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Brain Morphometry in Female Victims of Intimate Partner Violence with and without Posttraumatic Stress Disorder

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Background: *To examine neuroanatomical morphometry in adult female victims of intimate partner violence with and without posttraumatic stress disorder.*

Methods: *Seventeen nonvictimized comparison subjects and 22 victims of intimate partner violence, 11 with and 11 without posttraumatic stress disorder, were studied. Using quantitative magnetic resonance imaging, three mesial temporal lobe areas were measured: hippocampus, amygdala, and parahippocampal gyrus. Additionally, whole brain morphometry provided fluid, gray, and white matter volumes of the cortex and cerebellum for exploratory analyses. Relationships of morphometric measures to symptoms, abuse history, and neuropsychological function were examined.*

Results: *Intimate partner violence subjects with posttraumatic stress disorder did not demonstrate significantly smaller hippocampal or other mesial temporal lobe volumes. Overall, intimate partner violence subjects had smaller supratentorial cranial vaults and smaller frontal and occipital gray matter volumes relative to nonvictimized comparison subjects. Supratentorial cranial vault volume was negatively correlated with severity of childhood physical abuse, but not with intimate partner violence or posttraumatic stress disorder severity. Trails B performance was negatively correlated with frontal gray matter volume.*

Conclusions: *These findings are inconsistent with prior reports of smaller hippocampal volumes in patients with posttraumatic stress disorder. Rather, the findings point to cerebral abnormalities that may reflect the influence of early trauma on neurodevelopmental processes or denote brain morphometric characteristics of persons at increased risk for serious psychosocial adversity. Biol Psychiatry 2002;51:1089–1101 © 2002 Society of Biological Psychiatry*

Introduction

The study of neuroanatomical correlates of posttraumatic stress disorder (PTSD) has primarily focused on mesial temporal regions, largely the hippocampus, due to the known effects of long term stress on memory performance (Bremner et al 1995b; Bremner et al 1993; Pitman 1989; Sutker et al 1991; Uddo et al 1993; Villarreal and King 2001; Yehuda et al 1995) and the association of high levels of glucocorticoids and neuron loss in the hippocampus (McEwen and Magarinos 1997; Sapolsky et al 1990; Uno et al 1989). Several studies have found smaller volumes of the left or right hippocampus in male combat veterans with PTSD (Bremner et al 1995a; Gurvits et al 1996), adult survivors of childhood abuse with PTSD (Bremner et al 1997), and adult women with a history of severe sexual abuse (Stein et al 1997). These studies suggest that structural alterations in the hippocampal region may be a neuroanatomical correlate of PTSD. Other cognitive deficits associated with PTSD, such as impaired executive function and attention (Beckham et al 1998; Jenkins et al 2000; Sutker et al 1995), would suggest that additional brain regions also might be affected. Previous work reports that there is no significant volume difference in the caudate nucleus or the whole temporal lobe in PTSD subjects (Bremner et al 1995a; Bremner et al 1997; Gurvits et al 1996); however, one study found marginally smaller amygdalar volumes and larger left temporal lobe volumes in PTSD (Bremner et al 1997).

More recently, several reports have called into question the specificity of such hippocampal findings to PTSD. Bonne et al (2001) performed a longitudinal assessment of hippocampal volume in trauma survivors with and without PTSD. Magnetic resonance imaging (MRI) data were acquired at 1 week and 6 months after the traumatic event. Results suggest that there was no significant difference in

hippocampal volume for those subjects meeting criteria for PTSD at 6 months relative to those who did not. Furthermore, a recent study of individuals with borderline personality disorder (BPD), some of whom had PTSD, revealed significantly smaller hippocampal and amygdalar volumes in all BPD subjects (Driessen et al 2000); however, no difference was found between subjects with and without a PTSD diagnosis. Furthermore, no significant relationship was revealed between hippocampal volume and any measure of traumatic experience within the BPD group. Thus, PTSD alone did not account for smaller hippocampal volume in this study.

In addition, a recent study by De Bellis et al (1999) that focused on PTSD in children and adolescents with a history of childhood abuse assessed a more global set of volumetric measures. Estimates were obtained of volumes of total intracranial vault, ventricles, cerebrum, hippocampus, amygdala, basal ganglia, corpus callosum, and cortical regions in the frontal and temporal lobe. Interestingly, the 44 subjects with childhood abuse histories and PTSD had significantly smaller intracranial volumes, slightly larger ventricular volumes, and smaller cerebral volumes. There were no significant findings in any other regions, including the hippocampus. More recently, these researches found increased superior temporal gyrus volumes in maltreated youth with PTSD compared to non-maltreated youth (De Bellis et al 2002). The findings suggest possible influences of maltreatment on the development of the central nervous system (CNS). Although these findings are of great interest, the implications and interpretations of these findings with respect to PTSD are constrained by the lack of a comparison group of abused children that do not demonstrate PTSD symptomatology.

In an effort to assess the effects of PTSD on the whole brain, volumes of brain regions were examined in adult women with a recent history of intimate partner violence (IPV) and a comparison group of women without serious trauma histories. Half of the IPV women had a current diagnosis of PTSD, and half had never developed PTSD. The primary hypothesis to be examined was whether hippocampal volume was smaller in the IPV group with PTSD relative to NC and IPV groups without PTSD. Secondary analyses were planned to probe the integrity of neighboring mesial temporal gray matter regions, including the parahippocampal gyrus and a measure including the amygdala. Finally, whole brain morphometry was completed to provide measures of the supra and infratentorial cranial vaults, cortical lobar regions, subcortical regions, and cerebellar measurements, in addition to the MTL regions, for exploratory regional analyses. Strengths of the current study include morphometry completed on the entire brain for cerebrospinal fluid (CSF), gray, and white matter structures, as well as the inclusion of an additional comparison group with a history of IPV who did not meet diagnostic criteria for PTSD. Subjects also received assessments of abuse histories and neuropsychological performance, the results of which are included in the companion to this paper (Stein et al 2002).

Methods and Materials

SUBJECTS. Subjects were recruited through the use of advertisements from community services in San Diego specializing in domestic violence (e.g., the YWCA, Center for Community Solutions, Women's Resource Center). Seventeen nonvictimized healthy female adult volunteers (NC) and 22 female victims of intimate partner violence (IPV) were studied. All participants were part of a larger study examining the psychological and neurobiological effects of trauma in women. Subjects were chosen for MRI assessment on the basis of willingness to participate in and eligibility (see below) for this component of the study. Of the 22 IPV subjects, 11 had a current diagnosis of posttraumatic stress disorder (PTST+) and 11 did not meet the criteria for PTSD at any time during their life (PTSD-); the classification of PTSD was based on current DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID) complemented by the Clinician-Administered PTSD Scale (CAPS). This study was approved by the University of California San Diego School of Medicine Human Subjects Committee. All participants gave informed, written consent to participate.

