# Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum

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Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved December 28, 2011 (received for review September 19, 2011)

**Childhood maltreatment or abuse is a major risk factor for mood, anxiety, substance abuse, psychotic, and personality disorders, and it is associated with reduced adult hippocampal volume, particularly on the left side. Translational studies show that the key consequences of stress exposure on the hippocampus are suppression of neurogenesis in the dentate gyrus (DG) and dendritic remodeling in the cornu ammonis (CA), particularly the CA3 subfield. The hypothesis that maltreatment is associated with volume reductions in 3-T MRI subfields containing the DG and CA3 was assessed and made practical by newly released automatic segmentation routines for FreeSurfer. The sample consisted of 193 unmedicated right-handed subjects (38% male, 21.9 ± 2.1 y of age) selected from the community. Maltreatment was quantified using the Adverse Childhood Experience study and Childhood Trauma Questionnaire scores. The strongest associations between maltreatment and volume were observed in the left CA2-CA3 and CA4-DG subfields, and were not mediated by histories of major depression or posttraumatic stress disorder. Comparing subjects with high vs. low scores on the Childhood Trauma Questionnaire and Adverse Childhood Experience study showed an average volume reduction of 6.3% and 6.1% in the left CA2-CA3 and CA4-DG, respectively. Volume reductions in the CA1 and fimbria were 44% and 60% smaller than in the CA2-CA3. Interestingly, maltreatment was associated with 4.2% and 4.3% reductions in the left presubiculum and subiculum, respectively. These findings support the hypothesis that exposure to early stress in humans, as in other animals, affects hippocampal subfield development.**

child abuse | physical abuse | sexual abuse | allostatic load

The exquisite vulnerability of the hippocampus to the ravages of stress is one of the key translational neuroscience discoveries of the 20th century. Sapolsky et al. (1) provided early clues when they found that elevating corticosterone stress hormone levels into the high physiological range for an extended period reduced the number of hippocampal neurons in rats. Further studies showed that the deleterious effects of glucocorticoids could occur in other regions but that the hippocampus was the primary target. The outcomes of excessive exposure to glucocorticoids range from the reversible atrophy of dendritic processes and suppression of neurogenesis with acute exposure to frank neuronal death with chronic high-level exposure (2). The sensitivity of hippocampal neurons to stress and glucocorticoids has been confirmed in a host of other species, including nonhuman primates (3).

Evidence for potential effects of stress or excessive glucocorticoids on the human hippocampus emerged from neuroimaging studies of individuals with Cushing disease (4) and veterans with posttraumatic stress disorder (PTSD) (5). A large number of studies have since shown alterations in hippocampal volume in a multitude of psychiatric disorders, including major depression (MDD), PTSD, borderline personality disorder (BPD), schizophrenia, dissociative identity disorder (DID), and antisocial personality disorder (ASPD) (6).

More recently, attention has focused on the effects of childhood abuse or maltreatment on the hippocampus. These studies are particularly germane because childhood abuse is a risk factor for nearly all the psychiatric disorders associated with reduced hippocampal volume and may serve as a unifying mechanism [e.g., depression (7), PTSD (8), BPD (9), schizophrenia (10), DID (11), ASPD (12)]. Indeed, the Adverse Childhood Experience (ACE) study identified maltreatment as the leading preventable cause of major mental illness (13). Maltreatment-related early adversity accounted for 54%, 64%, and 67% of the population attributable risk fraction for current episodes of depression, addiction to illicit drugs, and suicide attempts, respectively (14, 15). High ACE levels were associated with a 10.3-fold and 17.3-fold increase in prescriptions for antipsychotic drug and mood stabilizer (16), respectively.

Consistent reports have emerged of diminished hippocampal volume (particularly on the left side) in adults with maltreatment histories (17–26) but not in maltreated children (27–30). Translational studies also show that effects of early stress on hippocampal synaptic density do not emerge until well after puberty (31). The hippocampus appears to be most vulnerable to childhood abuse between 3 and 5 y of age (23). Additional support for this observation comes from translational studies showing that synaptic density in the hippocampus, but not the prefrontal cortex, of rats was sensitive to the effects of early (preweaning) stress, whereas the opposite was true in regard to peripubertal stress (31, 32). Further, Rao et al. (33) reported that degree of parental nurturance at 4 y of age, but not at 8 y of age, predicted hippocampal volume at the age of 14 y.

Corticotropin-releasing hormone (CRH), a key limbic stress modulator, may also play a role in early stress susceptibility. There is a special population of cells in the immature hippocampus, but not in the adult hippocampus, that can release CRH in response to stress (34). Exposing the immature hippocampus to excessive CRH results in a delayed and progressive effect on cell survival and dendritic branching that models the effects of early stress (35).

At the cellular level, the key effects of stress are to suppress ongoing neurogenesis in the dentate gyrus (DG) and to provoke the remodeling of dendrites in the cornu ammonis (CA), particularly the CA3 subfield (36, 37). An unanswered critical question is whether exposure to childhood maltreatment (or any

Author contributions: M.H.T. and A.P. designed research; M.H.T., C.M.A., and A.P. performed research; C.M.A. contributed new reagents/analytic tools; M.H.T. and C.M.A. analyzed data; and M.H.T., C.M.A., and A.P. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1115396109/-/DCSupplemental.

other stressor) is associated with alterations in the same hippocampal subfields in humans as have been identified as vulnerable in preclinical studies.

This is a challenging problem because the hippocampus has a complex symmetry that needs to be defined by multiple boundaries, some of which are poorly delineated on MRI scans. Laborious manual tracing has been the gold standard for measuring total hippocampal volume, although high concordance between different raters has been hard to achieve (38). Further, MRI resolution and signal-to-noise ratios have previously been too low to visualize hippocampal subfields distinctly. Higher field strength scanners and improved sequences have brought these subfields into view, but the task of delineating their 3D structure by hand has been a daunting and excruciatingly time-consuming process (39). As a consequence, studies of hippocampal volume in psychiatric disorders have typically used small- to moderate-sized samples and have focused entirely on total volume measures.

Software has recently become available with the potential to advance research in this area markedly by providing an automatic means of delineating the volume of prominent hippocampal subfields (39). This method, developed by Van Leemput at al. (39), uses Bayesian inference to a statistical computational model of image formation around the hippocampus and a probabilistic atlas to provide fully automated subfield segmentation. A validation study comparing automated results with manual delineation on ultrahigh-resolution MRI scans from 10 individuals found a high degree of correlation in subfields containing the DG and CA ($r = 0.83$ and $r = 0.91$, respectively) (39).

