Evidence of resilience: Neuroimaging in former prisoners of war

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Received 10 May 2005; received in revised form 11 July 2005; accepted 15 July 2005

Abstract

In this study, single voxel proton magnetic resonance spectroscopic imaging (1H-MRS) and volumetric analysis of hippocampal magnetic resonance imaging (MRI) images were used to determine if any differences in hippocampal biochemistry or volume were present between former prisoners of war (POWs) with and without posttraumatic stress disorder (PTSD) and control subjects matched for age and education. This study did not find lower hippocampal concentrations of N-acetylaspartate (NAA), smaller hippocampal volumes, or more impaired memory function in older veterans with PTSD compared with a group matched for traumatic experience or a nontraumatized control group.

Published by Elsevier Ireland Ltd.

Keywords: Posttraumatic stress disorder; Hippocampus; Magnetic resonance spectroscopy; N-acetylaspartate

1. Introduction

Posttraumatic stress disorder (PTSD) has been a focus of attention for neuroimaging research over the last decade. During that time, a number of human research studies have implicated various brain regions in this condition, including portions of the frontal lobe, the amygdala, and the hippocampus (Villarreal and King, 2001). This last structure has received the most attention in structural imaging studies, due to the relationships between stress and hippocampal atrophy demonstrated in several animal studies (Sapolsky, 1996). To date, most studies of PTSD subjects using magnetic resonance imaging (MRI) have shown that these subjects have smaller hippocampal volumes than matched controls. Studies using proton magnetic resonance spectroscopy (1H-MRS) have typically also revealed abnormalities in hippocampal biochemistry in PTSD subjects, commonly showing lower levels of hippocampal N-acetylaspartate (NAA), an excitatory neurotrans-
mitter associated with neuronal integrity, in PTSD subjects relative to controls (Villarreal et al., 2002). Considerable debate continues regarding the meaning of these findings in PTSD subjects. Smaller hippocampal volumes or altered hippocampal biochemistry could either precede a traumatic event and predispose individuals to PTSD or follow the traumatic event as a consequence of neurobiological changes associated with extreme stress. Evidence for both arguments has been put forward (Gilbertson et al., 2002; Bremner et al., 1995). Given the widespread prevalence of PTSD in the population, another very practical focus for investigation is the study of possible ongoing negative neurobiological and cognitive consequences associated with chronic PTSD. Most neuroimaging studies that have shown significant differences in hippocampal biochemistry or structure among PTSD subjects have been completed in individuals who have had the disorder for decades. Studies of children or more recent victims of trauma typically do not reveal similar differences in hippocampal biochemistry or structure (Bonne et al., 2001; De Bellis et al., 2001), though there are exceptions (Wignall et al., 2004). This suggests that if the smaller hippocampal volumes and altered neurochemistry associated with PTSD are not purely premorbid to the index traumatic event, the processes leading to these deleterious outcomes may continue to act over the affected individual’s lifetime.

To investigate the possibility of accelerated neurobiological decline in subjects with chronic PTSD, investigators might need to construct longitudinal studies that last for decades, since longitudinal neuroimaging studies that have examined PTSD subjects over time frames of 6 months to 2 years have not shown significant changes in hippocampal structure during that time (Bonne et al., 2001; De Bellis et al., 2001). An alternative strategy that would not necessitate the logistical problems associated with longitudinal studies lasting decades would be to examine older subjects who have been exposed to significant, documented traumas earlier in life and who have met criteria for PTSD for the majority of their lives. Examining hippocampal morphometry and biochemistry in these subjects could shed light on the chronic neurobiological consequences of lifelong PTSD.

Former prisoners of war (POWs) have frequently been the focus of research efforts into the relationship of severe early adult trauma to psychopathology and cognitive functioning, though few neuroimaging studies have examined this population. Former POWs have been shown to have a high prevalence of PTSD. A number of studies suggest that 30% to 70% of former POWs meet lifetime criteria for PTSD (Sutker et al., 1993; Engdahl et al., 1997). In addition to experiencing a high rate of PTSD, former POWs have demonstrated a direct relationship between their weight loss during captivity and their current PTSD symptoms. We have found that the documented percentage weight loss during POW internment is strongly correlated with PTSD symptom severity six decades after the original trauma (Myers et al., 2005). Despite a clear research interest in this subject group, investigations of former POWs have tended to focus on issues of cognitive function (Sutker et al., 1990; Sulway et al., 1996) and reports of psychopathology (Sutker et al., 1993; Engdahl et al., 1997), with little attention paid to neuroimaging, though one early study did examine the relationship of sleep disturbances to the ventricle/brain ratio as determined by computed tomographic imaging (Peters et al., 1990) in former Japanese held POWs, and one more recent study (Brown et al., 2003) examined differences in medial temporal lobe (MTL) biochemistry between former POWs with and without PTSD using magnetic resonance spectroscopy (MRS).