All subjects were screened for any significant medical, psychiatric, intellectual, or neurologic disorders. Subjects were excluded if they had a history of 2 years or greater of drug or alcohol abuse or any current drug use (as assessed by the Addiction Severity Index), serious head injury (resulting in hospitalization), or diagnosed attention deficit disorder or learning disability during childhood. No subject had used psychotropic medication in the 3 months before study.

MEASURES. The Impact of Event Scale-Revised (IES-R) (Weiss and Marmar 1997), a 22-item self-report measure, was administered to examine severity of PTSD symptoms over the past week. Subjects were instructed to respond to each item, based on a 5-point Likert scale ranging from 0 = not at all, to 4 = extremely, regarding their experience with IPV. Severity of intimate partner violence was measured using the revised version of the Conflict Tactics Scale (CTS2) (Straus et al 1996), a 39-item self-report measure with 5 subscales (Negotiation, Psychological Aggression, Physical Assault, Sexual Coercion, and Injury) assessing various aspects of the domestic abuse experience. Level of depression was assessed in all subjects, using the Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff 1977), a 20-item self-report measure examining depressive symptoms within the past week. Level of anxiety was assessed using the Beck Anxiety Inventory (Beck et al 1988).

Subjects also completed the Childhood Trauma Questionnaire (CTQ), a standardized, retrospective measure of childhood trauma (Bernstein et al 1997; Bernstein et al 1994). In addition, subjects participated in neuropsychological testing (Stein et al 2002). We examined the relationship of morphometric variables

Table 1. Subject Demographic, Psychiatric, Posttraumatic Stress Disorder (PTSD), and Alcohol Information by Group and PTSD Status

	NC	IPV	MWU	PTSD+ IPV	PTSD− IPV	MWU
N	17	22	p	11	11	p
Age (years)	35.3 (12.5)	34.4 (9.8)	NS	33.5 (10.3)	35.4 (9.6)	NS
	range 19–57	range 19–49		range 19–49	range 22–48	
Education (years)	14.9 (2.1)	12.5 (2.2)	p < .001	12.4 (1.7)	12.6 (2.7)	NS
	range 12–18	range 8–18		range 9–16	range 8–18	
Estimated verbal IQ	114.2 (11.0)	101.5 (10.3)	p < .005	101.9 (13.0)	101.0 (7.0)	NS
	range 94–131	range 88–125		range 88–125	range 99–111	
	N = 14	N = 15		N = 8	N = 7	
Height (inches)	65.4 (3.1)	64.6 (2.5)	NS	65.7 (1.6)	63.9 (2.8)	NS
	range 60–69	range 60–68		range 63.5–68	range 60–68	
	N = 14	N = 13		N = 5	N = 8	
Handedness	14 right	17 right	—	9 right	8 right	—
	2 left	2 left		0 left	2 left	
	1 amb.	3 amb.		2 amb.	1 amb.	
Anxiety (BAI)	1.5 (2.6)	15.3 (14.5)	p < .001	24.6 (15.0)	5.9 (5.0)	p < .001
	range 0–7	range 0–53		range 2–53	range 0–13	
Depression (CES-D)	3.1 (2.9)	21.1 (13.9)	p < .001	28.7 (13.7)	13.5 (9.7)	p < .05
	range 0–8	range 0–47		range 0–47	range 1–26	
PTSD symptoms (IES-R)	N/A	28.8 (21.2)	—	40.9 (21.3)	16.6 (13.1)	p < .01
		range 0–72		range 6–72	range 0–35	
PTSD symptoms (CAPS)	N/A	43.6 (28.5)	—	58.0 (28.7)	26.0 (16.2)[a]	p < .05
		range 0–101		range 11–101	range 0–49	
Alcohol history (# of drinks in past year)	27.6 (37.2)	18.2 (32.2)	NS	28.2 (41.7)	8.3 (14.7)	NS
	range 0–120	range 0–144		range 0–144	range 0–48	

Data shown are mean (SD). Statistical significance levels from nonparametric Mann-Whitney U Tests (MWU) are presented. BAI, Beck Anxiety Inventory; CAPS, Clinician-Administered PTSD Scale; CES-D, Center for the Epidemiologic Studies Depression Scale; IES-R, Impact of Event Scale Revised; IPV, intimate partner violence victims; NC, nonvictimized comparison subjects.
[a] N = 9.

to a subset of neuropsychological functional domains that appeared different in IPV and comparison subjects, based on findings in Stein et al (2002). These included executive function (Trails B) and auditory working memory (Paced Auditory Serial Addition Task [PASAT]). Higher scores for Trails B (time taken to perform the task) reflect poorer performance. In contrast, higher scores for the PASAT (total correct) reflect better performance.

The subject characteristics for demographic, psychiatric, and abuse variables are presented in Tables 1 and 2. Groups did not differ significantly on age, handedness, height or alcohol history. However, NC subjects had significantly higher levels of education relative to the IPV group as a whole (Table 1) and compared with both subgroups (PTST+ IPV, p < .005; PTSD- IPV, p < .05). In a subset of subjects that had estimated verbal IQ (EVIQ) scores, the NC group also had higher EVIQ relative to the IPV group (Table 1) and relative to each IPV subgroup (PTST+ IPV, p < .05; PTSD- IPV, p < .01). The PTST+ and PTSD- IPV subjects did not differ significantly on education or EVIQ. Regarding psychiatric symptom characterization, the IPV group had significantly more evidence of anxiety and depression than the NC group, and the PTST+ IPV group more than the PTSD-IPV group (Table 1).

Because our methodology typically corrects for differences in head size by proportionalizing volumetric data to supratentorial cranial vault (STCN), height information was not originally collected; however, due to the unexpected findings of smaller STCN volumes in the IPV group (see below), participants were recontacted to attain their heights, and this information is provided in each table. Unfortunately, not all participants could be contacted to provide full datasets on height. In the available subjects, no significant differences were found between any groups on this variable (Table 1).

All scales reflecting severity of domestic violence (CTS) were significantly greater in the IPV group relative to NC subjects, except for the negotiation subscale (higher scores on this subscale reflect healthier or more mature intimate partner relationships); none of these variables was significantly different between the PTST+ and PTSD- IPV groups (Table 2). Furthermore, the IPV group had significantly greater reports of childhood trauma (CTQ) on all measures relative to NC subjects; the PTST+ and PTSD- IPV groups differed only on the measure of sexual abuse, with PTST+ subjects reporting significantly higher scores (Table 2).