The aim of the present study was to test the hypothesis that childhood maltreatment was most prominently associated with volume reductions in computer-segmented subfields containing the DG and CA3 (i.e., CA4-DG, CA2-CA3). In particular, we predicted that the CA4-DG and CA2-CA3 would show a stronger statistical association with maltreatment scores than other components of the hippocampus proper (CA1 or fimbria) or adjacent subicular regions. The subiculum and presubiculum are modified six-layered cortical regions that form part of the hippocampal complex and lay between the hippocampus proper and the entorhinal cortex. If our primary hypothesis resists rejection, it would lend further support to the premise that observed hippocampal differences are likely stress-induced alterations rather than preexisting abnormalities. Confirmation that subfields containing the DG and CA3 were most strongly related to maltreatment using a fully automated method would also provide the impetus to ascertain whether different therapeutic modalities affect specific subfields, and whether these subfields have unique sensitive periods when they are maximally susceptible to the effects of early stress (23).

## Results

**Demographics.** The demographic characteristics of the 193 subjects (73 male and 120 female) are summarized in Table 1. Briefly, this was an ethnically diverse sample that appeared to be predominantly middle-class and well-educated. Age was distributed fairly consistently over the range of 18–25 y. The majority of the younger subjects were enrolled in college, and the majority of the older subjects had graduated. This is consistent with the high student density of the Boston area. Fifty-eight percent of their fathers and 52% of their mothers had graduated from college, and many had gone on for further studies.

**Exposure History.** Table 2 shows exposure history as indexed by ACE and Childhood Trauma Questionnaire (CTQ) scores and clinical features of the sample. Forty-six percent of the sample had no exposure to childhood adversity as assessed retrospectively by ACE scores, and 16% reported exposure to three or more forms of maltreatment. Physical abuse and parental verbal abuse were the most common forms of maltreatment in this sample (38% and 32%, respectively). As expected, there were

**Table 1. Demographic features of the sample**

| Feature | Subjects, % |
|---|---|
| Race and ethnicity | |
| White | 72 |
| Asian | 12 |
| Black | 7 |
| American Indian/Native Alaskan | 1 |
| Other (unspecified) | 8 |
| Hispanic | 10 |
| Financial sufficiency | |
| Much less than enough money | 1 |
| Less than enough money | 20 |
| Enough money | 47 |
| More than enough money | 27 |
| Much more than enough money | 5 |
| Education | |
| Father | |
| <12 y | 6 |
| High school | 17 |
| Some college | 18 |
| College graduate | 21 |
| Master or equivalent | 17 |
| Doctorate or equivalent | 21 |
| Mother | |
| <12 y | 3 |
| High school | 17 |
| Some college | 27 |
| College graduate | 26 |
| Master or equivalent | 17 |
| Doctorate or equivalent | 10 |
| Subject | |
| <12 y | 2 |
| High school | 4 |
| Some college | 49 |
| College graduate | 45 |

significant interrelationships between exposure to maltreatment and sociodemographic factors. Parental education correlated inversely with maltreatment ratings (ACE: $r = -0.19$, $P = 0.007$; CTQ: $r = -0.33$, $P < 10^{-5}$). So too did ratings of perceived financial sufficiency (ACE: R = −0.40, $P < 10^{-8}$; CTQ: $r = -0.41$, $P < 10^{-8}$). Hence, parental education and perceived financial sufficiency were used as potential covariates along with age, gender, and subcortical gray matter volume (GMV).

**Clinical Features.** Mood disorders were diagnosed most frequently, with 25% of the sample having a past or current history of MDD (Table 2). PTSD was also fairly common (7%). An additional 5% of the sample met most of the requisite criteria for PTSD but fell short by a few items. Subjects meeting full criteria for PTSD had mean (±SD) ACE scores of 3.2 ± 1.8. Subjects meeting partial criteria had mean ACE scores of 2.3 ± 2.1. Overall, 53% of subjects with ACE scores ≥3 met lifetime criteria for MDD and 23% met full criteria for PTSD.

**ACE Scores and Subfield Volume.** Fig. 1 shows the percent variance ($s^2$) in subfield volume accounted for by degree of maltreatment, as assessed using variance decomposition (40, 41). The strongest associations were seen in the left CA4-DG [$F(1,190) = 9.46$, $P < 0.003$, $s^2 = 3.9\%$] and CA2-CA3 [$F(1,189) = 9.56$, $P < 0.003$, $s^2 = 3.7\%$]. Significant associations were also seen in the left subiculum [$F(1,190) = 6.88$, $P < 0.01$, $s^2 = 3.1\%$] and presubiculum [$F(1,190) = 7.19$, $P < 0.008$, $s^2 = 3.3\%$], and were of marginal significance in the left CA1 [$F(1,189) = 4.27$, $P < 0.04$, $s^2 = 2.0\%$] and nonsignificant for the fimbria [$F(1,189) = 2.04$,

**Table 2. Maltreatment history and clinical features of the sample**

| Feature | Subjects, % |
|---|---|
| ACE score distribution | |
| 0 | 46 |
| 1 | 23 |
| 2 | 15 |
| 3 | 10 |
| 4–7 | 6 |
| CTQ score distribution ($n$ = 180) | |
| 25–29 | 33 |
| 30–39 | 31 |
| 40–49 | 14 |
| 50–59 | 12 |
| 60–103 | 11 |
| Abuse/maltreatment | |
| Harsh corporal punishment | 33 |
| Any physical abuse | 38 |
| Familial physical abuse | 31 |
| Parental physical abuse | 20 |
| Nonfamilial physical abuse | 8 |
| Any sexual abuse | 14 |
| Familial sexual abuse | 5 |
| Nonfamilial sexual abuse | 9 |
| Witness domestic violence | 30 |
| Threat or assault of mother | 20 |
| Threat or assault of father | 4 |
| Threat or assault of sibling | 19 |
| Parental verbal aggression | 32 |
| Peer verbal aggression | 21 |
| Diagnostic history | |
| Any mood disorder | 31 |
| MDD | 25 |
| Bipolar disorder | 2 |
| Any anxiety disorder | 21 |
| PTSD | 7 |
| Panic disorder | 2 |
| Attention deficit hyperactivity | 3 |
| Eating disorder | 2 |
| Personality disorder | 2 |

$P > 0.1$, $s^2 = 0.7\%$]. Correlations between ACE scores and right hippocampal subfield volumes were of marginal significance for the CA1 [$F(1,188) = 4.56$, $P < 0.04$, $s^2 = 1.6\%$] and CA2-CA3 [$F(1,188) = 4.30$, $P < 0.04$, $s^2 = 1.5\%$], and were negligible for the fimbria, subiculum, and presubiculum.