Our goals in this study were to expand on our previous work by examining the \(^1\)H-MRS measures of hippocampal biochemistry, hippocampal volumes, and neuropsychological findings in three groups of subjects: former POW subjects with PTSD, former POW subjects without PTSD, and control subjects matched for age and education. Our intent was to determine if the presence of chronic PTSD would be associated with decreased hippocampal N-acetylaspartate/creatinine ratios (NAA/Cr) and smaller hippocampal volumes in subjects exposed to similar severe and well-documented traumatic experiences compared with a matched control group. Our previous work had shown a significant correlation between reported reexperiencing symptoms in PTSD subjects and medial temporal lobe (MTL) NAA/Cr ratios but had shown no significant differences in MRS-determined MTL NAA/Cr or choline/creatinine ratios (CHO/Cr) between POWs divergent for PTSD diagnosis (Brown et al., 2003); however, this earlier study had not compared POW subjects with a matched control group and had not examined hippocampal volumes between POW groups.

2. Methods

A total of 26 male veteran subjects (20 former POWs and 6 control subjects) participated in the study. The Human Use Committee of the University of Arkansas for Medical Sciences approved the research
protocol, and written informed consent was obtained from all subjects. All POW subjects had combat experience and had been held captive during either World War II (WW2) or the Korean War (KW). Eight of the ten former POWs with PTSD were former German POWs, and two were former Japanese POWs. Seven of the ten former POWs without PTSD were former German POWs, two were former Japanese POWs, and one was a former Korean POW. Five POW subjects (4 POWs with PTSD and 1 POW without PTSD) were also participants in our earlier study (Brown et al., 2003). Average length of imprisonment is noted in Table 1 for both POW groups. All study subjects were carefully selected using stringent exclusion and inclusion criteria. All subjects were Caucasian males, were right-handed by Edinburgh criteria (Oldfield, 1971), had no history of traumatic brain injury with loss of consciousness, had no history of neurological impairment or degenerative neurological illness, did not meet criteria for either current or lifetime alcohol dependence, and had Mini Mental Status Examination scores (MMSE) of 26 or higher. All research subjects completed the study without compensation of any kind.

POW subjects were recruited through a POW outreach program initiated by the Central Arkansas Veterans’ Healthcare System (CAVHS), and control subjects were recruited through primary care clinics within the CAVHS. Only four study subjects had a history of any previous psychiatric treatment; all four were POWs with PTSD. No study subject had a history of psychiatric hospitalization, alcohol or substance abuse treatment, or suicide attempt. The presence or absence of PTSD was ascertained with the use of the Clinician Administered PTSD Scale (CAPS-2) in all subjects (Weathers et al., 2001). CAPS-2 scores were tallied for all subjects in terms of both total score and symptom cluster scores (reexperiencing, avoidance, and arousal). In using the CAPS-2, we chose the more conservative “rule of 4” (Fleming and Difede, 1999)—i.e. the frequency and severity scores needed to meet symptom criteria had to add to a minimum of four. The Structured Clinical Interview for DSM-IV (First et al., 1995) was also administered to determine current and lifetime psychiatric diagnoses. Former POW subjects who met lifetime, but not current, diagnostic criteria for PTSD were not included in the study. Subjects were initially interviewed by a board-certified psychiatrist (TWF or TK), their medical histories were reviewed (LB), and they were then scheduled for neuroimaging if they qualified and consented. All subjects were interviewed for PTSD symptom severity, lifetime stressors, lifetime alcohol use, and lifetime medical and psychiatric treatment. Subjects also completed the Edinburgh Handedness Inventory (Oldfield, 1971), the Beck Depression Inventory (BDI), the Davidson Trauma Scale

