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Brief report

# Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: A meta-analysis

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**Abstract**

*Background:* Studies in animals showed that the hippocampus, a brain area involved in learning and memory, is sensitive to stress. Although several MRI studies showed smaller hippocampal volume in adults with chronic PTSD, others did not show significant differences from controls. These studies are typified by small sample sizes which may limit the ability to show significant differences. We therefore performed a meta-analytic study of all of these studies to clarify the role of hippocampal structural changes in subjects with PTSD.
*Methods:* Nine studies with a total of 133 adult subjects with chronic PTSD, 148 healthy controls, and 53 traumatized controls were included in the meta-analysis.
*Results:* There was significantly smaller volume in both right and left hippocampi in adult subjects with chronic PTSD in comparison with both healthy controls and traumatized controls.
*Conclusion:* These findings are consistent with smaller hippocampal volume in adult subjects with chronic PTSD.


*Keywords:* PTSD; Meta-analysis; Hippocampus; MRI; Hippocampal volume

## 1. Introduction

Posttraumatic Stress Disorder (PTSD) is a highly prevalent disorder affecting 8% of the population by some estimates (Kessler et al., 1995). Understanding

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the neurobiology of PTSD is important for the development of new treatments for this disorder. One area of intensive investigation has been related to the hippocampus, a brain area involved in learning memory, and probably emotional regulation.

Studies in animals suggest that stress results in structural changes in the hippocampus (McEwen et al., 1992; Sapolsky, 1996). Psychosocial stress in monkeys (Sapolsky et al., 1990; Uno et al., 1989) and tree shrews (Magarinos et al., 1996) resulted in decreased dendritic branching and/or neuronal loss in the CA3 region of the hippocampus. It was demonstrated in various animal species and across studies that direct glucocorticoid exposure resulted in decreased dendritic branching (Packan and Sapolsky, 1990; Virgin et al., 1991; Woolley et al., 1990), and alterations in synaptic terminal structure (Magarinos and McEwen, 1995; Magarinos et al., 1997). Stress also results in an inhibition of neuronal regeneration (Gould et al., 1998) within the hippocampus. Mechanisms proposed for these findings have included stress induced elevations in glucocorticoids (Armanini et al., 1990; Lawrence and Sapolsky, 1994; Sapolsky, 1986; Sapolsky et al., 1988) and/or or decreased brain derived neurotrophic factor (BDNF) (Nibuya et al., 1995). These findings are consistent with the hypothesis that stress is associated with hippocampal damage.

Stressors were also associated with deficits in memory function that are mediated by the hippocampus. Stress was associated with both deficits in working memory tasks, as well as an inhibition of long-term potentiation, which is dependent on the *N*-methyl-D-aspartate (NMDA; excitatory amino acid) receptor (highly concentrated in the hippocampus) felt to represent a model for memory at the molecular level (Diamond et al., 1995, 1996).

The first report regarding structural changes in the human central nervous system in PTSD showed smaller hippocampal volume as demonstrated with magnetic resonance imaging (MRI) volumetrics (Bremner et al., 1995). This study involved subjects with a history of Vietnam combat-related traumatic stress and the diagnosis of PTSD and suggested the possibility that exposure to extreme stressors may reduce the volume of the hippocampus in subjects with PTSD.

Since then, nine studies have been conducted which assessed hippocampal volume in adults with chronic PTSD. Although many studies showed smaller hippocampal volume in PTSD (Bremner et al., 1995, 1997; Bremner et al., 2003; Gurvits et al., 1996; Villarreal et al., 2002), others did not (Stein et al., 1997; Notestine et al., 2002; Schuff et al., 2001; Gilbertson et al., 2002). Studies in children with PTSD (De Bellis et al., 2001, 1999; Carrion et al., 2001) and subjects with new onset PTSD (Bonne et al., 2001) did not find changes in hippocampal volume. Furthermore, there was variation in the side in which significance was found. Since there were only a mean of 14.8 ($\pm$ 5.8 SD) (range 7–25, median 12.0) subjects with PTSD on average in these nine studies, there was not sufficient statistical power to consistently demonstrate an effect in many of these studies. Therefore, we performed a meta-analytic study that combines all of the known studies to better estimate the role of hippocampal structural changes in adult subjects with chronic PTSD. Meta-analysis provides a method for combining quantitative data (including confidence intervals of the overall effect size) from multiple studies. Furthermore, it has the advantage of producing more definitive overall conclusions with an increased statistical power. In addition, factors causing heterogeneity in the results reported by individual studies can be investigated (Thompson et al., 1997). We also compared other factors including trauma type, gender, right and left hippocampal volume, and whether findings were specific to PTSD or were a non-specific effect of traumatic exposure.