Table 3 shows that subfield volumes were smaller by 6.5%, 6.3%, 5.4%, 4.5%, 4.4%, and 1.3% in the left CA2-CA3, CA4-DG, presubiculum, CA1, subiculum, and fimbria in subjects with ACE scores ≥3 ($n$ = 31) vs. ACE scores = 0 ($n$ = 89). Effect size differences were moderate (d′ = 0.58–0.61) for the left CA2-CA3 and CA4-DG, and they were small for the subiculum, presubiculum, and CA1. The right CA1, CA2-CA3, and CA4-DG were also significantly smaller in subjects with ACE scores ≥3.

**CTQ Scores and Subfield Volume.** CTQ scores were available for 180 subjects. Fig. 2 shows the $s^2$ in subfield volumes accounted for by CTQ scores. The strongest associations were seen in the left CA4-DG [$F(1,177) = 9.37$, $P < 0.003$, $s^2 = 4.3\%$], CA2-CA3 [$F(1,177) = 9.26$, $P < 0.003$, $s^2 = 4.2\%$], and subiculum [$F(1,177) = 8.30$, $P < 0.005$, $s^2 = 4.1\%$]. There were also significant but weak associations between CTQ scores and volume of the left presubiculum [$F(1,177) = 4.31$, $P < 0.04$, $s^2 = 2.4\%$] and right CA1 [$F(1,175) = 4.52$, $P < 0.04$, $s^2 = 1.6\%$]. Associations between CTQ score and volume of the left CA1 [$F(1,176) = 2.68$, $P > 0.1$, $s^2 = 2.0\%$] and left fimbria [$F(1,176) = 0.28$, $P > 0.5$, $s^2 = 0.1\%$] were not significant; neither was the association between CTQ score and volume measures in the remaining subfields.

Fig. 3 portrays the regressive relationship between total CTQ scores and volume (adjusted for total subcortical GMV and scaled to show percent size relative to subjects without maltreatment). Data were fit to a natural spline with 2 df for illustrative purposes. These graphs show the graded relationship between total CTQ score and volume reduction in the left > right CA2-CA3, CA4-DG, subiculum, and presubiculum.

Comparing subjects with the lowest CTQ scores (range: 25–29, $n$ = 60) with subjects with CTQ scores ≥50 ($n$ = 40) indicated that volumes were 6.0%, 5.8%, 4.2%, 3.8%, 3.6%, 3.0%, and 0.6% lower in the left CA2-CA3, CA4-DG, presubiculum, fimbria, subiculum, and CA1, respectively (Table 4). Effect size differences were moderate for the left CA4-DG and left CA2-CA3 (d′ = 0.55). Effect sizes for the left subiculum and presubiculum were small (d′= 0.32–0.39) and fell short of significance. None of the right-sided volume comparisons were significant.

**Mediation by Depression or Posttraumatic Stress.** Structural equation modeling was used to ascertain the degree to which a lifetime diagnosis of MDD or PTSD mediated the association between maltreatment ratings and subfield volumes. The best-fitting model is illustrated in Fig. 4. Relationships proposed in the model

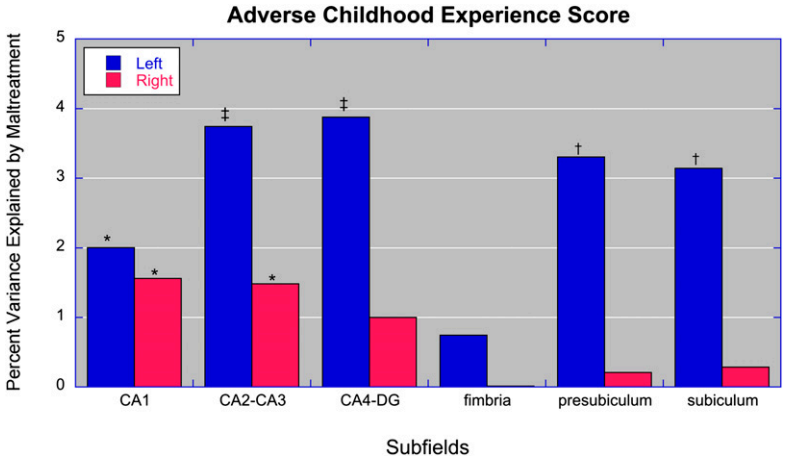


**Fig. 1.** Effect sizes ($s^2$ explained) in hippocampal subfield volume by exposure to childhood maltreatment as measured by subjects' ACE score ($n$ = 193). The $s^2$ is derived from linear regression using variance decomposition (40, 41). *$P < 0.04$; †$P < 0.01$; ‡$P < 0.003$.

**Table 3. Mean subfield volumes (measured in 0.5-mm$^3$ voxels), 95% confidence intervals, group differences, and effect sizes for subjects with ACE scores of 0 ($n$ = 89) vs. ACE scores ≥3 ($n$ = 31)**

