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Quantitative structural changes in white and gray matter 1 year following traumatic brain injury in rats

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Abstract There is evidence for chronic atrophy after human head trauma, which may be associated with long-term functional deficits. However, using established models of traumatic brain injury (TBI) only limited data are available for clarifying the extent of progressive gray and white matter atrophy. In the present study, male Sprague-Dawley rats underwent moderate (2.01–2.21 atm) parasagittal fluid percussion brain injury (n=7) or sham (n=3) surgery and were killed at 1 year post TBI. Semiserial sections were obtained through the neuraxis and double stained with hematoxylin and eosin to demarcate gray matter structures and Luxol fast blue for white matter visualization. Both ipsilateral and contralateral volume measurements were obtained for the following structures: cerebral cortex, hippocampus, dentate gyrus, thalamus, lateral ventricle, external capsule, internal capsule, cerebral peduncle and corpus callosum. Quantitative assessment of ipsilateral gray matter structures from TBI rats revealed significant reductions in cerebral cortical area measurements posterior from the trauma epicenter compared to sham animals. Importantly, several white matter tracts exhibited dramatic atrophy. A comparison of TBI and sham groups demonstrated a significant (P<0.05) decrease in the external capsule and cerebral peduncle volumes (P<0.007). In addition, there was a significant volume expansion (533% of control) of the ipsilateral lateral ventricle (P<0.03). These novel data emphasize the need to clarify the pathophysiology of progressive white matter damage after TBI and the development of therapeutic strategies to target white matter pathology.

Keywords Atrophy · Fluid percussion injury · Histopathology · Chronic · Rat

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Introduction

Human head trauma frequently results in chronic disability [18, 30, 31, 45, 54, 55] associated with long-lasting cognitive [18, 30, 31, 46, 54, 55] and motor [31, 54] problems. Persistence of functional deficits results in a poor prognosis for the head-injured patient population. To provide adequate treatment strategies for these behavioral abnormalities, an understanding of acute as well as progressive neuropathological changes after traumatic brain injury (TBI) must be clarified. Whether progressive damage is due to long-lasting consequences of the primary insult (i.e., Wallerian degeneration) [1, 24, 43, 49], or results from progressive secondary injury mechanisms remains to be determined [6, 10, 11, 20, 42].

Several clinical [3, 4, 12, 22, 49, 56] and experimental [5, 20, 47, 51] studies have reported evidence for progressive atrophic changes after TBI. After human TBI, Anderson and Bigler [3] reported widespread atrophy of both white and gray matter structures. In that study, the extent of ventricular expansion was positively correlated with more severe neuropsychological impairments in memory. Anderson and Bigler [2] further reported that trauma-induced dilation of the anterior horn of the lateral ventricle was associated with atrophy of the corpus callosum in patients. Interestingly, ventricular dilation was not associated with shrinkage of the caudate nucleus and, therefore, these investigators proposed that ventricular dilation was not primarily due to gray matter loss. Other investigators have demonstrated relationships between cognitive outcome and degrees of atrophy after injury [12, 45].

Atrophic changes in gray and white matter may underlie some of the chronic functional deficits observed in TBI patients following neuropsychological testing. This hypothesis is supported by clinical data reporting an association between head trauma and the late occurrence of several neurodegenerative diseases including Alzheimer's disease [33, 36]. However, only recently have experimental studies been concerned with more chronic histopathological and behavioral consequences of TBI. Bramlett et

al. [5] reported a decrease in volume of several ipsilateral gray matter structures, relative to the contralateral hemisphere and sham operated animals, at 2 months following moderate parasagittal fluid percussion (FP) brain injury. In that study, the ipsilateral structures that were affected included the cerebral cortex, thalamus, hippocampus and dentate gyrus with an enlargement of the lateral ventricle. This work was extended by Smith et al. [47], who reported progressive tissue loss within the cortex and hippocampus at various times up to 1 year following lateral FP injury. Both studies [5, 47] reported expansion of the lateral ventricle, a phenomenon which is also observed in TBI patients [3]. Additionally, Dixon et al. [20] recently reported similar findings in a model of controlled cortical impact trauma (CCI). Comparison of tissue obtained at 3 weeks and 1 year post-injury demonstrated a significant hemispheric volume loss, and again expansion of the ipsilateral lateral ventricle.