Due to the higher levels of education and EVIQ in the NC group relative to the IPV group, additional analyses were performed on a subsample of participants better matched on these variables. Twelve pairs of subjects were selected, one participant from each group, that were more closely matched on age and education, reducing the sample size for each group. The paired subjects were on average within 2 years on both age and level of education. Mean age and education level for the NC subjects was 33.8 (SD = 10.3) and 14.2 (SD = 1.8), respectively, and for the IPV subjects 34.7 (SD = 10.6) and 13.8 (SD

Table 2. Severity of Domestic Violence and Childhood Abuse by Group and Posttraumatic Stress Disorder (PTSD) Status

| | Severity of Domestic Violence: Conflict Tactics Scale (CTS-2) Scores | | | | | |
	NC	IPV	p	PTSD+ IPV	PTSD− IPV	p
Total	67.8 (51.7)	215.0 (182.8)	p < .005	287.6 (209.5)	155.7 (140.6)	NS
	range 0–159	range 0–663		range 0–663	range 0–443	
Injury	.1 (0.5)	16.5 (30.5)	p < .001	24.0 (39.9)	9.7 (17.9)	NS
	range 0–2	range 0–126		range 0–126	range 0–50	
Negotiation	61.9 (49.6)	45.4 (36.7)	NS	52.2 (32.0)	39.2 (41.1)	NS
	range 0–150	range 0–113		range 0–96	range 0–113	
Physical assault	0 (0)	58.6 (82.2)	p < .001	81.8 (95.6)	37.5 (65.2)	NS
		range 0–236		range 0–236	range 0–208	
Psychological aggression	5.6 (14.4)	71.8 (59.2)	p < .001	79.5 (62.4)	64.0 (57.7)	NS
	range 0–58	range 0–175		range 0–175	range 0–175	
Sexual coercion	.2 (1.0)	17.3 (37.1)	p < .05	30.5 (49.6)	5.4 (14.4)	NS
	range 0–4	range 0–138		range 0–138	range 0–48	

| | Childhood Trauma Questionnaire (CTQ) Scale Scores | | | | | |
	NC	IPV	p	PTSD+ IPV	PTSD− IPV	p
Total	30.9 (6.9)	58.1 (26.1)	p < .001	66.1 (27.5)	50.8 (23.7)	NS
	range 25–52	range 27–109		range 27–109	range 27–87	
Physical abuse	5.4 (.6)	9.8 (4.8)	p < .005	9.8 (5.1)	9.8 (4.8)	NS
	range 5–7	range 5–20		range 5–20	range 5–17	
Physical neglect	5.5 (.9)	9.9 (5.5)	p < .005	11.8 (5.6)	8.3 (5.1)	NS
	range 5–8	range 5–21		range 5–20	range 5–21	
Emotional abuse	6.8 (2.6)	13.2 (6.5)	p < .001	14.0 (7.2)	12.5 (6.0)	NS
	range 5–14	range 5–25		range 5–25	range 5–21	
Emotional neglect	7.9 (3.9)	13.9 (5.9)	p < .005	16.0 (6.0)	11.9 (5.4)	NS
	range 5–20	range 5–24		range 7–24	range 5–20	
Sexual abuse	5.4 (.7)	11.2 (7.1)	p < .05	14.5 (7.8)	8.3 (5.1)	p < .05
	range 5–7	range 5–25		range 5–25	range 5–19	

Data shown are mean (SD). Statistical significance levels from nonparametric Mann-Whitney U Tests (MWU) are presented. IPV, intimate partner violence victims; NC, nonvictimized comparison subjects.

= 1.9). In this smaller sample, NC and IPV groups did not differ significantly on these variables. EVIQ scores were marginally different ($p = .07$), although EVIQ scores were unavailable for some of these subjects. Neither of the IPV subgroups (7 PTST+ IPV; 5 PTSD- IPV) significantly differed from the NC subjects, although the PTSD- IPV subjects had marginally lower EVIQ scores ($p = .07$).

IMAGING PROTOCOL. Three whole-brain image series were collected for each subject. The first was a gradient-echo (SPGR) T1-weighted series with TR = 24 msec, TE = 5 msec, NEX = 2, flip angle = 45 degrees, field of view of 24 cm, and contiguous 1.2 mm sections. The second and third series were fast spin-echo (FSE) acquisitions yielding two separate image sets: TR = 3000 msec, TE = 17 msec, ET = 4 and TR = 3800 msec, TE = 102 msec, ET = 8. For all series, the field of view was 24 cm. Section thickness for the FSE series was 4 mm, no gaps (interleaved).

IMAGE ANALYSIS. The image-analytic approach is similar to that used in our recent studies (Jernigan et al 2001a; Jernigan et al 2001b). Trained anatomists who were blind to subject diagnosis, age, or any other identifying information subjected each image dataset to the following image analysis procedures: 1)

interactive isolation of intracranial regions from surrounding extracranial tissue; 2) three-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact; 3) reslicing of the volume to a standard orientation; 4) tissue segmentation using semi-automated algorithms; and 5) neuroanatomical region-of-interest analysis. These procedures were performed on the lower resolution FSE image volumes; however, the spatially registered SPGR volumes were visualized throughout the analyses to guide the operators. Each procedure is described briefly below.

After filtering, the image datasets are resectioned in a standard coronal plane defined relative to the decussations of the anterior and posterior commissures and the structural midline. Registration of the T1-weighted and spin-echo data sets is accomplished so that comparable sections from all three datasets are available to resolve anatomical boundaries. The tissue classification procedure is an interactive, supervised process. Operators manually designate the positions of three sets of tissue samples, one for each of the target tissues (gray, white, and CSF), on the resectioned images in standard anatomical locations within regions of homogeneous tissue. Two anatomists, working independently, applied the tissue classification method to 11 brain MRI volumes. Interoperator reliability estimates were .92 for
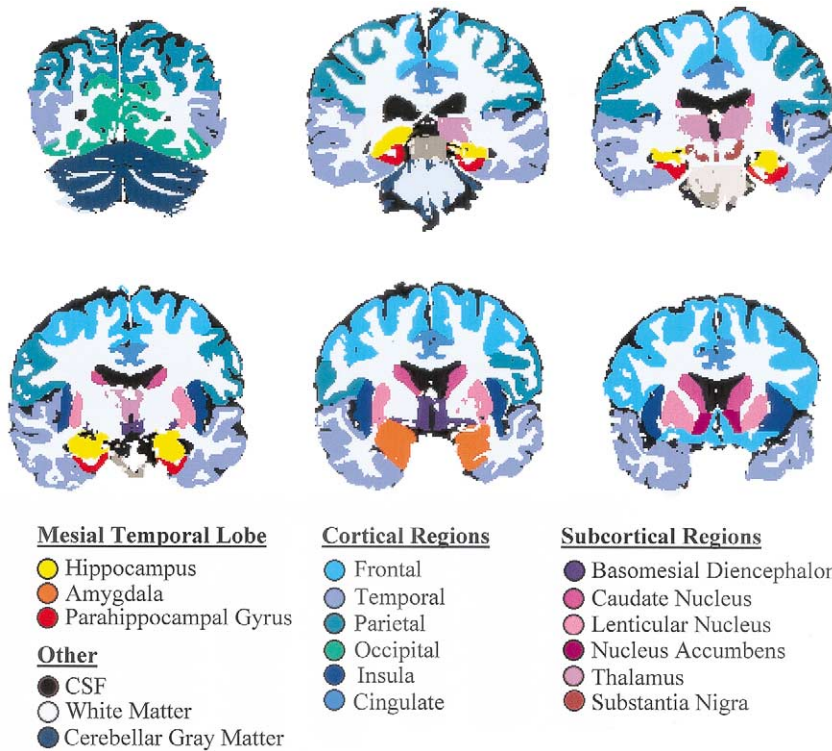
Figure 1. Example of processed images showing structural boundaries for gray matter regions.

white matter volume, .95 for gray matter volume, and .99 for CSF volume. Furthermore, scan-rescan reliability was estimated by applying the segmentation procedures independently and blindly to 11 pairs of image volumes from individuals imaged twice. Scan-rescan reliability estimates for the white matter, gray matter, and CSF volumes were .94, .94, .99, respectively.