| Measures | ACE = 0 (95% CI) | ACE ≥ 3 (95% CI) | Group F Group p | d′ (95% CI) |
|---|---|---|---|---|
| Right CA1 | 2,804 (2,745–2,863) | 2,652 (2,550–2,754) | 7.18 0.008 | 0.54 (0.20–1.00) |
| Right CA2-CA3 | 8,679 (8,490–8,868) | 8,221 (7,875–8,567) | 6.13 0.01 | 0.5 (0.10–0.90) |
| Right CA4-DG | 4,788 (4,685–4,891) | 4,587 (4,404–4,771) | 4.01 0.05 | 0.41 (0.00–0.80) |
| Right fimbria | 555 (531.6–578.5) | 562.6 (507.6–617.5) | 0.09 0.77 | 0.06 (–0.40 to 0.50) |
| Right subiculum | 5,465 (5,372–5,558) | 5,393 (5,189–5,597) | .66 0.42 | 0.15 (–0.30 to 0.60) |
| Right presubiculum | 3,995 (3,913–4,077) | 4,003 (3,835–4,170) | 0.01 0.93 | 0.02 (–0.40 to 0.50) |
| Left CA1 | 2,743 (2,663–2,824) | 2,619 (2,516–2,722) | 2.76 0.10 | 0.35 (0.00–0.70) |
| Left CA2-CA3 | 8,317 (8,118–8,516) | 7,778 (7,459–8,096) | 7.82 0.006 | 0.58 (0.20–1.00) |
| Left CA4-DG | 4,655 (4,554–4,756) | 4,361 (4,186–4,537) | 8.63 0.004 | 0.61 (0.20–1.00) |
| Left fimbria | 673.1 (646.1–700.1) | 681.8 (631.2–732.5) | 0.10 0.75 | 0.07 (–0.30 to 0.50) |
| Left subiculum | 5,627 (5,489–5,765) | 5,378 (5,167–5,589) | 3.53 0.06 | 0.39 (0.00–0.80) |
| Left presubiculum | 4,147 (4,054–4,240) | 3,925 (3,739–4,110) | 5.38 0.02 | 0.48 (0.00–1.00) |

95% CI, 95% confidence interval.

provide a plausible explanation of those that exist in the data and could not be rejected by the $\chi^2$ criteria ($\chi^2$ = 3.53, df = 2, $P$ = 0.17). The standardized root mean square residual (SRMR) was 0.013, indicating a good fit. Relative fit indices also indicated a very good fit [Normed Fit Index (NFI) = 0.996, Tucker–Lewis Index (TLI) = 0.979, Comparative Fit Index (CFI) = 0.998, and Incremental Fit Index (IFI) = 0.998]. For clarity, the illustration omits covariance interrelations between the two proposed mediators and between each of the dependent variables. As expected, there were very strong associations between CTQ total score and lifetime histories of MDD and PTSD. Further, there were significant direct pathways between CTQ score and volume measures for the left CA2-CA3, CA4-DG, subiculum, and presubiculum. However, there were no pathways between MDD and PTSD, and subfield volumes were significant. Similarly, self-report ratings of depression and PTSD showed no significant associations with subfield volumes on path analysis (*SI Text*). There was also no evidence for MDD and PTSD as mediators of the associations between ACE scores and diminished subfield volumes (*SI Text*).

## Discussion

These findings provide support for the hypothesis that the volumes of the left CA4-DG and CA2-CA3 were most robustly

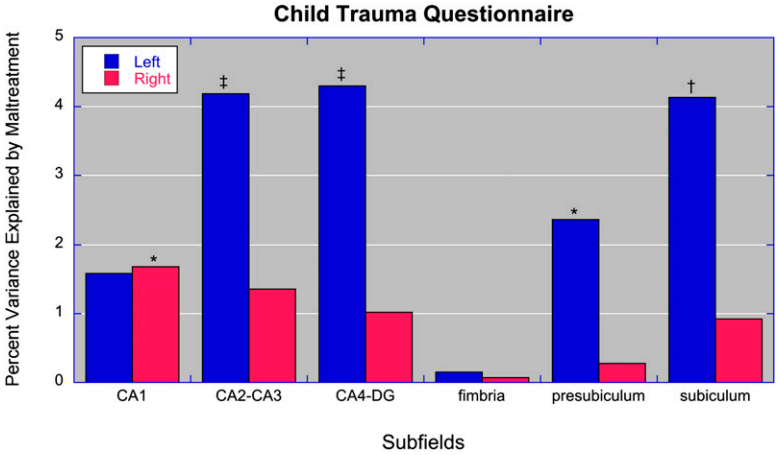


**Fig. 2.** Effect sizes ($s^2$ explained) in hippocampal subfield volume by exposure to childhood maltreatment as measured by subjects' CTQ total score ($n$ = 180). *$P$ < 0.04; †$P$ < 0.005; ‡$P$ < 0.003.

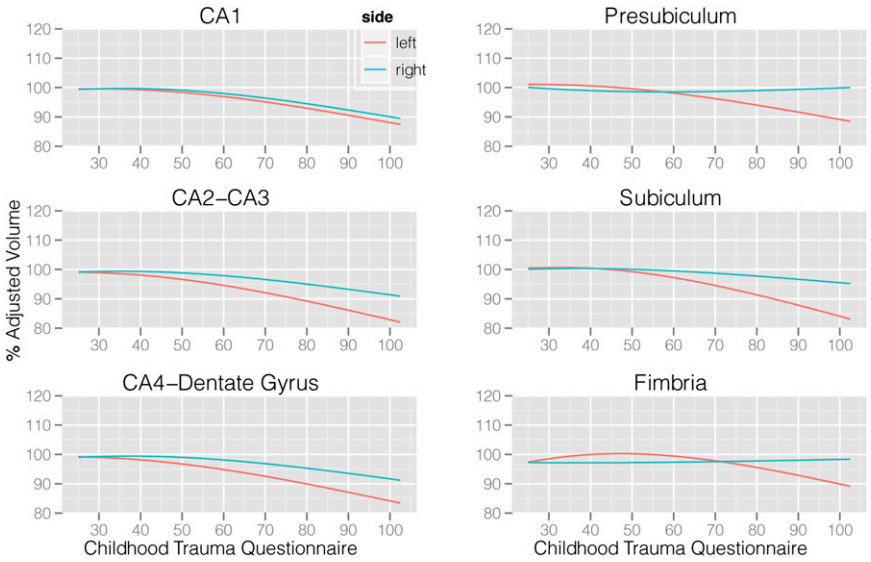


**Fig. 3.** Natural spline fits showing the regressive relationship between CTQ total scores and left and right hippocampal subfield volumes. Measures of hippocampal volume were expressed as a percentage of volume in each subfield relative to the mean volume of unexposed subjects (CTQ score = 25).



affected by exposure to childhood maltreatment. Comparing subjects with high vs. extremely low maltreatment scores showed a 6.3% and 6.5% volume reduction in the CA4-DG and CA2-CA3 by ACE score and a 5.8% and 6.0% volume reduction by CTQ score. Hence, it appears that the most stress- or glucocorticoid-sensitive subfields of the hippocampus identified in translational studies were most strongly associated with childhood maltreatment scores in humans (36, 37).

