Bright spots: correlations of gray matter volume with IQ in a normal pediatric population. *Neuroimage*. 2003;20(1):202-215.
29. Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. Structural brain variation and general intelligence. *Neuroimage*. 2004;23(1):425-433.
30. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry*. 1998;55(10):905-912.
31. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol Clin Exp Res*. 1997;21(3):521-529.
32. Jernigan TL, Butters N, DiTraglia G, Schafer K, Smith T, Irwin M, Grant I, Schuckit M, Cermak LS. Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. *Alcohol Clin Exp Res*. 1991;15(3):418-427.
33. Bossini L, Tavanti M, Calossi S, Lombardelli A, Polizzotto NR, Galli R, Vatti G, Pieraccini F, Castrogiovanni P. Magnetic resonance imaging volumes of the hippocampus in drug-naive patients with post-traumatic stress disorder without comorbidity conditions. *J Psychiatr Res*. 2008;42(9):752-762.
34. Van Essen DC, Drury DR, Joshi S, Miller MI. Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. *Proc Natl Acad Sci U S A*. 1998;95(3):788-795.
35. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis, I: segmentation and surface reconstruction. *Neuroimage*. 1999;9(2):179-194.
36. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis, II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999;9(2):195-207.
37. Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology*. 2002;58(5):695-701.
38. Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. Thinning of the cerebral cortex in aging. *Cereb Cortex*. 2004;14(7):721-730.
39. Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R, Maguire P, Rosas D, Makris N, Dale A, Dickerson B, Fischl B. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage*. 2006;32(1):180-194.
40. Dickerson BC, Fenstermacher E, Salat DH, Wolk DA, Maguire RP, Desikan R, Pacheco J, Quinn BT, Van der Kouwe A, Greve DN, Blacker D, Albert MS, Killiany RJ, Fischl B. Detection of cortical thickness correlates of cognitive performance: reliability across MRI scan sessions, scanners, and field strengths. *Neuroimage*. 2008;39(1):10-18.
41. Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp*. 1999;8(4):272-284.
42. Desai R, Liebenthal E, Possing ET, Waldron E, Binder JR. Volumetric vs. surface-based alignment for localization of auditory cortex activation. *Neuroimage*. 2005;26(4):1019-1029.
43. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355.
44. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004;14(1):11-22.
45. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980.
46. Psychological Corporation. *Wechsler Adult Intelligence Scale, Third Revision*. San Antonio, TX: Harcourt Brace; 1997.
47. Blake D, Weathers F, Nagy L, Kaloupek D, Klauminzer G, Charney DS, Keane TM, Buckley TC. *Clinician-Administered PTSD Scale (CAPS) Instructional Manual*. Boston, MA: National Center for PTSD; 2000.
48. Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured Clinical Interview for DSM-IV*. New York: Biometrics Research Department, New York State Psychiatric Institute; 1996.
49. Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA. Clinical evaluation of a measure to assess combat exposure. *Psychol Assess*. 1989;1(1):53-55.
50. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.
51. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97(20):11050-11055.
52. Reiss AL, Hennessey JG, Rubin M, Beach L, Abrams MT, Warsofsky IS, Liu AM, Links JM. Reliability and validity of an algorithm for fuzzy tissue segmentation of MRI. *J Comput Assist Tomogr*. 1998;22(3):471-479.
53. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. New York, NY: Harper Collins; 1989.
54. Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, Macklin ML, Pitman RK. Visual imagery and perception in posttraumatic stress disorder: a positron emission tomographic investigation. *Arch Gen Psychiatry*. 1997;54(3):233-241.
55. 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(7):806-816.
56. Corbo V, Clement MH, Armony JL, Pruessner JC, Brunet A. Size versus shape differences: contrasting voxel-based and volumetric analyses of the anterior cingulate cortex in individuals with acute posttraumatic stress disorder. *Biol Psychiatry*. 2005;58(2):119-124.
57. De Bellis MD, Keshavan MS, Spencer S, Hall J. N-acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. *Am J Psychiatry*. 2000;157(7):1175-1177.
58. Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RW, Gati JS, Menon RS. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psychiatry*. 2002;52(4):305-311.
59. Bryant RA, Felmingham KL, Kemp AH, Barton M, Peduto AS, Rennie C, Gordon E, Williams LM. Neural networks of information processing in posttraumatic stress disorder: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2005;58(2):111-118.
60. De Bellis MD, Keshavan MS, Frustaci K, Shifflett H, Iyengar S, Beers SR, Hall J. Superior temporal gyrus volumes in maltreated children and adolescents with PTSD. *Biol Psychiatry*. 2002;51(7):544-552.
61. Cochran WG. Analysis of covariance: its nature and uses. *Biometrics*. 1957;13:261-281.
62. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt S, ed. *Sociological Methodology 1982*. Washington, DC: American Sociological Association; 1982:290-312.
63. Rauch SL, Wright CI, Martis B, Busa E, McMullin KG, Shin LM, Dale AM, Fischl B. A magnetic resonance imaging study of cortical thickness in animal phobia. *Biol Psychiatry*. 2004;55(9):946-952.
64. Aguirre GK, Detre JA, Alsup DC, D'Esposito M. The parahippocampus subserves topographical learning in man. *Cereb Cortex*. 1996;6(6):823-829.
65. Maguire EA, Frith CD, Burgess N, Donnett JG, O'Keefe J. Knowing where things are: parahippocampal involvement in encoding object locations in virtual large-scale space. *J Cogn Neurosci*. 1998;10(1):61-76.
66. Bar M, Aminoff E, Ishai A. Famous faces activate contextual associations in the parahippocampal cortex. *Cereb Cortex*. 2008;18(6):1233-1238.
67. Fenske MJ, Aminoff E, Gronau N, Bar M. Top-down facilitation of visual object recognition: object-based and context-based contributions. *Prog Brain Res*. 2006;155:3-21.
68. Gilbertson MW, Williston SK, Paulus LA, Lasko NB, Gurvits TV, Shenton ME, Pitman RK, Orr SP. Configural cue performance in identical twins discordant for posttraumatic stress disorder: theoretical implications for the role of hippocampal function. *Biol Psychiatry*. 2007;62(5):513-520.
69. Grillon C, Morgan CA III, Davis M, Southwick SM. Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biol Psychiatry*. 1998;44(10):1027-1036.
70. Grillon C, Morgan CA III. Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. *J Abnorm Psychol*. 1999;108(1):134-142.
71. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. *Behav Res Ther*. 2000;38(4):319-345.
72. Corcoran KA, Desmond TJ, Frey KA, Maren S. Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. *J Neurosci*. 2005;25(39):8978-8987.
73. Corcoran KA, Maren S. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. *J Neurosci*. 2001;21(5):1720-1726.
74. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci*. 1992;106(2):274-285.
75. Bar M, Aminoff E. Cortical analysis of visual context. *Neuron*. 2003;38(2):347-358.
76. Bar M. Visual objects in context. *Nat Rev Neurosci*. 2004;5(8):617-629.
77. Bar M. A cortical mechanism for triggering top-down facilitation in visual object recognition. *J Cogn Neurosci*. 2003;15(4):600-609.

78. Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmid AM, Schmidt AM, Dale AM, Hämäläinen MS, Marinkovic K, Schacter DL, Rosen BR, Halgren E. Top-down facilitation of visual recognition [published correction appears in *Proc Natl Acad Sci U S A*. 2006;103(8):3007]. *Proc Natl Acad Sci U S A*. 2006;103(2):449-454.
79. Gronau N, Neta M, Bar M. Integrated contextual representation for objects' identities and their locations. *J Cogn Neurosci*. 2008;20(3):371-388.
80. Blatt GJ, Pandya DN, Rosene DL. Parcellation of cortical afferents to three distinct sectors in the parahippocampal gyrus of the rhesus monkey: an anatomical and neurophysiological study. *J Comp Neurol*. 2003;466(2):161-179.
81. Powell HW, Guye M, Parker GJ, Symms MR, Boulby P, Koepp MJ, Barker GJ, Duncan JS. Noninvasive in vivo demonstration of the connections of the human parahippocampal gyrus. *Neuroimage*. 2004;22(2):740-747.
82. Cavada C, Compañy T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suárez F. The anatomical connections of the macaque monkey orbitofrontal cortex: a review. *Cereb Cortex*. 2000;10(3):220-242.
83. Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Eur J Neurosci*. 2002;16(2):291-310.
84. Chun MM, Jiang Y. Contextual cueing: implicit learning and memory of visual context guides spatial attention. *Cogn Psychol*. 1998;36(1):28-71.
85. Ganis G, Kutas M. An electrophysiological study of scene effects on object identification. *Brain Res Cogn Brain Res*. 2003;16(2):123-144.
86. Brockmole JR, Castelhana MS, Henderson JM. Contextual cueing in naturalistic scenes: global and local contexts. *J Exp Psychol Learn Mem Cogn*. 2006;32(4):699-706.
87. De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Dahl RE, Axelson DA, Birmaher B, Hall J, Moritz G, Ryan ND. Superior temporal gyrus volumes in pediatric generalized anxiety disorder. *Biol Psychiatry*. 2002;51(7):553-562.
88. Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, Evans A, Rapoport J, Giedd J. Intellectual ability and cortical development in children and adolescents. *Nature*. 2006;440(7084):676-679.
89. Van Petten C, Luka BJ. Neural localization of semantic context effects in electromagnetic and hemodynamic studies. *Brain Lang*. 2006;97(3):279-293.
90. Matsumoto A, Iidaka T, Haneda K, Okada T, Sadato N. Linking semantic priming effect in functional MRI and event-related potentials. *Neuroimage*. 2005;24(3):624-634.
91. McNally RJ. Experimental approaches to cognitive abnormality in posttraumatic stress disorder. *Clin Psychol Rev*. 1998;18(8):971-982.
92. Vythilingam M, Blair KS, McCaffrey D, Scaramozza M, Jones M, Nakic M, Mondillo K, Hadd K, Bonne O, Mitchell DG, Pine DS, Charney DS, Blair RJ. Biased emotional attention in post-traumatic stress disorder: a help as well as a hindrance? *Psychol Med*. 2007;37(10):1445-1455.
93. Huster RJ, Westerhausen R, Kreuder F, Schweiger E, Wittling W. Morphologic asymmetry of the human anterior cingulate cortex. *Neuroimage*. 2007;34(3):888-895.
94. Fornito A, Whittle S, Wood SJ, Velakoulis D, Pantelis C, Yucel M. The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. *Neuroimage*. 2006;33(3):843-854.
95. Nesvåg R, Lawyer G, Varnas K, Fjell AM, Walhovd KB, Frigessi A, Jönsson EG, Agartz I. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. *Schizophr Res*. 2008;98(1-3):16-28.
96. Scherk H, Falkai P. Effects of antipsychotics on brain structure. *Curr Opin Psychiatry*. 2006;19(2):145-150.