Anatomists then circumscribe regions on the tissue-segmented images. Standardized rules are applied for delineating a set of subcortical structures and cortical regions. Subcortical structures include the cerebral ventricles, the caudate nucleus, the nucleus accumbens, the lenticular nucleus, the thalamus, the substantia nigra, and a region referred to as basomesial diencephalon (which includes septal nuclei, mamillary bodies and other hypothalamic structures, the bed nucleus of the stria terminalis, and the diagonal band of Broca). Cortical regions include the temporal lobe, frontal lobe, parietal lobe, occipital lobe, cingulate cortex, and insular cortex. Separate measures are obtained of three mesial temporal lobe structures: the hippocampus, the amygdala (which includes some adjacent entorhinal and perirhinal cortex), and the parahippocampal gyrus. The four major cortical lobes are drawn to include cortical gray matter, underlying white matter, and CSF. Volumes of each tissue are estimated separately within each lobe, and white matter and CSF volumes are also measured in a deep subcortical zone not within any of the cortical lobes. Gray matter and adjacent CSF of the cingulate cortex and insular cortex are defined separately. Representative fully processed images from a normal brain, illustrating the regional boundaries of the measured brain structures, are

shown in Figure 1. Two anatomists performed region of interest analysis of 10 tissue-segmented brain datasets independently. Interoperator reliability for estimated volumes of the 15 primary gray matter structures ranged from .85 to .99, with reliability for most measures exceeding .95.

Given the specific interest in the mesial temporal lobe regions in relation to the effects of PTSD, these region definitions will be described in detail. The mesial temporal lobe subregions include the amygdala area, the parahippocampal region, and the hippocampal region. The hippocampal and parahippocampal regions extend posterior to the pulvinar of the thalamus where they lie inferior to the corpus callosum. These two regions extend anteriorly to (but not including) the section immediately posterior to the section in which the long columns of the fornix appear; i.e., the anterior boundary is defined in part stereotactically. The transition to the amygdala region occurs in the section immediately posterior to the long columns of the fornix, and the region extends anteriorly to and including the section at which the temporal pole is entirely separated from the frontal lobe by the lateral sulcus. Within the posterior zone, the parahippocampal region includes entorhinal, parahippocampal, and some lingual gyrus. The inferior boundary is the collateral sulcus and the superior boundary is defined by following the white matter through the bend in the parasubicular region, separating the subiculum (hippocampal region) from the entorhinal cortex. The more superior hippocampal region is primarily the hippocampal formation and retrosplenial gyri. In posterior sections where the

temporal horns of the cerebral ventricles are seen, the hippocampal region includes the tail of the hippocampus, the fasciola cinerea, and the gyrus fasciolaris. The amygdala region includes amygdala, some very anterior hippocampus, contiguous entorhinal cortex, and the uncus (which includes perirhinal cortex).

STATISTICAL METHODS. Because of the modest sample sizes and concern about skewed distributions, nonparametric Mann–Whitney U scores were used to compare groups initially, and Spearman rank-order tests were employed to examine correlations between variables. Then, given the evidenced disparity in education between the NC and IPV groups and the wide age range of the subjects studied herein (ranging from 19–57 years), and in light of the known effects of age on regional volumes (Jernigan et al 2001a), regression analyses incorporating both age and education with group as independent variables were used to predict various tissue volumes. In the text, regression results are explicitly noted only when findings differ from the Mann–Whitney U comparisons. The variables examined (see Figure 1) included mesial temporal lobe gray matter volumes of the hippocampus, amygdala region, and parahippocampal gyrus; cortical gray matter volumes of the major lobes, the insula, and the cingulate; gray matter volumes of the cerebellum, basomesial diencephalon, caudate nucleus, lenticular nucleus, nucleus accumbens, thalamus, and substantia nigra; white matter volumes of the four major lobes of the cerebellum, and of the deep subcortical zone; and the volumes of cortical sulcal CSF, ventricular CSF, and cerebellar CSF. Primary planned analyses focused on comparisons of hippocampal volumes; secondary analyses examined other mesial temporal gray matter regions (the amygdala and parahippocampal gyrus). Finally, exploratory analyses were conducted to examine regional effects outside of the MTL area; given the descriptive and exploratory nature of these final analyses, we did not attempt to control for test multiplicity. Bilateral volumes were examined for all regions; left and right volumes were examined for mesial temporal lobe regions only.

Planned analyses were meant to employ volumes proportionalized to the volume of the cranial vault (supratentorial vault [STCN] for cerebral measures and infratentorial vault for cerebellar measures) to control for individual differences in head size; however, the first analyses comparing groups on the raw volume of STCN yielded an unexpected significant finding (Figure 2): the IPV group as a whole demonstrated significantly smaller STCN volumes relative to NC subjects (see Table 3). Posttraumatic stress disorder-positive IPV subjects tended to have smaller STCN volumes, although these differences did not reach significance (MWU $p = .07$; $\beta_{group} = .25$, $t = 1.1$, $p > .05$), and PTSD- IPV subjects had significantly smaller STCN volumes (MWU $p < .01$; $\beta_{group} = -0.49$, $t = 2.5$, $p < .05$). Therefore, primary analyses were performed on raw volumes, although secondary analyses examined proportionalized volumes as described in the results section.

Results

Subjects in the IPV group, including PTST+ and PTSD- IPV subjects, demonstrated smaller supratentorial cranial
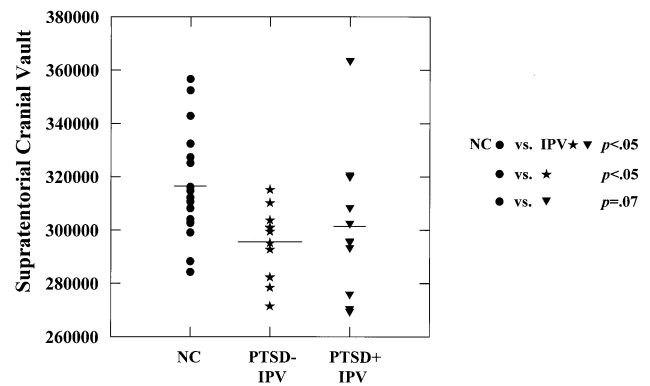

Figure 2. Raw values for supratentorial cranial vault (STCN) volume. Horizontal lines represent group means, symbols represent individual subject volumes. Statistical comparisons using nonparametric Mann–Whitney U scores are noted in the legend.

vault (STCN) volumes relative to NC subjects (see Figure 2). This finding remained statistically significant even within the regression model controlling for age and education (see Table 3). Since the use of STCN to control for differences in head size, as done in our previous studies, relies on no difference between groups on this measure, the use of proportionalized volumes was not justifiable. This finding will be investigated further in posthoc exploratory analyses following the primary comparisons.