### Table 1
Comparison of POW subjects with and without PTSD and control subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>POW subjects with PTSD (N=10)</th>
<th>POW subjects without PTSD (N=10)</th>
<th>Control subjects (N=6)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td>79.6 ± 3.2</td>
<td>79.8 ± 2.8</td>
<td>80.8 ± 3.5</td>
<td>NS*</td>
</tr>
<tr>
<td>Duration of imprisonment (months)</td>
<td>18.0 ± 14.1</td>
<td>23.5 ± 19.9</td>
<td>–</td>
<td>NS**</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.1 ± 2.6</td>
<td>15.7 ± 3.9</td>
<td>12.5 ± 2.6</td>
<td>NS*</td>
</tr>
<tr>
<td>Years of employment (including military service)</td>
<td>43.8 ± 5.5</td>
<td>46.1 ± 12.3</td>
<td>43.0 ± 6.4</td>
<td>NS*</td>
</tr>
<tr>
<td>CAPS total</td>
<td>53.3 ± 13.9</td>
<td>14.2 ± 11.3</td>
<td>3.5 ± 4.2</td>
<td>F=67.4, P&lt;0.001</td>
</tr>
<tr>
<td>Combat Exposure Scale score</td>
<td>15.3 ± 8.3</td>
<td>8.7 ± 7.3</td>
<td>7.6 ± 16.3</td>
<td>NS*</td>
</tr>
<tr>
<td>Dissociative Experiences Scale score</td>
<td>12.9 ± 5.7</td>
<td>11.5 ± 9.9</td>
<td>5.4 ± 6.1</td>
<td>NS*</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>11.2 ± 4.4</td>
<td>8.4 ± 4.3</td>
<td>6.8 ± 3.6</td>
<td>F=3.3, P=0.05</td>
</tr>
<tr>
<td>Davidson Trauma Scale total score</td>
<td>45.8 ± 23.1</td>
<td>9.4 ± 6.3</td>
<td>10.9 ± 14.3</td>
<td>F=18.4, P&lt;0.001</td>
</tr>
<tr>
<td>Right hippocampal NAA/Cr</td>
<td>1.57 ± 0.63</td>
<td>1.50 ± 0.50</td>
<td>1.29 ± 0.18</td>
<td>NS*</td>
</tr>
<tr>
<td>Right hippocampal volume (mm³)</td>
<td>2746.0 ± 677.9</td>
<td>2841.9 ± 273.5</td>
<td>2955.1 ± 531.1</td>
<td>NS*</td>
</tr>
<tr>
<td>Left hippocampal NAA/Cr</td>
<td>1.49 ± 0.36</td>
<td>1.41 ± 0.28</td>
<td>1.18 ± 0.23</td>
<td>NS*</td>
</tr>
<tr>
<td>Left hippocampal volume (mm³)</td>
<td>2640.7 ± 433.1</td>
<td>2715.9 ± 296.9</td>
<td>2866.4 ± 351.2</td>
<td>NS*</td>
</tr>
<tr>
<td>Right hippocampal CHO/Cr</td>
<td>1.35 ± 0.26</td>
<td>1.21 ± 0.29</td>
<td>1.26 ± 0.32</td>
<td>NS*</td>
</tr>
<tr>
<td>Left hippocampal CHO/Cr</td>
<td>1.43 ± 0.64</td>
<td>1.32 ± 0.28</td>
<td>1.02 ± 0.21</td>
<td>NS*</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test—5th trial</td>
<td>8.7 ± 2.2</td>
<td>8.6 ± 2.5</td>
<td>8.7 ± 2.3</td>
<td>NS*</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test—total</td>
<td>33.3 ± 6.9</td>
<td>34.1 ± 10.1</td>
<td>34.5 ± 8.9</td>
<td>NS*</td>
</tr>
<tr>
<td>Logical Memory—theretic score</td>
<td>8.9 ± 3.3</td>
<td>8.6 ± 3.9</td>
<td>8.7 ± 4.5</td>
<td>NS*</td>
</tr>
<tr>
<td>Logical Memory—recall score</td>
<td>11.2 ± 4.0</td>
<td>9.0 ± 3.7</td>
<td>9.5 ± 4.3</td>
<td>NS*</td>
</tr>
<tr>
<td>Recognition Memory (faces)</td>
<td>38.8 ± 5.7</td>
<td>41.2 ± 2.9</td>
<td>38.7 ± 2.4</td>
<td>NS*</td>
</tr>
</tbody>
</table>

* One-way analysis of variance.
** Two-tailed t-test.
and the seven-item Combat Exposure Scale (CES) (Keane and Caddell, 1989). Memory was tested using the Rey Auditory Verbal Learning Test, Logical Memory (Wechsler, 1987), and the Recognition Memory Test for Faces (Warrington, 1984). All testing and self-reports were completed on the day of scanning.