It is important to emphasize that previous experimental studies primarily restricted their analysis to gray matter structures. This point is important because clinical studies have reported white matter atrophy [2, 3, 22, 49]. In TBI patients who present with deficits in higher cortical function, structural abnormalities in white matter tracts may underlie the lack of long-term functional improvement. The present study was therefore designed not only to assess gray matter atrophy in a clinically relevant model of TBI, but the existence of white matter atrophy. Using stains that target both gray and white matter, we report gray matter atrophy and for the first time white matter atrophic changes after moderate parasagittal FP injury at 1 year.

Materials and methods

Surgical procedures

Ten young adult male Sprague-Dawley rats were used for this experiment. Animals were maintained on a 12/12 (light/dark) cycle and given food ad libitum. All animal procedures followed the National Institutes of Health 'Guide for the Care and Use of Laboratory Animals' and were approved by the university's animal care and use committee. Animals were anesthetized 24 h prior to injury with equithesin (1.0 ml) and surgically prepared for parasagittal fluid percussion (FP) injury to the right hemisphere as described previously [15]. Briefly, a craniotomy (4.8 mm) was performed at 3.8 mm posterior to bregma and 2.5 mm lateral to the midline [40]. A plastic injury tube was placed over the exposed dura and bonded by adhesive. Dental acrylic was used to affix the injury tube to the skull. The scalp was then sutured closed and the animal was allowed to recover before being returned to the home cage.

After fasting overnight, a FP device was used to produce experimental TBI via the injury tube [19]. Intubated anesthetized rats (70% nitrous oxide, 0.5% halothane, and 30% oxygen) were subjected to a pressure pulse of moderate (2.01–2.21 atm) intensity (TBI, n=7). Prior to TBI, catheters were placed in the right femoral artery to monitor arterial blood pressure and blood gases. Rectal temperature and brain temperature were maintained at normothermic (37°C) levels prior to and 30 min after TBI. Sham animals underwent all surgical procedures except for the actual injury (Sham, n=3). Following these procedures, rats were placed in a standard housing environment consisting of a 17 inch×8.5 inch×8 inch plastic cage.

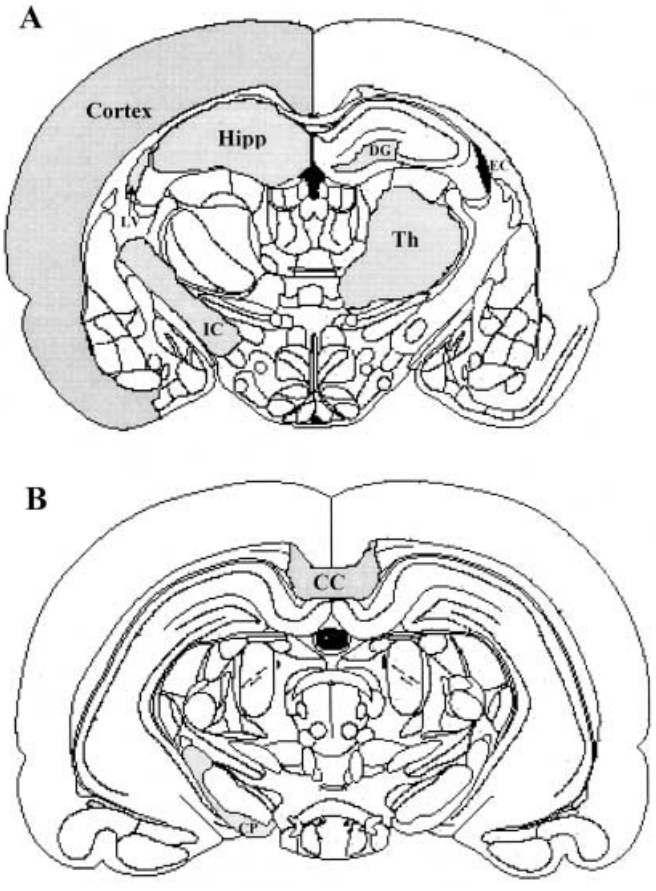

Fig. 1A, B Illustration of representative bregma levels from which structures were drawn [40]. **A** Level 3.3 posterior from bregma outlining cerebral cortex, hippocampus (*Hipp*), dentate gyrus (*DG*), lateral ventricle (*LV*), internal capsule (*IC*), thalamus (*Th*) and external capsule (*EC*). **B** Level 4.8 posterior from bregma outlining corpus callosum (*CC*) and cerebral peduncle (*CP*). Figures adapted from Paxinos and Watson [40]