## 2. Materials and methods

### 2.1. Study ascertainment

Published reports that evaluated hippocampal volume differences between adult subjects with chronic PTSD and comparison subjects using MRI techniques were obtained through the use of computerized databases (MEDLINE, PsycINFO), using the words “PTSD”, “MRI”, and “hippocampal volume”, and by searching the bibliographies of relevant studies. To be included, published studies had to meet the following inclusion criteria: (1) studies must involve a comparison of adults with chronic PTSD to comparison subjects; (2) means and standard deviations for hippocampal volumes had to be reported, and; (3) the

Table 1
Demographic and scan information for 133 patients with PTSD, 148 healthy control subjects, and 53 traumatized control subjects

| Study | Population | Age patients (years ± SD) | Age healthy controls (years ± SD) | Age traumatized controls (years ± SD) | Gender of patients | Number of patients | Number of healthy controls | Number of traumatized controls | Slice width (mm) | Diagnostic criteria |
|---|---|---|---|---|---|---|---|---|---|---|
| Bremner et al., 1995 | Vietnam Combat | 46.0 ± 1.8 | 44.5 ± 7.3 | N/A | Male | 25 | 22 | N/A | 3.0 | DSM-III-R (SCID[a]), Mississippi Scale for Combat-Related PTSD |
| Bremner et al., 1997 | Abuse | 40.1 ± 5.7 | 42.4 ± 7.3 | N/A | Male 12, Female 5 | 17 | 17 | N/A | 3.0 | DSM-III-R or psychiatric interview |
| Bremner et al., 2003 | Abuse | 35 ± 6 | 38 ± 7 | 32 ± 8 | Female | 10 | 11 | 12 | 3.0 | DSM-IV (SCID) |
| Gurvits et al., 1996 | Vietnam Combat | 44.4 ± 1.7 | 38.1 ± 10.0 | 47.6 ± 2.9 | Male | 7 | 8 | 7 | 3.0 | DSM-III-R (SCID, CAPS[b]) |
| Stein et al., 1997 | Abuse | 32.0 ± 6.3 | 30.2 ± 6.4 | N/A | Female | 21 | 21 | N/A | 4.0 | DSM-IV(SCID, SCID-D[c], CAPS) |
| Notestine et al., 2002 | Partner violence | 33.5 ± 10.3 | 35.3 ± 12.5 | 35.4 ± 9.6 | Female | 11 | 17 | 11 | 4.0 | DSM-IV (SCID, CAPS) |
| Villarreal et al., 2002 | Variousness | 43 ± 9.3 | 44 ± 11.4 | N/A | Male 2, Female 10 | 12 | 10 | N/A | 1.5 | DSM-IV (SCID, CAPS) |
| Gilbertson et al., 2002 | Vietnam Combat | 53.1 ± 3.3 | 51.8 ± 2.3 | 51.8 ± 2.3 | Male | 12 | 23 | 23 | 3.0 | DSM-IV (SCID, CAPS) |
| Schuff et al., 2001 | Combat-related | 51.2 ± 2.5 | 51.8 ± 3.2 | N/A | Male | 18 | 19 | N/A | 3.0 | DSM-IV (SCID, CAPS) |

[a] Structured interview for DSM.
[b] Clinician-administered PTSD scale.
[c] DSM-IV dissociative disorders.

study could not have used duplicate subjects from another published study. This search identified 9 studies published between 1995 and 2003 (listed in Table 1).

### 2.2. Statistical analysis

All analyses were conducted in SAS using a series of macros developed for meta-analysis (Winfred et al., 2001). First, standardized mean differences were computed for each study using the Hedges $g_U$. This estimator was chosen among other effect size estimators because it is unbiased and has good properties for small sample sizes (Hedges and Olkin, 1985). Subsequently, a pooled estimate of the combined estimator for the effect size was calculated by weighing each effect size estimate by the inverse of its variance. The 95% confidence interval around the pooled estimate was also calculated.