Hippocampal Comparisons

The primary hypothesis of smaller hippocampal volumes in PTST+ IPV subjects relative to NC and PTSD- IPV subjects was examined. Groups were compared first on bilateral raw hippocampal volumes (see Table 4; Figure 3). The PTST+ IPV group did not differ significantly from either the NC or the PTSD- IPV group on this measure ($p > .05$). Although hippocampal volumes tended to be smaller in the PTSD- IPV group, the difference between NC and PTSD- IPV subjects did not reach significance (MWU $p > .05$; REGR $\beta_{group} = -0.37$, $t = 1.8$, $p = .08$). These results remained nonsignificant even with STCN proportionalized values. In summary, no evidence was found for smaller bilateral hippocampal volumes in the PTST+ IPV subjects relative to NC or PTSD- IPV subjects.

Given previous findings of smaller lateralized hippocampal volumes in PTSD, raw left and right volumes were examined (Table 4); PTST+ IPV subjects were not significantly different on left or right hippocampal volume measures relative to either NC or PTSD- IPV groups (all $p > .05$).

OTHER MESIAL TEMPORAL REGION COMPARISONS. Overall mesial temporal (MTL) gray matter and the additional MTL regions including the amygdala and para-

Table 3. Raw Volume Measures in Number of Voxels for Each Group (Mean [SD])

Bilateral Region	NC	IPV	MWU p	Regression Group Effect β	p	Data for Reference PTSD+	PTSD−
STCN total	316,541 (20,665)	298,560 (21,113)	.006	−.40	.03	301,483 (27,159)	295,638 (14,403)
STCN gray	186,727 (13,824)	176,612 (14,217)	.03	−.41	.01	180,309 (17,763)	173,252 (9706)
STCN white	108,658 (12,203)	104,106 (13,166)	NS	−.22	NS	104,672 (13,947)	103,592 (13,077)
STCN fluid (CSF)	21,157 (10,075)	17,967 (7388)	NS	−.02	NS	17,056 (7803)	18,794 (7265)
Cortical gray	175,843 (1309)	165,938 (1347)	.02	−.42	.01	169,324 (16,986)	162,859 (9033)
Cortical (sulcal) fluid	17,088 (8846)	13,420 (6034)	NS	−.10	NS	13,014 (6108)	13,789 (6240)
Ventricular fluid	3904 (1538)	4419 (2179)	NS	.32	.09	3999 (2143)	4840 (2,234)
Frontal gray	68,546 (6234)	64,496 (7299)	.06	−.41	.01	66,090 (8728)	62,901 (5488)
Parietal gray	39,203 (3873)	37,561 (3342)	NS	−.25	NS	37,411 (3868)	37,710 (2907)
Occipital gray	27,805 (3037)	24,880 (3153)	.01	−.44	.009	25,489 (3324)	24,272 (3003)
Temporal gray	35,509 (3384)	33,844 (2960)	NS	−.21	NS	34,609 (3183)	33,148 (2700)
Subcortical gray	10,884 (1087)	10,651 (849)	NS	−.13	NS	10,908 (837)	10,393 (817)
Cerebellar gray	29,234 (2497)	29,114 (2610)	NS	−.03	NS	29,829 (3060)	28,464 (2055)
Cerebellar white	10,375 (1923)	10,835 (1791)	NS	−.00	NS	10,786 (1749)	10,881 (1912)

Statistics presented reflect the comparison of the NC and IPV groups. The level of significance of Mann-Whitney U (MWU) nonparametric comparisons and results of the effect of group in the prediction of each volume in a linear regression analysis from education, age, and group are presented. Negative β values represent smaller volumetric measures for the IPV subjects than for the NC subjects.

STCN, Supratentorial Cranial Vault, global measures; IPV, intimate partner violence victims; NC, nonvictimized comparison subjects; PTSD, posttraumatic stress disorder.

hippocampal gyrus were examined as planned (Table 4; Figure 3). Groups were compared on bilateral, left, and right raw volumes; PTST+ IPV subjects were not significantly different from the NC group on any raw volume measure (all $p > .05$). The PTSD- IPV group, however, had smaller bilateral MTL gray overall relative to NC and PTST+ IPV subjects (see Table 4). Examination of lateralized measures revealed that this smaller volume in the PTSD- IPV subjects was primarily caused by a larger difference on the right MTL gray matter, particularly in the parahippocampal region (see Table 4). The PTST+ IPV group showed no difference in any MTL regions relative to either control group. In fact, the PTSD- IPV group had the smallest volumes.

Regional Effects of Cranial Vault Finding

The unexpected finding of smaller cerebral cranial vaults in the IPV group, with tendencies present in both PTST+ and PTSD- subjects, warranted further investigation (Fig-

ure 2). Before proceeding with the regional analyses, the NC subjects were compared with a separate cohort of 13 female controls (ages 18–61 years) from a separate study (Jernigan et al 2001a) to assure that their STCN volumes were within the norm. The NC group from the present study (Table 3) was not different from this separate cohort (mean = 317,808, SD = 22,315), validating that the NC group's mean STCN volume was not out of the ordinary. It should be noted that the following regional analyses are posthoc, descriptive, and exploratory in nature; therefore, we did not attempt to control for test multiplicity.

Cerebrospinal fluid spaces were examined first to assess whether there was brain volume *loss* in addition to smaller cerebral cranial vault size. Overall CSF (STCN fluid) and cortical (sulcal) fluid were not significantly different between groups for either raw or proportionalized (to STCN) measures. Although ventricular volumes were not significantly different in direct Mann–Whitney comparisons, regression analyses of ventricular volumes revealed differences between

Table 4. Raw Mesial Temporal Lobe (MTL) Volumes in Number of Voxels for Bilateral, Left, and Right Measures for All Groups (Mean [SD])

| Region | Data for Reference | | | | MWU | Group Effect from Regression | |
	NC	IPV	PTSD+ IPV	PTSD− IPV	p	β	p
Bilateral MTL Gray	6190	5833	6163	5534	.01	−.43	.06
	(515)	(702)	(609)	(667)			
Hippocampus	2954	2848	2929	2774	NS	−.13	NS
	(301)	(382)	(310)	(440)			
Parahippocampal Gyrus	1334	1250	1332	1176	NS	−.37	NS
	(202)	(219)	(210)	(207)			
Amygdala	1902	1735	1901	1584	.08	−.35	NS
	(388)	(484)	(410)	(513)			
Left MTL Gray	3015	2796	2897	2704	.07	−.27	NS
	(287)	(325)	(263)	(359)			
Hippocampus	1474	1429	1431	1428	NS	.08	NS
	(153)	(208)	(192)	(231)			
Parahippocampal Gyrus	652	616	638	595	NS	−.22	NS
	(116)	(100)	(87)	(110)			
Amygdala	889	751	828	681	.06	−.31	NS
	(243)	(267)	(237)	(284)			
Right MTL Gray	3174	3037	3265	2830	.005	−.52	.02
	(283)	(412)	(369)	(344)			
Hippocampus	1480	1419	1498	1346	NS	−.33	NS
	(206)	(202)	(158)	(217)			
Parahippocampal Gyrus	681	635	694	580	.04	−.43	.07
	(107)	(138)	(130)	(126)			
Amygdala	1013	984	1073	903	NS	−.35	NS
	(192)	(255)	(230)	(260)			