Histopathology

Animals were killed 1 year after TBI or sham surgery. Animals were anesthetized and perfused transcardially with isotonic saline at a pressure of 100–120 mm Hg for 15 s. This was followed by fixative for 20 min (FAM, a mixture of 40% formaldehyde, glacial acetic acid and methanol; 1:1:8 by volume). After perfusion, the heads were immersed in FAM at 4°C for 24 h. The brains were then blocked and embedded in paraffin. Tissue sections (10 μm thick) were taken at 500-μm intervals throughout the neuraxis. Sections were then double stained with Luxol-fast blue and hematoxylin and eosin for histopathological assessment.

Coronal sections at multiple levels (0.8, 1.8, 3.3, 4.3, 5.8, 6.8, 7.3 mm posterior to bregma) were used for volumetric measurement [61]. Volume measurements for each structure were computed using area components from multiple semiserial sections using numeric integration of successive areas. Areas were determined by tracing the boundaries of each structure at a power of 1× from a minimum of three coronal sections at different bregma levels depending on the size of the structure using a camera lucida microscope attachment. Areas were calculated by retracing these drawings onto a digitizing tablet that was interfaced with a computer. The following ipsilateral and contralateral structures were analyzed: cerebral cortex, dentate gyrus, hippocampus, thalamus, lateral ventricle, external capsule, internal capsule, cerebral peduncle and corpus callosum. Figure 1 depicts the structures at representative bregma levels that were included in the analysis.