Separate meta-analyses were performed for studies that used healthy controls and for studies that used non-PTSD traumatized controls. Data for left and right hippocampus were pooled separately, and subsequently combined in order to test whether results differed according to side (left or right) using random-effects ANOVA models. In addition to side, in these models we tested whether study results differed according to gender, i.e., according to whether the studies used male or female subjects or both. This method also allowed for the testing of heterogeneity within study groups (Hedges, 1994). Specifically, the total heterogeneity statistic can be partitioned into two components: (a) heterogeneity between groups of studies and (b) heterogeneity within groups of studies. Two statistics can be calculated: $Q_{\mathrm{BETWEEN}}$, which tests the null hypothesis that there is no variation in mean effect sizes between $p$ groups of studies classified according to specific characteristics (in our meta-analysis, brain side and gender); and $Q_{\mathrm{WITHIN}}$, which tests the null hypothesis that there is no variation in $k$ mean effect sizes within $p$ groups of studies. If $Q$ exceeds the upper-tail critical value of the chi-square distribution with $p-1$ degrees of freedom for between-group comparisons and $k$–$p$ degrees of freedom for within-group comparisons, the observed heterogeneity in study effect sizes is significantly greater than expected under the null hypotheses.

## 3. Results

Our search identified 9 studies published between 1995 and 2003. Demographic information on adult subjects with chronic PTSD and control subjects and other characteristics of the studies included in this analysis are provided in Table 1. Gilbertson's study (Gilbertson et al., 2002) includes two types of twin pairs. The one is trauma exposed subject with PTSD (ExP+) and his co-twin who had no exposure without PTSD (UxP+). The other is trauma exposed subject without PTSD (ExP−) and his co-twin who had no exposure without PTSD (UxP−). We counted ExP+ into adults with chronic PTSD, ExP− into traumatized non-PTSD control subjects, UxP− into healthy subjects. However, UxP+ was not considered in the present study because it might be affected by hereditary factors.

In some studies, smaller hippocampal volume was found in adults with chronic PTSD in comparison with healthy control subjects for *both left and right hippocampus* (Bremner et al., 2003; Gilbertson et al., 2002; Gurvits et al., 1996; Villarreal et al., 2002); in others, on the *left side alone* (Bremner et al., 1997; Stein et al., 1997) and yet in others on the *right side alone* (Bremner et al., 1995). Other studies did not show significantly smaller volume of the hippocampus in comparison with healthy subjects (Notestine et al., 2002; Schuff et al., 2001). Studies comparing PTSD to traumatized non-PTSD control subjects showed significantly smaller volumes in some studies (Bremner et al., 2003; Gurvits et al., 1996) but not in others (Notestine et al., 2002; Schuff et al., 2001).

Individual study results are provided in Table 2. The study effect sizes are expressed as standardized mean difference using the Hedges' $g_U$ estimator. If the upper limit of the 95% confidence interval is negative, the hippocampus of subjects with PTSD is significantly smaller than the hippocampus of control subjects. The pooled results are shown in Table 3. The pooled effect size estimate and its 95% confidence interval showed a significantly smaller volume of the hippocampus for both right and left hippocampi in adult subjects with chronic PTSD when compared with healthy control subjects, as well as when compared with trauma control subjects. The test of heterogeneity indicated no significant *between*

Table 2
Mean hippocampal volume, effect size (Hedges' $g_U$) and 95% confidence interval (CI)