Statistics presented reflect the comparison of PTSD+ and PTSD− IPV groups; NC and IPV data are provided for comparison only. The significance of Mann-Whitney U (MWU) comparisons and the effect of group in the prediction of each volume in a linear regression analysis from education, age, and group are presented. Negative β values represent smaller volumetric measures for the PTSD− IPV subjects than for the PTSD+ IPV subjects.

IPV, intimate partner violence victims; NC, nonvictimized comparison subjects; PTSD, posttraumatic stress disorder.

NC and IPV groups for raw values (Table 3) and for volumes proportionalized to STCN (β = −0.38, p < .05). That is, the regression model identified a significant independent contribution of education, and the remaining variance could be attributed to a difference between groups. This ventricular finding was driven by a significant difference between NC and PTSD− IPV subjects (MWU p < .05; REGR β = −0.48, p < .05); no differences were evidenced in comparisons of NC and PTST+ IPV subjects. Although the implications of this finding are unclear, it may be reflective of either tissue loss or a neurodevelopmental effect specific to the PTSD-IPV group.

To examine whether the cerebrum and cerebellum were differentially affected, the volume of the cerebellar cranial vault was expressed as a proportion of the volume of total cranial vault (STCN plus cerebellar vault). The difference between NC and IPV groups approached significance, suggesting that the cerebrum may be more affected than the cerebellum (p = .09). Next, within the cerebrum, each lobe was expressed as a proportion of the total cerebral volume (STCN gray and white matter). None of these measures, however, were significantly different between the NC and

IPV groups. To examine the possibility that either gray or white matter was disproportionately affected, we computed separately for the cerebrum and cerebellum the proportion of brain volume that was gray matter. These measures were not significantly different between groups, suggesting that there was no disproportionate effect on gray or white matter; however, regional examination of gray and white matter volumes suggested a significant reduction in cortical gray matter (Figure 4; Table 3) and no difference in subcortical gray matter or cerebral white matter volumes in the IPV group relative to the NC group. This cortical gray matter difference was largely attributable to smaller frontal and occipital gray matter regions in IPV subjects (Table 3). Differences in parietal and temporal gray matter regions did not reach significance, and groups did not differ on any cerebellar measures.

Better Matched Subgroups

As mentioned previously, participants in the IPV group were significantly different in level of education and EVIQ relative to the NC group. In the previous section, we addressed this concern with a linear regression model that included education and age. In addition, we examined a
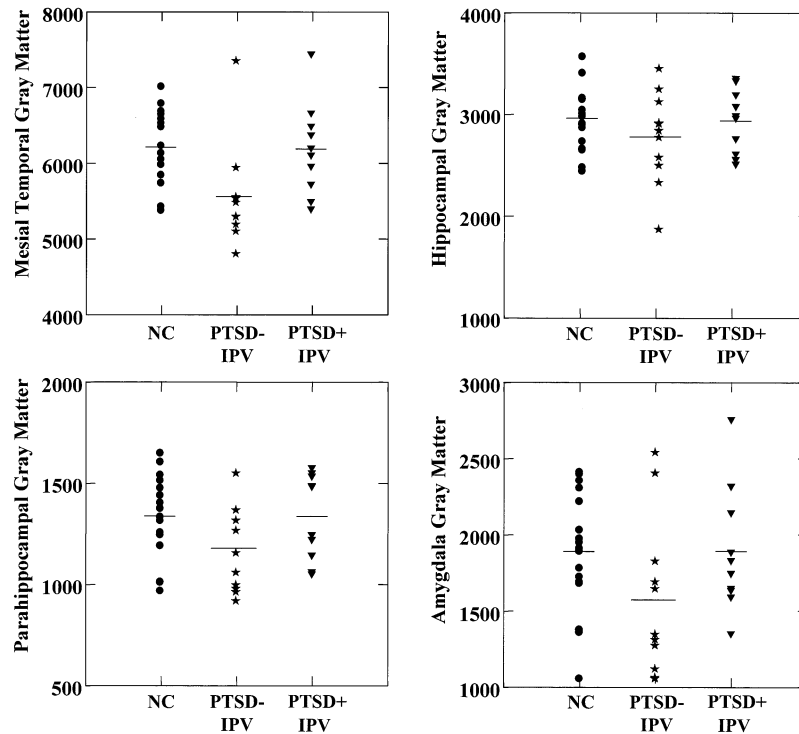
Figure 3. Raw values for overall mesial temporal gray matter and its components including hippocampus, parahippocampal gyrus, and amygdala regions. Horizontal lines represent group means, symbols represent individual subject volumes.

sample of subjects from each of the studied groups better matched on these variables (see Methods for description of subject groups). The findings were similar to those of the overall group study. There was no evidence for smaller

Figure 4. Raw values for cortical gray matter volume. Horizontal lines represent group means, symbols represent individual subject volumes.

hippocampal or other MTL gray matter region volumes in the PTST+ IPV group relative to either NC or PTSD- IPV subjects. In this comparison, however, PTSD- IPV subjects had significantly smaller right hippocampal volumes ($p < .05$) relative to both groups. Further investigation of the differences between the NC and IPV groups revealed similar findings of smaller STCN, occipital, and frontal volumes, with significantly smaller occipital and frontal gray matter volumes ($p < .05$). Interestingly, within this smaller group, proportional comparisons revealed that the temporal lobe and temporal gray matter, as proportions of overall lobar tissue and overall cortical gray matter respectively, now accounted for a significantly larger proportion in the IPV than in the NC group ($p < .05$).
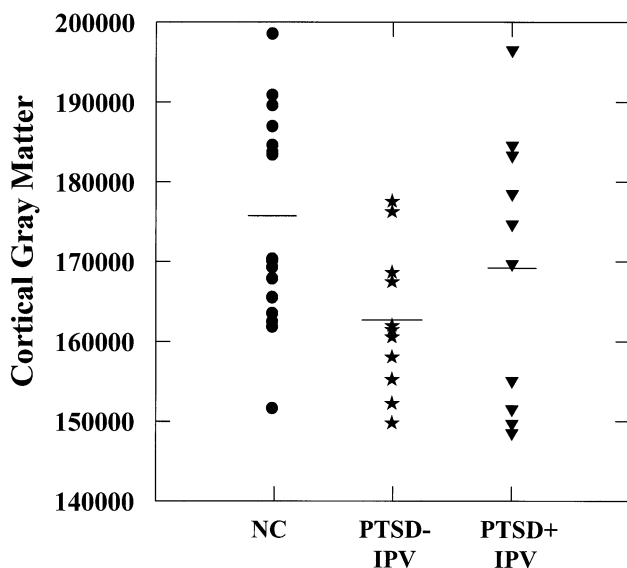
Correlational Analyses in IPV Subjects Only