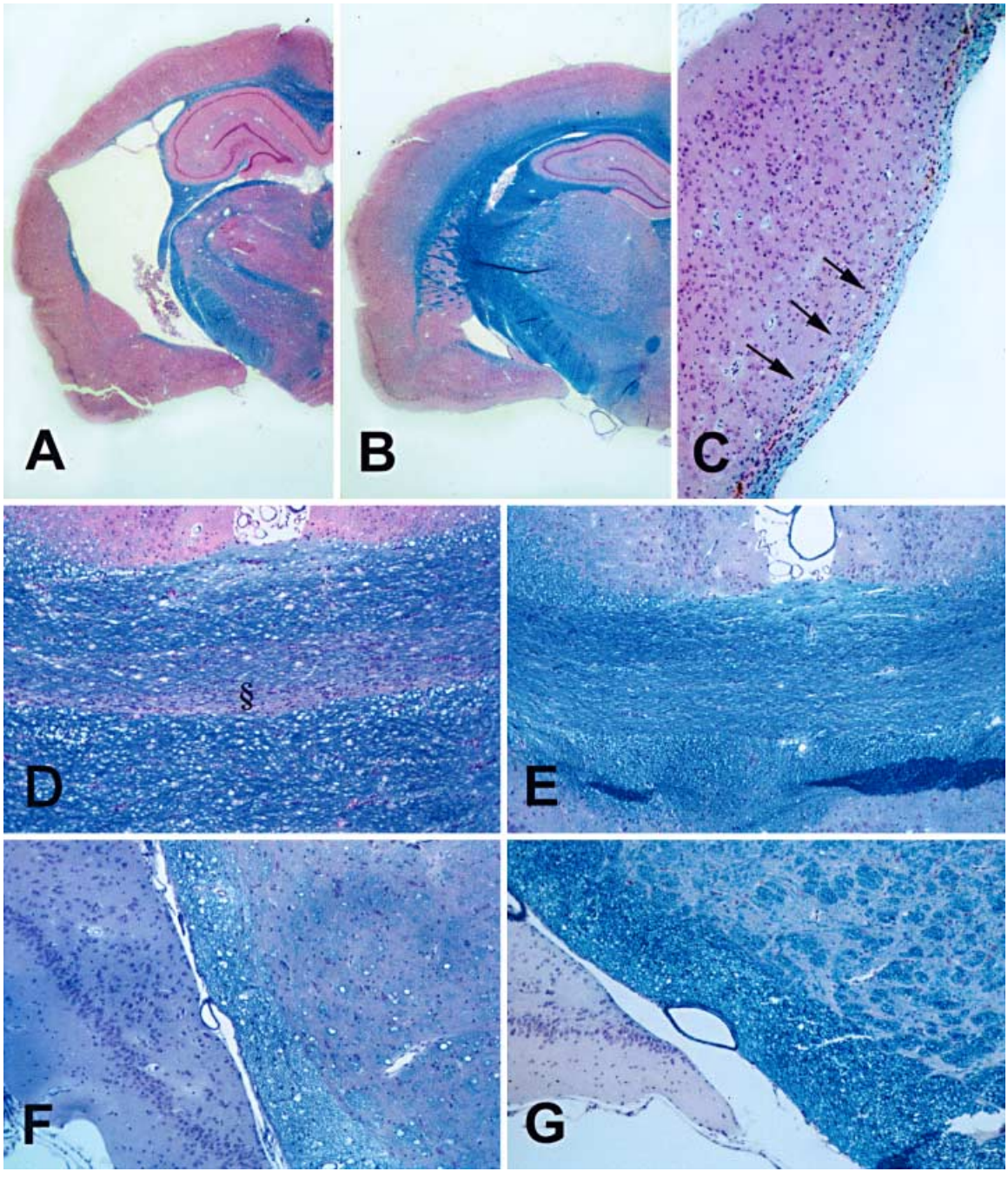

Fig. 2A–G Double-stained H&E and Luxol-fast blue sections 1 year after TBI or sham procedure. **A** TBI animal showing gross atrophy with marked expansion of the ipsilateral lateral ventricle. **B** Sham-operated animal appearing unremarkable. **C** Higher magnification of external capsule thinning (*arrows*) after TBI. **D** Loss of white matter staining in the corpus callosum following injury, possibly indicating demyelination (§). **E** Sham animal showing normally stained white matter fibers. **F** TBI animal demonstrating atrophic changes within ipsilateral cerebral peduncle. In contrast, sham animal shows unremarkable cerebral peduncle (**G**) (*TBI* traumatic brain injury). **A**, **B** ×25; **C**–**E** ×220; **F**, **G** ×96

Statistical analysis

Histopathological data were expressed as mean ± standard error (± SEM). Repeated measures analysis of the cerebral cortex areas was performed across bregma levels posterior from the epicenter followed by Tukeys test. Ipsilateral and contralateral volume measurement comparisons between groups were analyzed using one-way ANOVA, $P<0.05$ for significance.

Results

Histopathology

At 1 year following FP brain injury extensive atrophy of the ipsilateral hemisphere and expansion of the lateral ventricle was clearly evident (Fig. 2A). In contrast, sham animals at 1 year demonstrated a normal symmetrical ap-

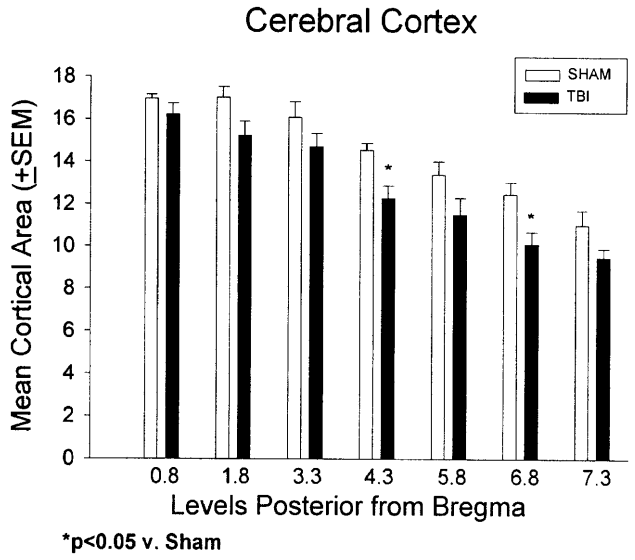

Fig. 3 Cerebral cortical area measurements at several posterior bregma levels. Values from TBI animals were reduced compared to sham animals across all bregma. Two levels (4.3 and 6.8) demonstrated significant area loss compared to sham values

pearance to the tissue (Fig. 2B). Higher magnification of the traumatized hemisphere demonstrated a general thinning of the cortical layer and a marked thinning of the external capsule (Fig. 2C). Furthermore, abnormal Luxol-fast blue staining within the middle fibers of the corpus callosum (Fig. 2D) compared to sham animals was observed (Fig. 2E). This abnormal appearance may indicate a loss of myelin. In addition to dramatic atrophy within the external capsule, there was also white matter tissue loss in the ipsilateral cerebral peduncle of TBI animals (Fig. 2F) compared to sham-operated rats (Fig. 2G) at 1 year.