| Study of adult patients with chronic PTSD | Mean hippocampal volume ($mm^3$) | | | | | | Effect size | |
|---|---|---|---|---|---|---|---|---|
| | Patients (± SD) | | Healthy control subjects (± SD) | | Traumatized control subjects (± SD) | | Hedges' $g_U$ (95% CI; lower, upper) | |
| | Left | Right | Left | Right | Left | Right | Left | Right |
| Bremner et al., 1995 | 1186 (138) | 1184 (142) | 1233 (163) | 1286 (175) | N/A | N/A | −0.308 (−0.884, 0.269) | −0.634 (−1.22, −0.0466) |
| Bremner et al., 1997 | 1050 (152) | 1062 (169) | 1193 (142) | 1116 (190) | N/A | N/A | −0.949 (−1.66, −0.2401) | −0.293 (−0.969, 0.383) |
| Bremner et al., 2003 | 973 (162) | 915 (179) | 1150 (189) | 1101 (174) | 1150 (189) | 1101 (174) | −0.961 (−1.87, −0.0570) | −1.01 (−1.92, −0.103) |
| Gurvits et al., 1996 | 3200 (300) | 3200 (600) | 4400 (300) | 4600 (400) | 4300 (300) | 4100 (400) | −3.76 (−5.45, −2.08) | −2.62 (−4.01, −1.24) |
| Stein et al., 1997 | 2097 (169) | 2194 (181) | 2160 (210) | 2307 (193) | N/A | N/A | −0.324 (−0.933, 0.285) | −0.593 (−1.21, 0.0254) |
| Notestine et al., 2002 | 5031 (675) | 5267 (556) | 5183 (538) | 5203 (724) | 5021 (812) | 4768 (763) | −0.247 (−1.01, 0.514) | 0.092 (−0.666, 0.851) |
| Villarreal et al., 2002 | 2950 (310) | 3010 (290) | 3380 (490) | 3350 (370) | N/A | N/A | −1.03 (−1.92, −0.138) | −0.996 (−1.89, −0.107) |
| Schuff et al., 2001 | 3240 (417) | 3460 (424) | 3292 (399) | 3364 (384) | N/A | N/A | −0.125 (−0.770, 0.521) | 0.233 (−0.414, 0.879) |
| Gilbertson et al., 2002 | 3340 (460) | 3320 (590) | 3630 (450) | 3610 (480) | 3650 (500) | 3760 (540) | −0.625 (−1.34, 0.0881) | −0.558 (−1.27, 0.152) |

and *within* variation in study effect sizes according to side (left or right) or gender. An analysis of studies in children found no differences in hippocampal volume between children with PTSD (Carrion et al., 2001; De Bellis et al., 2001, 1999) and comparison subjects when results from the individual studies were pooled.

## 4. Discussion

This meta-analysis of published magnetic resonance imaging (MRI) volumetric studies in the field of PTSD showed that adult subjects with chronic PTSD have smaller hippocampal volume in comparison to both healthy subjects and traumatized subjects without PTSD. PTSD subjects showed smaller volumes for both the left and the right hippocampus. Furthermore, smaller volumes were also shown in both for subjects with PTSD related to combat exposure and with childhood abuse, and for both men and women. Smaller hippocampal volume was not seen in children with PTSD, or subjects with new onset PTSD. These studies suggest that smaller hippocampal volume may be related to illness duration or aging. The findings suggest that smaller hippocampal volume is specific to PTSD (i.e., that it is not a non-specific outcome following exposure to traumatic stress), and does not preferentially affect the left or right side. The findings also suggest that smaller hippocampal volume is not affected by gender or trauma type.

There are several possible explanations for smaller hippocampal volume in PTSD. As reviewed above in the introduction of this paper, stress is associated with several factors that could be associated with hippocampal neuronal damage and subsequent reduction in volume, including increased glucocorticoid secretion,

Table 3
Results of meta-analysis

| | Hedges' $g_U$ | 95% CI (lower, upper) |
|---|---|---|
| *Adults PTSD vs. healthy controls* | | |
| *Left* hippocampus | −0.568[a] | −0.813, −0.322 |
| *Right* hippocampus | −0.491[a] | −0.735, −0.247 |
| *Adults PTSD vs. traumatized controls* | | |
| *Left* hippocampus | −0.732[a] | −1.18, −0.287 |
| *Right* hippocampus | −0.560[a] | −0.998, −0.122 |

[a] $p < 0.002$.