Interestingly, we also found evidence for an association between maltreatment and volume of the subiculum and presubiculum. Effects on these subfields were more modest. The average reductions in volume between subjects with high vs. low ACE and CTQ scores were 31% and 33% lower in the left subiculum and presubiculum, respectively, than in the left CA2-CA3. Similarly, volume reductions in the CA1 (bilaterally) and left fimbria were 44% and 60% lower than in the left CA2-CA3.

**Table 4. Mean subfield volumes (measured in 0.5-mm$^3$ voxels), 95% confidence intervals, group differences, and effect sizes for subjects with low CTQ scores (range: 25–29, *n* = 60) vs. high CTQ scores (range: 50–103, *n* = 40)**

| Measures | CTQ 25–29 (95% CI) | CTQ ≥ 50 (95% CI) | Group F Group p | D′ (95% CI) |
|---|---|---|---|---|
| Right CA1 | 2,817 (2,740–2,895) | 2,716 (2,618–2,814) | 2.66 0.11 | 0.33 (−0.10 to 0.80) |
| Right CA2-CA3 | 8,654 (8,417–8,890) | 8,329 (8,052–8,606) | 3.10 0.08 | 0.36 (0.00–0.80) |
| Right CA4-DG | 4,780 (4,647–4,912) | 4,631 (4,477–4,786) | 2.07 0.15 | 0.3 (−0.10 to 0.70) |
| Right fimbria | 555.5 (526.6–584.4) | 526.8 (491.2–562.4) | 2.39 0.13 | 0.26 (−0.10 to 0.70) |
| Right subiculum | 5,488 (5,362–5,613) | 5,363 (5,214–5,512) | 2.44 0.12 | 0.26 (−0.10 to 0.60) |
| Right presubiculum | 4,033 (3,936–4,130) | 3,951 (3,822–4,080) | 1.06 0.30 | 0.21 (−0.20 to 0.60) |
| Left CA1 | 2,690 (2,614–2,766) | 2,706 (2,605–2,806) | 0.09 0.76 | 0.05 (−0.30 to 0.50) |
| Left CA2-CA3 | 8,290 (8,058–8,522) | 7,788 (7,486–8,090) | 7.08 0.009 | 0.55 (0.10–0.90) |
| Left CA4-DG | 4,638 (4,517–4,760) | 4,369 (4,204–4,535) | 7.14 0.009 | 0.55 (0.10–1.00) |
| Left fimbria | 680.4 (647.7–713.2) | 654.9 (610.5–699.2) | 1.36 0.25 | 0.19 (−0.20 to 0.60) |
| Left subiculum | 5,583 (5,443–5,724) | 5,413 (5,249–5,576) | 2.76 0.10 | 0.32 (−0.10 to 0.70) |
| Left presubiculum | 4,152 (4,028–4,277) | 3,975 (3,841–4,109) | 3.60 0.06 | 0.39 (0.00–0.80) |

95% CI, 95% confidence interval.

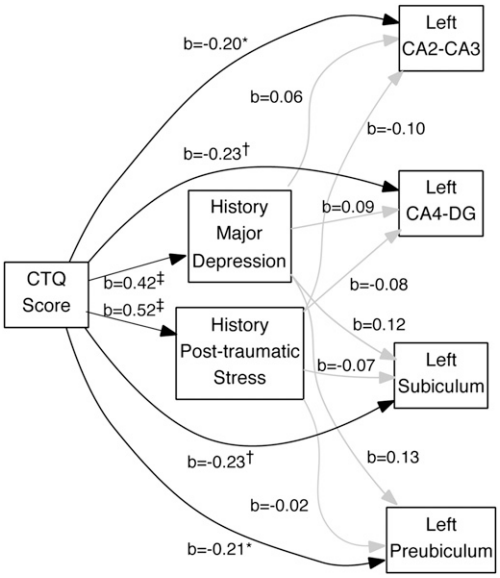


**Fig. 4.** Structural equation model illustrating the best-fitting relationship (b) between CTQ total scores, life histories of MDD or PTSD, and hippocampal subfield volumes showing the strongest associations to maltreatment. Pathways in gray were not significant. Covariance relations between the four subfields and between the two potential mediators were omitted for clarity. $^{*}P < 0.02$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 10^{-6}$.

The apparent vulnerability of the subiculum to maltreatment stress makes sense because it contains a high density of glucocorticoid binding sites (42), perhaps even higher than in the CA1, CA3, CA4 (43), or DG (44). A recent translational study confirmed this vulnerability by showing that elevating corticosterone levels in rats had a robust effect on subicular volume (45). A human autopsy study showed rare but convincing evidence of apoptosis in the subiculum (along with the DG, CA1, and CA4) of patients with chronic MDD (46), and a neuroimaging study of 21 women with unremitting MDD reported that the shape of the left inferior subiculum was deformed (47).

The ventral portion of the subiculum, which is the primary output of the hippocampus, appears to integrate cognitively processed stimuli into appropriate neuroendocrine and behavioral responses to stress (48). A key role of the ventral subiculum is to inhibit hypothalamic-pituitary-adrenal (HPA) axis activity following psychological but not systemic stressors (48, 49). It does so by projecting to the anterior bed nucleus of the stria terminalis, which, in turn, acts as a GABAergic relay to inhibit the paraventricular hypothalamic nuclei responsible for initiating HPA axis response (50).

Further, the ventral subiculum plays a major role in regulating the dopaminergic response to stressors or challenges that are context-dependent (e.g., fear conditioning, drug sensitization) (51). These actions appear to take place through a ventral subiculum-nucleus accumbens pathway (51, 52). The pathway from the subiculum to the accumbens and then to the ventral pallidum and ventral tegmental area (VTA) indirectly regulates the tonic firing pattern of dopamine neurons and the tonic release of dopamine from the VTA into the nucleus accumbens (51). Drug-induced sensitization, a process in which the repeated administration of stimulants, such as cocaine or amphetamine, results in a heightened response to subsequent administrations, depends on this pathway. Inactivating the ventral subiculum in amphetamine-sensitized rats reduces sensitivity to pretreatment levels (51). It is presumably through this pathway that stress exposure interacts with the dopaminergic reward system to produce stress-induced craving and stress-induced relapse (51). Hence, it is plausible that exposure to early stress alters the developmental trajectory of the subiculum and, by doing so, modulates both the HPA axis and dopaminergic responses to subsequent stressors. Several studies have reported HPA axis abnormalities in maltreated individuals (53–55), as well as alterations in blood flow to dopamine-rich regions (56) and reduced left basal ganglia activation to anticipated rewards (57).