Area and volume measurements

Repeated measures analysis of ipsilateral cerebral cortical areas (Fig. 3) demonstrated significant differences ($P<0.05$) between TBI and sham-operated rats. One-way ANOVA analysis for each bregma level revealed two levels posterior from bregma (4.3 and 6.8) that were significantly different ($P<0.05$) from sham-operated animals. Although overall cortical volume was not significantly different between TBI and sham-operated rats, significant differences in cortical areas were seen at specific bregma levels (Fig. 2A). The areas included somatosensory cortex, parietal, auditory and visual cortices ipsilateral to the injury [40]. Analysis of other gray matter structures (Fig. 4) revealed no significant reductions in overall structural volume.

In contrast to the findings in gray matter structures, TBI volume measurements of the ipsilateral external capsule (Fig. 5A) were significantly ($P<0.05$) different from sham animals. The TBI group had a mean volume of 4.93 mm^3 compared to 7.92 mm^3 for sham-operated animals. The cerebral peduncle (Fig. 5B) also exhibited atrophic changes after TBI. Sham animals had a significantly ($P<0.007$) larger volume for the ipsilateral cerebral peduncle than FP-injured animals. Significant differences were not observed for volume measurements of the internal capsule or corpus callosum. However, as described above, a lack of Luxol-fast blue staining within the corpus callosum of TBI animals was observed compared to sham-operated rats.

As previously observed at 2 months after FP injury [5] there was a significant ($P<0.03$) increase in the area and volume of the ipsilateral lateral ventricle (Fig. 6). There was an approximately fivefold expansion of the lateral ventricle at 1 year following TBI. In contrast to these findings on ipsilateral structures, there were no significant differences between TBI and sham animals on any contralateral structures analyzed.

Discussion

The present data support previous studies showing significant gray matter atrophy after experimental TBI in the injured cortex with chronic survival periods and extend these structural abnormalities to white matter changes. These findings are important because white matter changes would be expected to result in circuit dysfunction and possibly underlie many of the long-term behavioral abnormalities associated with TBI.

In modeling human TBI, it is important to describe components of the model that are clinically relevant. Until recently, only gray matter atrophy has been observed after chronic experimental TBI. However, white matter atrophy has been reported in head-injured patient populations [2, 3, 22]. In the present study a double staining procedure was utilized to critically demarcate both gray and white matter structures. Although no significant differences were observed within the overall cerebral cortex volume measurements, when analyzing specific bregma area measurements, significant differences were evident. It would be expected that evidence for regionally specific cortical thinning would be diluted by assessing the entire cerebral cortex. In this regard, progressive atrophy within specified ranges of bregma levels posterior from the injury epicenter has been reported by Smith et al. [47]. In addition, although the present study does not report on earlier time points, Smith et al. documented progressive atrophy at various time points up to 1 year. In particular, their values for tissue loss within the cortex increased over time, possibly indicating an actively expanding deterioration of tissue.

Our laboratory has previously described acute axonal pathology at the light and ultrastructural levels using the present TBI model [6, 14]. Others have also reported axonal pathology after experimental TBI and clarified the pathophysiology of the injury process [26, 39, 41, 42, 43]. Following FP injury, there is an acute swelling of axons