### Correction

**Error in Table.** In the Original Article by Dick et al titled "Role of *GABRA2* in Trajectories of Externalizing Behavior Across Development and Evidence of Moderation by Parental Monitoring," published in the June 2009 issue of the *Archives* (2009;66[6]:649-657), Table 1 contained an error in the fourth column. The numeral 1 was added after the decimal point to each value in the column in error. The corrected Table 1 is published below.

**Table 1. Markers Genotyped in *GABRA2***

Marker <sup>a</sup>	Position <sup>b</sup>	Alleles, Minor/Major <sup>c</sup>	MAF <sup>d</sup>
rs497068	45945434	C/T	0.423
rs548583	45958101	T/C	0.419
rs279871	46000490	G/A	0.430
rs279858	46009350	G/A	0.429
rs279845	46024480	A/T	0.453
rs1440130	46028010	C/T	0.451
rs279826	46028966	G/A	0.454
rs279827	46029459	G/A	0.453
rs279828	46029567	C/A	0.453
rs279836	46033827	A/T	0.441

Abbreviations: MAF, minor allele frequency; SNP single-nucleotide polymorphism.

<sup>a</sup>Markers are shown as rs numbers from the SNP database (dbSNP).

<sup>b</sup>Position is in nucleotides from chromosome 4pter, as shown in dbSNP (build 129) or by blasting against the National Center for Biotechnology Information Human Genome assembly (build 36.3).

<sup>c</sup>Markers rs497068, rs548583, rs279871, and rs279858 were genotyped on the minus strand of chromosome 4; all other SNPs were typed on the plus strand.

<sup>d</sup>Minor allele frequency in the present sample.