The vulnerability of the presubiculum to maltreatment was not presaged by translational findings, although few, if any, studies provided data on the sensitivity of the presubiculum to stress or glucocorticoids. This structure is well-situated to play an important role in working and spatial memory. First, it serves as a bridge between the dorsolateral prefrontal cortex (DLPFC) and hippocampus. Fibers from the DLPFC connect with the presubiculum predominantly through the cingulum bundle (58) and provide the anatomical substrate for a functional interaction between the DLPFC and the hippocampal memory system for the monitoring of information within working memory (59). Second, through interconnections with the entorhinal cortex and inferior parietal cortex, the presubiculum plays an important role in visual spatial integration, navigation, and memory (60). This system for spatial navigation and memory provides a set of processes that likely form the basis for other types of memory, including episodic autobiographical memory (61). Memory problems have often been reported in individuals with maltreatment histories (62, 63).

The present finding that childhood maltreatment was associated most strongly with the volume of the left hippocampal subfields is noteworthy. Prior studies exploring the association between abuse and total hippocampal volume in adults have also reported greater left-sided than right-sided effects. For example, Bremner et al. (17), Stein et al. (19), and Vythilingam et al. (21) reported significant associations between maltreatment and reduced left, but not right, hippocampal volume, and Frodl et al. (18) reported a greater left-sided than right-sided effect. Subjects in these studies were primarily diagnosed with PTSD or depression. A number of studies have reported bilateral hippocampal volume deficits in maltreated individuals with BPD (22, 24–26) or DID (20). In contrast, no studies have reported exclusively right-sided hippocampal deficits in maltreated subjects. Fifty-three percent of subjects with ACE scores ≥3 in the present study had histories of MDD, and 40% met full or partial criteria for PTSD. In contrast, only 13% met criteria for a personality disorder. Hence, we would expect this sample to show primarily left-sided effects (17–19, 21).

Interestingly, unilateral effects have also been observed in translational studies. Zach et al. (45) exposed Long–Evans rats to 3 wk of elevated corticosteroid levels. The volume of the CA1-CA3, DG, and subiculum were substantially reduced but only on the right side. Similarly, neonatal exposure to novelty in Long–Evans rats (a potentially beneficial experience) was found in adulthood to increase right hippocampal volume (64) and to augment short- and long-term potentiation in the right but not left hippocampus (65). Unfortunately, few translational studies examining stress-related effects on the hippocampus provide information on laterality.

One might expect that elevated circulating levels of corticosterone would affect both sides equally, but there are reasons why this need not be so. First, the deleterious effects of glucocorticoids on hippocampal neurons are not direct (2) but may be mediated through an NMDA receptor-dependent mechanism (66). Similarly, the suppressive effects of glucocorticoids on hippocampal neurogenesis depend on NMDA receptors (67). Hence, excess glucocorticoid levels may target hippocampal neurons receiving the greatest degree of glutamatergic stimulation. Second, transmitter systems and receptors are frequently lateralized in density and distribution. Of particular note is the differential distribution of NMDA receptor Glu receptor ε2

subunits in the adult mouse hippocampus between the left and right sides (68). This asymmetry translates into significant differences in NMDA receptor function and degree of synaptic plasticity between the left and right hippocampi (68), which, in turn, may lead to lateralized differences in stress-susceptibility.

This study differs from prior reports examining the relationship between maltreatment and hippocampal volume in a number of ways. It is the largest study reported to date and provides data on specific hippocampal subfields. Software advances (39) made this possible. Subjects were recruited based on exposure without regard to psychopathology. Previous studies in adults have focused on subjects with PTSD, MDD, DID, or BPD. By recruiting subjects based on exposure, we can provide a potentially less biased assessment of the impact of maltreatment, because our sample included some resilient individuals who were exposed to high levels of early adversity but failed to meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD, PTSD, or a personality disorder (i.e., 43% of the sample with ACE scores ≥3). Further, such a heterogeneous sample made it possible to ascertain the degree to which MDD or PTSD mediated the association between maltreatment and subfield volumes. Interestingly, neither MDD nor PTSD was a significant mediator. We suspect that reduced subfield volume is a consequence of maltreatment and a risk factor for developing PTSD following exposure to further traumas, as suggested by Gilbertson et al. (69).

The study also differs because we focused on a narrow age range (18–25 y), which probably helped to reduce between-subject variance attributable either to maturational or aging effects on the hippocampus. Further, we eliminated subjects with exposures to other highly stressful or traumatizing events (e.g., motor vehicle accidents, near drowning) and included only unmedicated individuals. Subjects in the sample were highly educated and came from predominantly middle-class families. The sample was selected to be as free as possible from confounding factors and to provide a good test of our hypotheses. On the other hand, this sample is not fully representative of subjects seen in clinical practice, given their educational attainments, upbringing, and lack of exposure to potential confounding factors. We suspect that hippocampal subfields of less educated and less privileged individuals with exposure to additional forms of early stress may be affected by maltreatment to at least the same degree.

A limitation of the present study, and of all studies reporting potential effects of childhood maltreatment on the adult hippocampus, is the retrospective assessment of maltreatment. Some critics have raised concern about false or "recovered" memories (70) and recall bias, suggesting that subjects in emotional distress will describe their childhood as more stressful or abusive (71). Consequently, one might expect high false-positive rates for adult reports of childhood abuse. The opposite is true, however; adults underreport their degree of exposure (72, 73). Individuals reporting abuse retrospectively were those who typically endured the most severe abuse on prospective assessment (73). This fits with other studies showing that adult reports of abuse are verifiable (74). Exposure to childhood maltreatment in this study was assessed remotely through online report, through in-office self-report, and through an extensive semistructured Traumatic Antecedents Interview (TAI). Subjects reporting maltreatment were consistent across measures and had persistent (not recovered) memories of the experience. The present finding that retrospectively assessed exposure to maltreatment was associated with the greatest effect sizes on hippocampal subfields identified as stress-sensitive in translational studies provides convergent support for the potential accuracy of their reports.