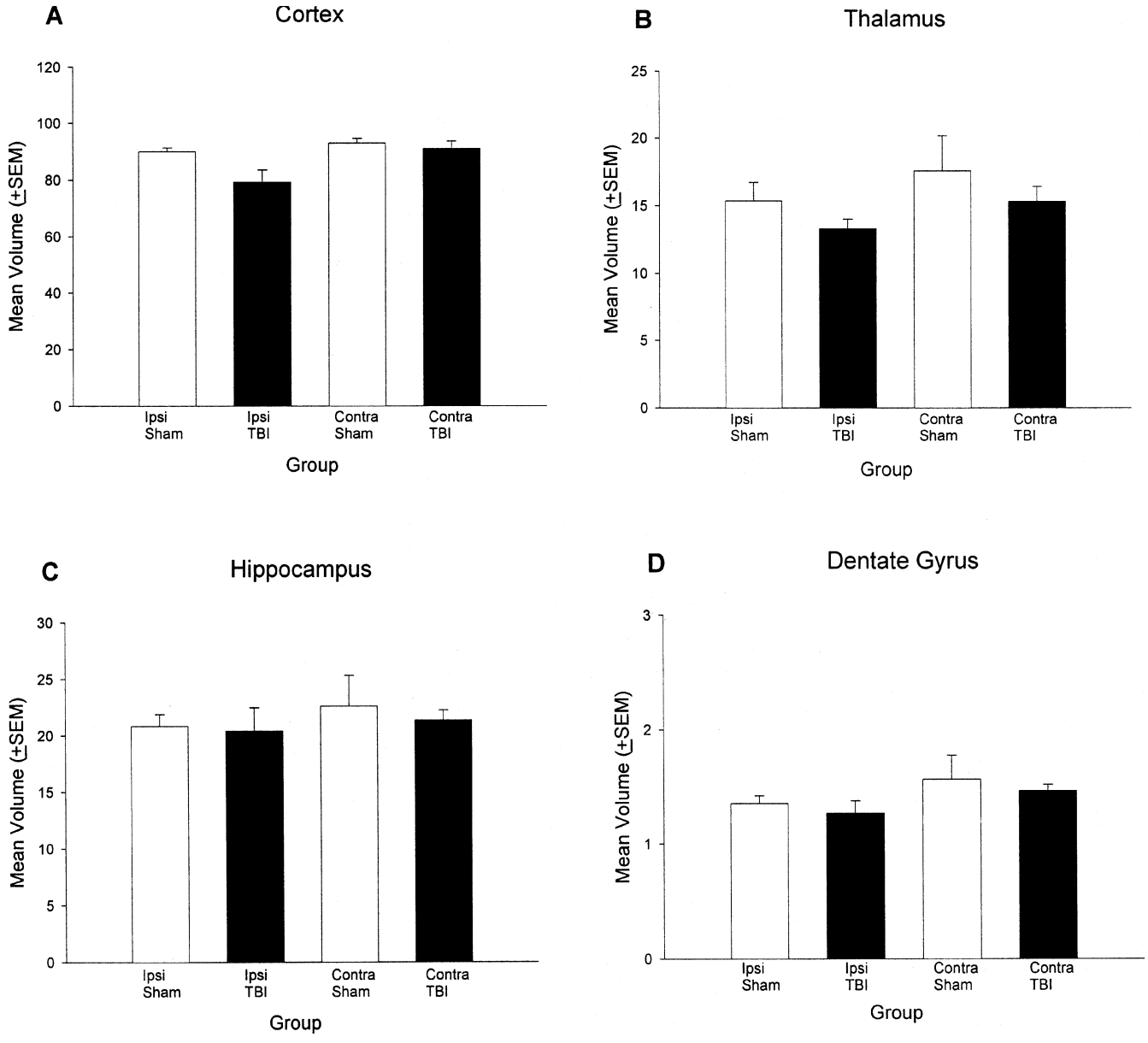

Fig. 4A–D Volume measurements for gray matter structures. **A** Ipsilateral TBI cortical volume measurement is reduced but not significantly different from sham. **B–D** There is also no significant difference between TBI and sham animals in thalamic, hippocampal, or dentate gyrus volumes

and marked intra-axonal ultrastructural changes [14, 41, 43]. Besides morphological changes, we and others have utilized β-amyloid precursor protein (β-APP) as a marker of axonal pathology [6, 42, 48]. An early but transient appearance of β-APP profiles within the ipsilateral striatum after FP injury was demonstrated [6]. In contrast, thalamic accumulation of β-APP within the ventral posterior nucleus was delayed and did not appear until 7 days after trauma. Pierce et al. [42] reported the sustained presence of β-APP from 1 month to 1 year post-injury. In that study, β-APP accumulation was present in the dorsomedial striatum, thalamus, subcortical white matter and cortical regions near the cortical cavity. Based on the present findings, it is unclear whether these white matter changes represent active or passive degenerative processes. Therefore, an important question is whether chronic white matter damage is due to progressive axonal pathology (i.e., Wallerian degeneration) or is a consequence of other white matter disturbances including myelin degeneration.