Neuroimaging investigations were performed on a 1.5-T General Electric Signa MRI system with a standard head coil using the automated PROBE/SV routine with minor modifications. A set of spin-echo localizer MRI scans in three orthogonal planes was first acquired with the following parameters: repetition time (TR) = 500 ms, echo time (TE) = 8 ms, field of view (FOV) = 24 cm, and slice thickness = 3 mm. After localization of the hippocampi, an oblique localizer scan parallel to the hippocampal axis was acquired with TR = 500 ms, TE = 10 ms, FOV = 24 cm, and slice thickness = 1.5 mm. Voxel locations were chosen in the oblique plane in the right and left medial temporal lobes by an individual blind to the diagnostic status of the subject. After localization of an approximately 1 × 1 × 4 cm³ voxel within the hippocampus, magnetic field homogeneity and water suppression were optimized automatically. A set of water reference scans and a water-suppressed, point-resolved spectroscopy (PRESS) spectrum were acquired with TE = 144 ms, TR = 2 s, 128 transients, and spectral width = 2500 Hz in 2048 points. The data were transferred to an off-line SPARC (Sun Microsystems) workstation and processed automatically to correct spectral phase, the effects of residual eddy currents, and baseline. An automated Marquardt-fitting routine yielded the ratios of the peak intensities of NAA and CHO to Cr. When the automated routine failed, the fitting routine was directed to the peaks of interest to insure a fit. Spectra were rejected if the resolution between the CHO and Cr peaks was not at least 50% of the distance from peak maximum to apparent baseline, or if obvious artifacts interfered. Additional details have been given previously (Freeman et al., 1998).

Determinations of hippocampal volumes were made using 1.5-mm contiguous coronal slices collected with a T1-weighted gradient echo 3D sequence with TR = 24 ms, TE = 5 ms, and flip angle = 45°. Using the technique of Watson et al. (1992), two raters with good interrater reliability (x = 0.92) and who were blind to the subject’s diagnostic status performed volumetric analyses on all subjects after head rotation was corrected and slices were created perpendicular to the long axis of the hippocampi.

3. Results

The three subject groups did not differ in age or years of education (Table 1). Former POW groups did not differ in combat exposure, duration of imprisonment, or years of employment. In the former POW group with PTSD, four (40%) of the subjects met lifetime criteria for major depression, three (30%) met lifetime or current criteria for panic disorder, and none met lifetime criteria for either alcohol dependence or abuse. Six (60%) of the ten POW subjects with PTSD did not meet SCID criteria for any psychiatric illness other than PTSD, current or lifetime. None of the POW subjects with PTSD reported a history of psychiatric hospitalization, and only four reported any history of psychiatric treatment at all. In the former POW group without PTSD, three subjects (30%) met lifetime criteria for major depression and none met lifetime or current criteria for panic disorder or alcohol dependence or abuse. Seven (70%) of the former POW group without PTSD did not meet criteria for any Axis I disorder. Two control subjects (33%) met criteria for lifetime, but not current, alcohol abuse. The three groups did differ significantly in reported psychopathology with POWs with PTSD expressing significantly higher CAPS-2 subscale and total scores, and higher DTS and BDI scores than the other two groups. Within the POW group as a whole, CAPS-2 total scores correlated strongly with DTS scores (r = 0.723, P < 0.001), but not with BDI scores.

The three subject groups did not differ in hippocampal NAA/Cr or CHO/Cr ratios. Likewise, no differences found in hippocampal volumes, total brain volumes, or hippocampal/total brain ratios between groups. When the POW group as a whole was compared with the control group, no differences were found in hippocampal NAA/Cr or CHO/Cr ratios. Unlike our previous study (Brown et al., 2003), we found no correlation among the POW group with PTSD between reexperiencing symptoms and hippocampal NAA ratios. Neither CAPS total symptom scores nor DTS scores correlated with hippocampal NAA ratios in POWs with PTSD. As noted in Table 1, neuropsychological testing showed no significant differences between groups.