The use of software to measure the volume of hippocampal subfields is potentially a great advantage because it makes it possible to provide measures in large samples and to produce results that can be easily duplicated between laboratories. On the other hand, it is also a potential weakness. Although the software provided good agreement with manual measures for the larger subfields, the degree of agreement for the smaller subfields is low (39). The Dice overlap coefficient, a widely used segmentation evaluation metric, was 0.74 for the CA2-CA3 and subiculum, 0.68 for the CA4-DG and presubiculum, 0.62 for the CA1, and 0.51 for the fimbria (39). This suggests that these measures provide a reasonable and reproducible estimate but are not in complete accord with manual measures. A recent study showed that semiautomated hippocampal subfield measures accorded with expert human raters to the same degree as results from one human rater accorded with those of another human rater (75). Both the fully automated and semiautomated measures provided results in which the average boundary differences between human- and computer-delineated subfields were less than the size of a voxel (39, 75).

Childhood maltreatment increases risk for an array of psychiatric disorders and is associated with an earlier age of onset, more severe course, and poorer response to treatment (e.g., 76–78). This is likely attributable, at least in part, to early stress-induced alterations in trajectories of brain development (79). The hippocampus is a primary target, and delineating the effects of maltreatment on specific hippocampal subfields may shed new light onto these associations. Perhaps the most intriguing finding to emerge from this study was evidence for maltreatment-related alterations in the subiculum, given the importance of this region in the regulation of the HPA axis (50), dopaminergic responses to stress, and risk for substance abuse and psychosis (51). The present study also underscores the potential of translational research to identify neurobiological consequences of exposure to early stress that prefigure and augment neuroimaging findings in maltreated individuals (80).

## Materials and Methods

**Subjects.** This study was approved by the McLean Hospital Institutional Review Board. All subjects provided informed written consent. Our goal was to recruit a sample of subjects from the general community that would provide a rigorous test of our proposed hypotheses with as few confounding factors as possible, and without the subjects' awareness of our specific entry criteria. To meet this aim, we recruited unmedicated, right-handed, 18- to 25-y-olds from the community through advertisements on mass transit and in newspapers with the tag line "Memories of Childhood." Interested subjects were informed that we were conducting a study on the influence of early experience on brain development and provided with a URL and password to an online enrollment system that collected extensive information (2,342 fields) about their developmental and medical history, degree of exposure to various forms of childhood maltreatment, and current symptomatology. Collected information was reviewed to exclude subjects with premature birth or birth complications, maternal substance abuse during pregnancy, or medical disorders that could affect brain development. Subjects were required to be free from neurological disease (including migraine headaches) or head trauma resulting in loss of consciousness for more than a few seconds, or for any duration if head scans were obtained. Subjects were also excluded who had experienced multiple unrelated forms of adversity, including natural disaster, motor vehicle accidents, animal attack, near-drowning, house fire, mugging, witnessing or experiencing war, gang violence or murder, riot, or assault with a weapon. Overall, 1,662 subjects provided complete online information. (The number of subjects meeting specific exclusion criteria is provided in *SI Text*.)

We invited all subjects who appeared to meet criteria to the laboratory for interviews. Subjects selected for interview had no history of childhood maltreatment, reported exposure to a specific type of childhood maltreatment (e.g., parental verbal abuse), or exposure to one or more maltreatment-related events (i.e., physical abuse, sexual abuse, witnessing of domestic violence) that fulfilled the DSM-IV axis 1 and axis 2 criteria for a traumatic experience. Subjects were selected without regard to psychiatric history, except for relatively high levels of drug or alcohol use, which were grounds for exclusion. Selecting subjects meeting criteria for a specific disorder could bias results by only including the most severely affected subjects. Conversely, selecting subjects without any psychiatric history could bias results in the opposite direction. Nearly all subjects invited for interviews came in ($n = 452$), although 60 of the interviewed subjects were eliminated for ongoing drug use or because their experiences as elaborated on during the interview differed in significant ways from their online responses and rendered them

ineligible. From the fully assessed sample of 392, a subset of 193 subjects (~50%) underwent neuroimaging as per protocol. Neuroimaged subjects used alcohol to only a modest extent (median of 7 drinks per month), and degree of use was unrelated to early adversity [e.g., ACE score: $F(1,191) = 0.001$, $P > 0.9$]. Similarly, drug use was extremely low (median of 0 d per month) and unrelated to early adversity [e.g., ACE score: $F(1,181) = 0.50$, $P > 0.4$]. No subjects met criteria for drug or alcohol dependence on interview. All subjects tested negative for drug use by urinalysis and for recent alcohol consumption by breath test. Subjects were paid $20 for completing the online assessment; $50 per interview and assessment session (typically two 4-h sessions); and $150 for the MRI protocol, which lasted up to 2 h.

**Assessments.** The Structured Clinical Interview for DSM-IV axis I and II psychiatric disorders (SCID) (81), supplemented by the attention deficit/hyperactivity disorder section of the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (82), was used for diagnoses. Maltreatment was assessed using the 100-item semistructured TAI (83). This interview evaluates reports of physical or sexual abuse, witnessing violence, physical or emotional neglect, significant separations or losses, verbal abuse, or parental discord (84). The reliability of the TAI variables ranges from acceptable to excellent (median intraclass $r = 0.73$) (84). Subjects were also evaluated using the CTQ (85, 86), and both self-report and interview versions of the Conflict-Tactic Scales (CTS) (87). Information from the TAI and CTS was used to determine their ACE score (88, 89) based on criteria delineated by Anda et al. (16). ACE scores indicate the number of different types of adversity an individual experienced during his or her first 18 y of life. These include recurrent emotional abuse; recurrent physical abuse; sexual abuse; living with an alcoholic or substance abuser; having a depressed, mentally ill, or suicidal household member; having a mother or stepmother treated violently; having a household member go to prison; and parental separation or divorce. Subjects received one point for each different type of adversity experienced; scores range from 0–8. The CTQ (85, 86) is a 28-item self-report inventory that provides a brief, reliable, and valid screen for histories of abuse and neglect. It inquires about five types of maltreatment: emotional, physical, and sexual abuse and emotional and physical neglect. Scores on each part (range: 5–25) were summed to provide a total score (potential range: 25–125).

Low income and poverty may be important developmental risk factors. Young adult subjects were often uncertain about parental income while they were growing up. However, they were well aware of the degree of perceived financial sufficiency or stress they experienced during this time. This was rated from 1 (much less than enough money for our needs) to 5 (much more than enough money for our needs). In all cases, perceived financial sufficiency explained a greater share of the variance in ratings of depression, anxiety, anger-hostility, and dissociation than combined family income. Instead of a composite measure of socioeconomic status, we included both the subject's level of perceived financial stress and parental education, because studies suggest that these factors may provide more meaningful covariates than a composite score (90). Certified mental health clinicians (psychologists with a doctoral degree, clinical nurse specialists) conducted the assessment and evaluation interviews and were blinded to the neuroimaging results.