Given the unexpected cranial vault findings in all IPV subjects, regardless of PTSD status, we performed posthoc correlational analyses between demographic measures, measures of abuse and PTSD symptom severity, and morphometric findings with nonparametric Spearman's correlation tests. Furthermore, the relationship between morphometric findings and the pertinent neuropsychological measures were examined as planned. First, the relationship between the finding of smaller STCN volumes and stature of subjects was examined. Information was
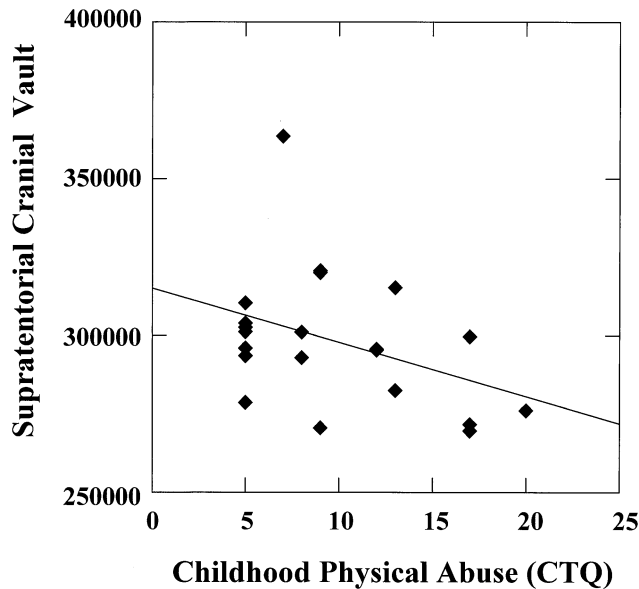
Figure 5. Relationship between supratentorial cranial vault (STCN) volume and Childhood Trauma Questionnaire Physical Abuse (CTQPA) scores in IPV subjects only. Each symbol represents an individual subject; the line represents a linear estimate of the relationship between STCN and CTQPA scores.

collected for 14 of the 17 NC subjects and 13 of the 22 IPV subjects, and no significant height difference was found between the NC and IPV groups ($p > .1$; see Table 1) or between the PTST+ IPV and PTSD- IPV subjects ($p > .1$). Within the IPV group ($n = 13$), there was no significant relationship between height and STCN volume ($r_s = .32, p > .05$). Based on this limited information, it would appear that stature alone could not account for the STCN differences in this study. Second, neither socioeconomic status ($r_s = -0.01; n = 22$) nor estimated verbal IQ ($r_s = -0.04; n = 15$) was significantly related to STCN volume.

Examination of the relationship between STCN volume and measures of abuse, however, did reveal significant findings with respect to measures of childhood abuse (CTQ) but not to measures of proximate adult domestic violence (CTS2). Supratentorial cranial vault volume was significantly negatively related to the CTQ measure of Physical Abuse in IPV subjects ($r_s = -0.38, p < .05, n = 21$; Figure 5); that is, greater physical abuse was associated with smaller STCN. The strength of this correlation was not weakened when the IPV participant with the largest STCN volume was removed from the analysis; the correlation coefficient was unchanged ($r_s = -0.38$). There were no significant relationships between morphometric measures and measures of abuse related to IPV (CTS2; all $r_s < .20$) or PTSD symptom severity (IES-R; $r_s = -0.12$) within the IPV group as a whole.

Examination of functional domains that were impaired in IPV subjects in Stein et al (2002) produced several interesting findings. Not all IPV subjects had complete neuropsychological batteries, so the sample sizes are provided with the statistics. With respect to executive function impairment, Trails B time (longer time indicates poorer performance) was significantly negatively related to cortical gray matter ($r_s = -0.42, p = .05, n = 21$), driven by a significant relationship with frontal gray matter ($r_s = -0.46, p < .05$; Figure 6). That is, longer performance times were related to smaller frontal gray matter volumes. Performance on an auditory working memory task, the PASAT, was positively related (higher PASAT scores indicate better functioning) to mesial temporal gray matter ($r_s = .48, p < .05, n = 14$).

With respect to PTSD status, PTST+ IPV subjects ($n = 10$ with neuropsychological measures) demonstrated the same significant relationship between Trails B time performance and cortical gray matter ($r_s = -0.63, p = .05$) or frontal gray matter ($r_s = -0.69, p < .05$). That is, longer performance times were related to smaller gray matter volumes. No other correlations reached significance in this small group of subjects.

Discussion

Adult victims of IPV with PTSD did not demonstrate any differences in bilateral, left or right hippocampal volume
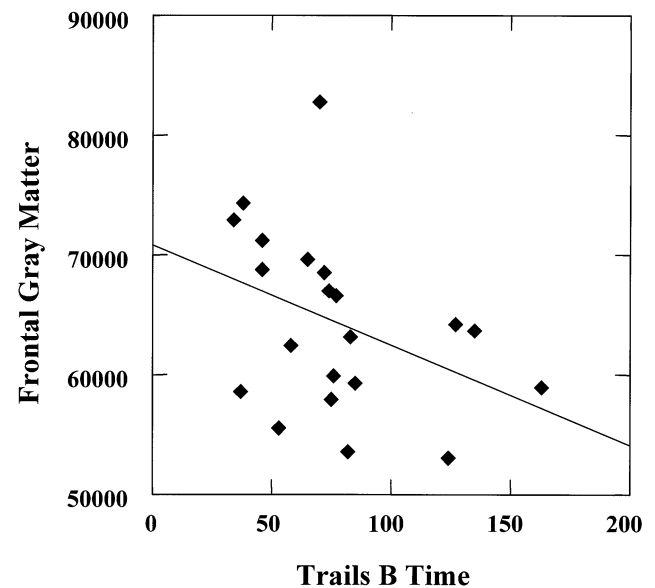

Figure 6. The relationship between frontal gray matter volume and Trails B Time performance in IPV subjects. Each symbol represents an individual subject; the line represents a linear estimate of the relationship between the morphometric volume and the neuropsychological score.

when compared with healthy adult volunteers (NC) without histories of serious psychological trauma. Furthermore, PTSD+ IPV subjects did not differ significantly on hippocampal volumes relative to the PTSD- IPV group, which was better matched on history of abuse and education. These results are in contrast to several MRI studies of veterans (Bremner et al 1995a; Gurvits et al 1996) and adult victims of childhood abuse (Bremner et al 1997; Stein et al 1997) that have reported smaller volumes of the hippocampus in participants with PTSD, although some recent studies have not found evidence for smaller hippocampal volumes in direct relation to PTSD (Bonne et al 2001; De Bellis et al 1999; Driessen et al 2000). The findings to date have not shown a specific relationship between PTSD symptomatology or severity and hippocampal volume. In fact, hippocampal volume was significantly related to the severity of dissociative disorder and not PTSD in one study of adult victims of childhood abuse (Stein et al 1997). Furthermore, a study of borderline personality disorder revealed that significantly smaller hippocampal volumes were not related to PTSD diagnosis or severity, whereas this hippocampal measure was significantly related to a measure of childhood trauma (Driessen et al 2000).