inhibition of neurogenesis, and reductions in BDNF. It is also possible that subjects with smaller hippocampal volume are predisposed to develop PTSD following exposure to a traumatic event. It is known that a considerable portion of the variance in PTSD is genetic (Goldberg et al., 1990). Studies showing increases in hippocampal volume following treatment with selective serotonin reuptake inhibitors (SSRIs), however, are not consistent with this hypothesis (Vermetten et al., 2003). Some authors have argued that other factors, such as alcohol abuse, substance abuse, or depression, may account for smaller hippocampal volume in PTSD. Alcohol has been shown to be associated with hippocampal damage in animal studies (Walker et al., 1993). Alcoholics with recent alcohol exposure have smaller hippocampal volume that does not correlate with quantity of alcohol exposure (Sullivan et al., 1995), as well as enlarged ventricles and decreased gray and white matter volumes (Jernigan et al., 1991; Pfefferbaum et al., 1992; Sullivan et al., 1995). Gray and white matter deficits, however, continue to revert to normal for up to 1 year after abstinence (Pfefferbaum et al., 1995). Since published studies of adults with chronic PTSD excluded patients without 6 months or a year of abstinence, this makes alcohol a less likely explanation of smaller hippocampal volume in PTSD. There is less evidence for an effect of other substances on the hippocampus. With regard to depression, the published studies in PTSD show a greater magnitude of change in hippocampal volume than studies in depression. It was also recently shown that women with depression and early childhood abuse (but not women with depression without early trauma) have smaller hippocampal volume than non-depressed, non-traumatized women (Vythilingam et al., 2002). These findings suggest that traumatic stress plays an important role to find small hippocampal volume in a psychiatric disorder.

Using voxel-based morphometry, Yamasue et al. (2003) demonstrated a reduction in gray-matter volume in anterior cingulate cortex but not in hippocampus in traumatized subjects with PTSD. This study had a small number of subjects, not all of whom had current PTSD. In addition, PTSD was not chronic and was associated with less comorbidity.

The results of this study suggest that smaller hippocampal volume is seen only in adults with chronic PTSD. Studies have not found smaller hippocampal volume in children with PTSD. A pooled analysis of three published studies in children with PTSD (Carrion et al., 2001; De Bellis et al., 2001, 1999) showed no difference in hippocampal volume between PTSD and controls. A single study of patients with new onset PTSD (Bonne et al., 2001) showed no difference in volume in comparison to controls. The current study included in a single meta-analysis studies of adult patients with chronic PTSD. We elected not to include children and studies of new onset PTSD because: (1) these represent different populations; (2) there were large differences in effects seen, suggesting a difference in the relationship between hippocampal volume and diagnosis compared to adults with chronic PTSD. Some authors have suggested that neurodevelopmental plasticity and normal developmental increases in the hippocampus may mask any effects of traumatic stress on children with PTSD (De Bellis et al., 2001). It is also not known whether the children in these studies will go on to develop chronic PTSD as adults, and whether this factor determines the development of smaller hippocampal seen in adults with chronic PTSD from childhood abuse.

Gilbertson et al. (2002) hypothesized that smaller hippocampal volume precedes the development of PTSD and constitutes a risk factor for the development of chronic PTSD. Their study in twins is consistent with a genetic contribution to smaller hippocampal volume in PTSD. The current meta-analysis is consistent with smaller hippocampal volume in PTSD; however, the results do not provide any data for or against the genetic or environmental hypotheses of smaller hippocampal volume in PTSD.

There are several limitations to the current study which are worthy of mention. First of all, the lack of publication of studies with negative results may lead to a publication bias that inappropriately gives greater weight to positive studies. We have tried to find all publications related to this topic. We are not aware of any studies that have not been published, however we cannot rule out the possibility that there are unpublished studies with negative results. Because of the interest in the topic we feel that most of the methodologically sound studies would have had the opportunity to be published, and that a publication bias is unlikely. Second of all, meta-analyses have been criticized for including studies with varying methods

(Hunter and Schmidt, 1990). MRI volumetric studies typically show considerable variation in a variety of factors. The studies included in the meta analysis show great variability in scanner type, slice thickness, scanner resolution, field of view, software, methods for definition of the hippocampus, and so on. Probably because of this, values for hippocampal volume in the studies included in the current meta-analysis show considerable variation. These differences between studies, however, would add greater variability in the results, leading to a tendency to reduce the ability to show differences between PTSD and comparison groups in a meta-analysis, rather than the opposite.

In summary, this meta-analysis is consistent with smaller hippocampal volume in adults with chronic PTSD. Future longitudinal studies are required to more fully explore the relationship between hippocampal volume and PTSD.

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