**MRI Acquisition.** High-resolution, T1-weighted MRI datasets were acquired on a Trio Scanner (3-T; Siemens AG, Siemens Medical Solutions). An inversion, 3D, magnetic prepared rapid acquisition gradient echo sequence was used with an eight-element, phased-array, radiofrequency reception coil (Siemens AG). The generalized autocalibrating partially parallel acquisition (GRAPPA) acquisition and processing were used to reduce the scan time, with a GRAPPA factor of 2. Scan parameters were as follows: the sagittal plane, echo time/repetition time/inversion time/flip angle = 2.74 ms/2.1 s/1.1 s/12°; 3D matrix of $256 \times 256 \times 128$ on a $256 \times 256 \times 170$-mm field of view; bandwidth = 48.6 kHz; and scan time = 4 min and 56 s.

**MRI Analysis.** Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (91–98). Briefly, this process includes motion correction, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure (94), automated Talairach transformation, segmentation of the subcortical white matter and deep GMV structures (93, 96), intensity normalization (99), tessellation of the gray matter/white matter boundary, automated topology correction (97, 100), and surface deformation following intensity gradients to place the gray/white and gray/cerebrospinal fluid borders optimally at the location where the greatest shift in intensity defines the transition to the other tissue type (91, 92, 98).

The hippocampus was analyzed from the FreeSurfer "aseg.mgz," "nu.mgz," and "talairach.xfm" files via a tetrahedrical mesh-based probabilistic atlas that is deformed from its reference position by sampling from a Markov random field model regulating the position of the mesh nodes (39). The segmentations used for atlas computation were based on manual delineations of hippocampal subfields in ultrahigh-resolution, T1-weighted MRI scans. These delineations include the fimbria, CA1, CA2-CA3, CA4-DG, subiculum, and presubiculum. Analyses were conducted on a cuboid region of interest (ROI) that encompasses all the delineated structures. Segmentation of structures within the ROI proceeded by first estimating the model parameters from the data using an iterative generalized expectation-maximization algorithm, and the optimal segmentation solution was then generated by assigning each voxel to the label with the highest posterior probability (39).

**Statistics.** Data analyses were conducted in R (101). We sought to test the hypothesis that childhood maltreatment was associated with maximal statistical effects on hippocampal subfields containing the DG and CA3 using multiple regression/analysis of covariance procedures. Degree of exposure to maltreatment was measured in two ways. First, we used the subjects' ACE score, which indicates the number of different types of maltreatment-related adversity events they experienced (16). Several studies have shown a graded "dose-dependent" relationship between ACE score and risk for psychopathology (14, 15, 102). However, because the ACE score only focuses on the number of different types of maltreatment experienced and ignores severity or frequency, we used participants' total CTQ score as a second metric. The ACE and CTQ provide complementary but relatively distinct perspectives ($r = 0.682$). Because subjects differed in their degree of exposure to childhood maltreatment, we assessed whether there was a graded relationship between extent of exposure and subfield volume controlling for differences in subcortical GMV, age, gender, and socioeconomic factors, provided that the covariates had at least a modest relationship to the dependent variable ($P < 0.2$) and that the elimination of poorer fitting covariates did not significantly worsen overall fit. In this way, we assessed the relationship between exposure and subfield volume using parsimonious models. Using full models with all covariates produced nearly identical results (parsimonious vs. full models: ACE score, $r = 0.995$; CTQ score, $r = 0.994$). Using ACE and CTQ scores as quantitative measures and assessing the percentage of variance explained by these ratings provides more power than dividing the sample into discrete groupings. However, comparisons were also made between subjects with the lowest scores and subjects with high levels of exposure on each instrument.

Quantile-comparison plots of the studentized residuals were used to check for normality of distributed errors, which was met to a satisfactory degree, and spread level plots were used to check for heteroscedasticity, which was acceptable. We used a state-of-the-art approach to gauge the relative importance of the individual regressors in the multiple regression as a measure of effect size. Assessment of relative importance in linear models is simple in the special case in which all regressors are uncorrelated. Each regressor's contribution is then its univariate $r^2$, and all univariate $r^2$ values add up to the full-model $r^2$. This is rarely true with observational data. Regressors are typically correlated, such that special computational techniques are required to break down model $r^2$ into shares from the individual regressors (41). Hence, we used a technique for variance decomposition developed by Lindeman et al. (40) to gauge relative importance more accurately. Briefly, this technique decomposes $r^2$ by calculating the sequential contribution of each regressor (in which the contribution of a regressor depends on the regressors that come before) by averaging over all possible sequential orderings (R package "relaimpo").

Structural equation models (R package "OpenMx") were used to assess the interrelationship between CTQ scores, volume measures, and lifetime history of MDD and/or PTSD as a potential mediator, based on the hypothesis that a history of MDD or PTSD (particularly during childhood or adolescence) may have had an impact on trajectories of brain development and may be more meaningful than current scores on a rating scale. A separate analysis was also conducted using current depression (103) and PTSD scores (104) instead of lifetime histories. Subjects were assigned a score of 1 for MDD or PTSD if they met past or present DSM-IV criteria. A score of 0.5 was given to subjects who met almost all the criteria but were a few items short. Otherwise, they received a score of 0. Goodness of fit was evaluated using a combination of absolute fit and relative fit indices to minimize type I and type II errors (105). Absolute fit was evaluated by $\chi^2$ and SRMR. A significant $\chi^2$ indicates that the model can be rejected. SRMR values less than 0.08 are indicative of a good fit (105). Relative fit indices (NFI, TLI, CFI and IFI) with values greater than 0.95 are indicative of good fits.

**ACKNOWLEDGMENTS.** We thank Dr. Carryl P. Navalta, Dr. Catherine Flag, and Ms. Karen Rabi for assessing the subjects and Ms. Cynthia McGreenery and Elizabeth Bolger for recruitment and study coordination. Financial support was provided by National Institute of Mental Health RO1 Awards MH-66222 and MH-091391 as well as National Institute of Drug Abuse RO1 Awards DA-016934 and DA-017846 (to M.H.T.), along with support from the National Alliance for Research on Schizophrenia and Depression to M.H.T. as a John W. Alden Trust Investigator.

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