4. Discussion

Overall, we found no differences in MRS-determined hippocampal NAA/Cr or CHO/Cr ratios, brain volumetric measures, or memory measures between the subject groups. This negative study replicates our ear-
that stress may be tied to accelerated aging (Epel et al., 2003), and adds to that finding in that no significant differences in hippocampal biochemistry or hippocampal volumes were found between either POW group or an age- and education-matched control group. This study is unusual among neuroimaging studies of PTSD subjects in that the majority of our PTSD sample did not meet criteria for any psychiatric disorder other than PTSD. In addition to the unusual opportunity to study a PTSD population with minimal comorbid psychiatric illness, this study also offered the opportunity to compare a group of former POWs with PTSD with a group of former POWs with documented, similar traumatic experiences (but without a history of PTSD) using two different neuroimaging techniques.

Our findings potentially support two possible and rather broad conclusions. First, these findings support a lack of observable hippocampal pathology associated with chronic PTSD. However, this conclusion runs counter to the bulk of neuroimaging studies in PTSD subjects—both those suggesting that PTSD-related hippocampal pathology is primarily a predisposing factor for the acquisition of PTSD and those suggesting that hippocampal pathology is a direct consequence of deleterious neurobiological processes associated with traumatic experience. A second possible conclusion also supported by our findings is more complex, and is related to evidence suggesting excessive medical morbidity and mortality in veterans exposed to war trauma. There are numerous studies that suggest that individuals with PTSD are prone to excessive levels of medical morbidity (Boscarino, 2004); other studies suggest that simply being exposed to combat in youth is associated with early mortality (Lee et al., 1995). More recent work has suggested that stress may be tied to accelerated aging (Epel et al., 2004), and a recent longitudinal follow-up study of Vietnam veterans with PTSD revealed a remarkably high mortality rate over a 6-year period (Johnson et al., 2004). A study of former Vietnam POWs (Guest and Venn, 1992) showed an elevated mortality rate immediately after the war. These findings support another conclusion—namely that former POWs who were more affected by the traumatic experiences of their youth were unavailable to us as subjects due to attrition, leaving a healthier and less affected group for study. The subjects available for this study were remarkably healthy and vital, and longer-lived than average. It should also be noted that the majority (60%) of former POW subjects with PTSD did not meet SCID criteria for any Axis 1 disorder other than PTSD, and the majority (70%) of former POW subjects without PTSD did not meet SCID criteria for any Axis 1 psychiatric illness at all. Our PTSD subjects exhibited remarkably low levels of psychiatric morbidity and expressed far lower levels of PTSD symptom severity than our Vietnam veteran study populations. This latter conclusion would also explain the report of Golier et al. (2001), who found no difference in hippocampal volume in elderly Holocaust survivors with PTSD.

Our clinical impression of the vitality and relative lack of severe psychopathology found in these elderly former POW groups is entirely consistent with their lack of tested neuropsychological impairment or cerebral pathology. This is not the clinical impression we typically perceive when we examine younger veteran populations with chronic PTSD. The comparative lack of psychiatric comorbidity in these former POW groups, together with the lack of differences in MRS and MRI volumes between groups, suggests that the frequent comorbid psychiatric and medical illnesses found in Vietnam veteran populations with PTSD may be coupled to neuroimaging findings in veteran PTSD populations to date. This would suggest that studies of elderly PTSD populations—especially those composed of very old subjects—might reveal a less impaired group than studies of younger PTSD populations, with the presumption that older populations have already been subject to the attrition of more impaired individuals.

Research using former POWs offers opportunities to study a remarkably resilient group of individuals with histories of unquestionably severe, well-documented early adulthood traumatic experience, but who are remarkably free of much of the comorbid psychiatric illness that often accompanies neuroimaging research into PTSD. It may be that not only are there groups of individuals that are especially vulnerable to traumatic experience, there may be populations that are especially resilient to the effects of severe trauma. As has been suggested recently (Charney, 2004), research using resilient populations may offer unique insights into the psychobiological effects of extreme stress and healthy aging.

References