Several possible explanations exist for the variability between studies, including differences in characteristics of the samples studied, differences in measurement methodology, and the influence of childhood abuse on brain development. Entry criteria for the present study were meticulous in their exclusion of subjects with substantial past or current alcohol or other substance abuse. The current sample may be less confounded, then, in terms of the possible influence of alcohol or drug abuse on hippocampal volume (Agartz et al 1999; Jernigan et al 1991; Sullivan et al 1995).

The morphometric methods applied in the present study required rigorous standards and have been shown to be sensitive to changes in hippocampal volume in a recent study of normal aging (Jernigan et al 2001a). Due to the findings of hippocampal volume loss with normal aging, statistical comparisons controlled for the effects of age, as well as education, on volumetric measures. In addition, the present methodology provides a whole brain volumetric analysis and measurement of the supratentorial cranial vault (STCN), a measure including cerebrum and cerebrospinal fluid. This provides numerous comparison regions, a measure of brain volume loss, and a method to estimate differences in head size. No previous study described above provides all of this information.

The unexpected finding of significantly smaller STCN volumes in adult victims of IPV regardless of PTSD classification is interesting in light of this cohort's childhood abuse history. In particular, the volume of supratentorial cranial vault (STCN) was negatively correlated with a self-report measure of childhood physical abuse. That is, IPV subjects with smaller STCN volumes reported increased exposure to childhood physical abuse. This finding in adult IPV subjects, both with and without PTSD, remained significant even after attempts to better control for education and estimated verbal IQ. Thus, it appears that the findings of smaller STCN volumes may be related to a neurodevelopmental effect, perhaps related to childhood physical abuse. One need not, however, invoke a causal link in this particular direction. It is possible that smaller STCN volumes (perhaps indicative of as-yet-unspecified deficits in cognitive function) may put an individual at increased risk for abuse and other forms of serious psychosocial adversity. This competing hypothesis must be seriously considered in future work.

In an effort to assess the effects of IPV and PTSD on the whole brain, this study examined the regionality of gray matter differences. In particular, the frontal and occipital gray matter volumes were significantly smaller in all IPV subjects without significant findings of increased subarachnoid CSF spaces; however, the PTSD- IPV group evidenced smaller proportionalized ventricular volumes and appeared to be more affected than the PTST+ IPV subjects, despite no demographic differences between the groups and the PTSD subjects' more severe history of sexual abuse. Although the implications of this finding are unclear, it may be reflective of either tissue loss or a neurodevelopmental effect in the PTSD- IPV subjects.

Further investigations of the brain-behavior relationships, driven by executive function deficits found in this cohort (Stein et al 2002), revealed that smaller frontal gray matter volumes were related to increased Trails B Time performance in all IPV subjects and in the PTST+ IPV group only. In addition, performance on the PASAT, an auditory working memory task, was positively related to mesial temporal gray matter, suggesting a relationship between the integrity of the mesial temporal lobe and working memory performance. These findings, which await replication in other samples, suggest that at least some aspects of neuropsychological impairment in IPV victims are rooted in frontal and mesial temporal abnormalities.

These findings bear comparison with studies of children with PTSD (De Bellis et al 1999; Carrion et al 2001). Both investigations found smaller cerebral volumes in children with PTSD and both failed to find differences in hippocampal volume related to PTSD, particularly when comparisons controlled for brain volume. De Bellis et al (1999) demonstrated smaller intracranial and cerebral volumes in children with PTSD, and proportionally larger lateral ventricles. In their childhood PTSD group, the intracranial volume was significantly related positively

with age of onset of abuse and IQ and negatively with the duration of maltreatment; these effects were all greater in the male than in the female subjects. The authors suggest that the lack of hippocampal volume differences in this study could be due to comorbidity issues in previously reported adult studies of PTSD, differences in methodology, or the influence of neurodevelopmental plasticity on these effects (Jernigan and Sowell 1997). The stress of childhood abuse may lead to abnormal neurodevelopment, and neurodevelopmental changes or neural plasticity may mask any hippocampal stress-related loss, or it might not occur in these subjects.

In the present study, a PTSD- IPV comparison group was employed and provided added insight into the relationship of brain abnormalities to PTSD. Our findings suggest that PTSD itself may not be responsible for the majority of differences found between NC and IPV victims, most of whom also had a history of child abuse. Instead, the IPV group as a whole may have abnormalities resulting from the effects of child abuse and stress on neurodevelopment. A recent review on child abuse and neglect supports such a view of changes in the brain during development caused by both stress and nonstress related influences that are not yet well understood (Glaser 2000).

Our study has a number of limitations. First, although the sample sizes are in the same range as most other studies in the area, the sample size is relatively small, leaving us open to possible Type II errors. Second, in light of the findings by Schuff et al (2001) that a biochemical index of neuronal density –MR spectroscopic measurement of N-acetylaspartate –was low in the hippocampi of PTSD patients even in the absence of volume loss, we must acknowledge the probable insensitivity of MR morphometry to more subtle changes in neuronal microarchitecture. Thus, hippocampal neuronal structure (and function) may well be abnormal in PTSD, even in the absence of morphometrically detectable changes. Third, although we made every effort to recruit nonvictimized comparison subjects who matched our IPV subjects on education, our groups were not well matched in this regard. This selection bias could explain our findings of smaller SCTN volume in IPV victims, although our attempts to control for this difference yielded the same results; however, this selection bias would not explain our failure to find differences between groups in hippocampal or other mesial temporal lobe volumes. On the other hand, given the likelihood that childhood trauma results in neuropsychological dysfunction (Carrey et al 1995; Perez and Widom 1994; Saigh et al 1997) and thereby reduces the likelihood of academic success and educational advancement, matching subjects on education (or IQ) might introduce a serious bias in the

opposite direction, forcing the inclusion of especially "resilient" trauma victims (i.e., those whose neuropsychological function was *not* affected by childhood trauma). A possible solution to the problem (though none is ideal) would involve matching subjects not on education or current IQ, but rather on a measure of premorbid intellectual function, such as the ANART (Grober and Sliwinski 1991). We are using this approach in our ongoing work in this area in the hope that it will lead to a clearer understanding of the role of psychological trauma on CNS structure and function, and its relationship to PTSD and other psychiatric disorders.

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