The incidence of Wallerian degeneration following TBI has been described by many investigators [1, 43, 49]. Povlishock [43] reported that axonal degeneration results from a disconnection within the axon and a rapid degeneration of the distal axonal segment. These axonal changes have been reported to occur rapidly in lower order animals but much more rapidly in higher order animals and humans. However, after human TBI, structural changes within the thalamus can be delayed and not observed until 3 months post-injury [1]. Although loss of cortical neurons (i.e. nutritive centers for the axon) may initially con-

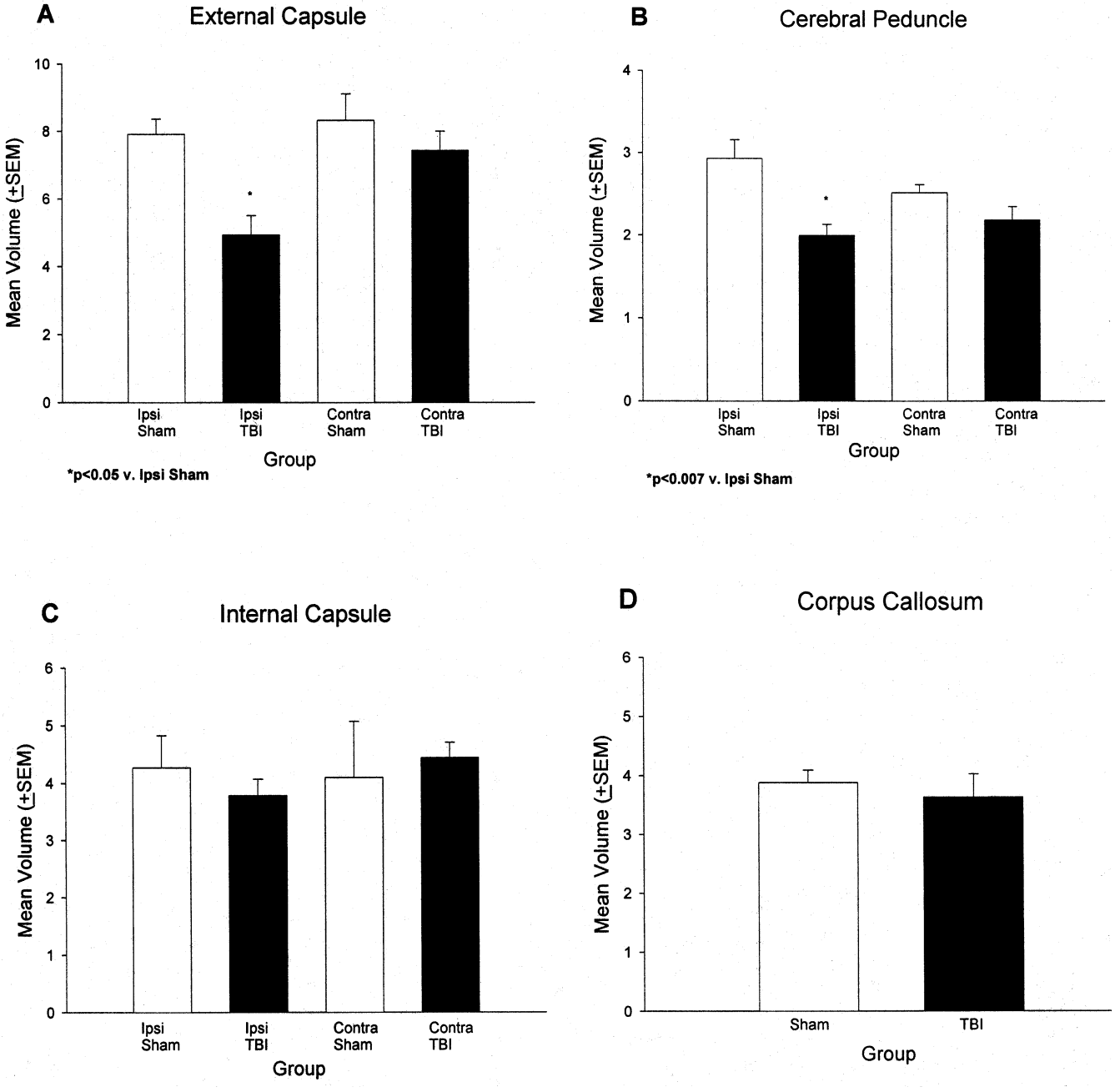

Fig. 5A–D Volume measurements for white matter structures. **A** The external capsule volume is significantly reduced 1 year after trauma compared to sham animals. **B** The ipsilateral cerebral peduncle also showed a significant decrease in volume. **C**, **D** Both internal capsule and corpus callosum demonstrate no significant decrease in volume following trauma compared to sham animals

tribute to axonal loss it is possible secondary mechanisms of injury may also contribute to the gross atrophy observed in the white matter tracts in the present study. One argument against this suggestion is that the frontal parietal cortical damage produced by this FP model does involve sensory motor areas which have major projections to the external capsule and cerebral peduncle [57]. Therefore, the observed responses in the white matter may be a direct result of anterograde degeneration rather than some other traumatically induced response capable of causing progressive white matter change. This paper by no means resolves this issue but does question whether Wallerian degeneration is the only mechanism underlying the pathogenesis of white matter damage after chronic TBI.

Although the specific pathological pathways contributing to progressive tissue loss after TBI have not been well clarified, several possible mechanisms have been proposed. These include apoptotic cell death ([8, 9, 10, 11, 21, 28, 37, 58], for review see [44]), inflammation [25, 35, 38] and excitotoxicity in white matter tracts [27, 34, 50]. Another mechanism that may participate in progressive damage is prolonged regional hypoperfusion. In this regard, acute and subacute hemodynamic abnormalities have been

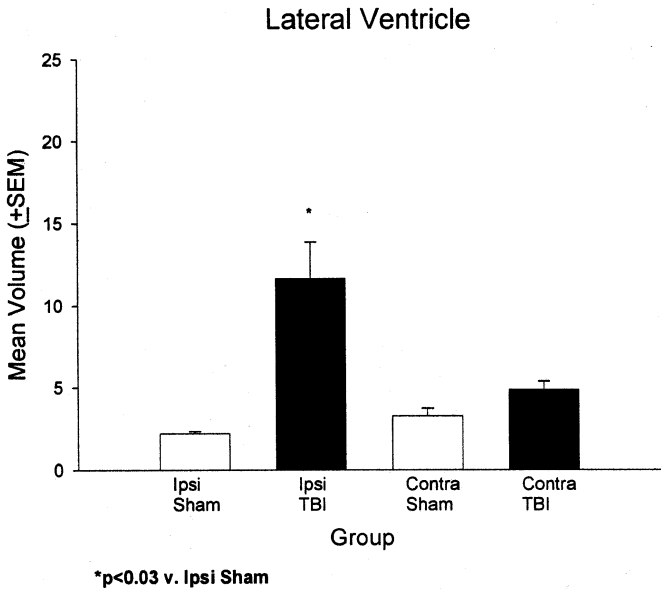

Fig. 6 Volume measurements for the lateral ventricle. There is marked expansion of the ipsilateral lateral ventricle after TBI when compared to sham animals. The increase us greater than that previously reported at 2 months from this laboratory [5], indicating continued atrophic changes at more chronic time points

described by various laboratories after TBI [7, 13, 16, 17, 23, 32, 59, 60]. Importantly, several clinical studies have reported the presence of areas of hypoperfusion chronically after trauma [4, 52]. Terayama and colleagues [52] demonstrated chronic reductions in lCBF within the putamen, thalamus and subcortical white matter more than six years after human TBI. Cognitive recovery after trauma has also been reported to correlate with improvements in white matter blood flow [53]. A recent study by Kurumatani et al. [29] reported changes in neurofilament-H and myelin basic protein in white matter following two months of chronic hypoperfusion. Interestingly, in that study damage to the myelin sheath was reported to precede axonal damage. At this time, it is unknown whether the present TBI model produces chronic hypoperfusion. If this is the case, then appropriate treatment strategies may be tested to improve post-traumatic perfusion and/or inhibit ischemic pathophysiological mechanisms leading to white matter vulnerability.

Whether progressive damage after brain injury is due to long lasting post-traumatic consequences primarily resulting from the initial insult and/or result from active secondary injury mechanisms remains to be determined. In order to provide effective treatment strategies for behavioral abnormalities after experimental TBI, the pathogenesis of acute as well as progressive injury mechanisms must be clarified. The present model of progressive gray and white matter atrophy appears to be an appropriate model in which to clarify these issues.

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