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Long-term global and regional brain volume changes following severe traumatic brain injury: A longitudinal study with clinical correlates

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ABSTRACT

Traumatic brain injury (TBI) results in neurodegenerative changes that progress for months, perhaps even years post-injury. However, there is little information on the spatial distribution and the clinical significance of this late atrophy. In 24 patients who had sustained severe TBI we acquired 3D T1-weighted MRIs about 8 weeks and 12 months post-injury. For comparison, 14 healthy controls with similar distribution of age, gender and education were scanned with a similar time interval. For each subject, longitudinal atrophy was estimated using SIENA, and atrophy occurring before the first scan time point using SIENAX. Regional distribution of atrophy was evaluated using tensor-based morphometry (TBM). At the first scan time point, brain parenchymal volume was reduced by mean 8.4% in patients as compared to controls. During the scan interval, patients exhibited continued atrophy with percent brain volume change (%BVC) ranging between −0.6% and −9.4% (mean −4.0%). %BVC correlated significantly with injury severity, functional status at both scans, and with 1-year outcome. Moreover, %BVC improved prediction of long-term functional status over and above what could be predicted using functional status at ~8 weeks. In patients as compared to controls, TBM (permutation test, FDR 0.05) revealed a large coherent cluster of significant atrophy in the brain stem and cerebellar peduncles extending bilaterally through the thalamus, internal and external capsules, putamen, inferior and superior longitudinal fasciculus, corpus callosum and corona radiata. This indicates that the long-term atrophy is attributable to consequences of traumatic axonal injury. Despite progressive atrophy, remarkable clinical improvement occurred in most patients.

Introduction

Traumatic brain injury (TBI) affects about 235 per 100,000 individuals each year in Europe (Tagliaferri et al., 2006) and is a major cause of death and severe morbidity worldwide. In survivors of severe TBI, long-term impairment of consciousness is usually attributable to traumatic axonal injury (TAI, also known as diffuse axonal injury). TAI results from rotational acceleration-deceleration causing shear strain deformation and subsequent disconnection of axons. It is characterized by microscopic lesions scattered throughout the white matter in particular, with certain regions being characteristically involved, namely the dorsolateral rostral brain stem, the corpus callosum and the subcortical parasagittal white matter. Other regions susceptible to TAI are the internal and external capsules, the deep grey matter, the cerebellum, various tracts in the brain stem and the cerebellar peduncles (Graham et al., 2002). It has been repeatedly observed in animals (Smith et al., 1997; Bramlett and Dietrich, 2002; Rodriguez-Paez et al., 2005) and in humans (Graham et al., 2002) that TBI results in widespread brain atrophy that progresses over several months and perhaps even years post-injury. While it is remarkable that atrophy continues in the chronic phase of TBI, concurrently with clinical recovery, the clinical significance of this late atrophy remains unclear. The progressive degeneration is thought to involve Wallerian degeneration of the white matter tracts disrupted by TAI, but other mechanisms such as apoptosis, inflammation, excitotoxicity, and prolonged hypoperfusion may also play a role (Bramlett and Dietrich,

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2002; Rodriguez-Paez et al., 2005). Characterising the spatial distribution of late atrophy might contribute to the understanding of its pathogenesis.

Few longitudinal MRI studies have quantitatively examined progressive atrophy following TBI and the correlation to clinical parameters. In seven patients with mild to moderate TBI, scanned twice at least 3 months (up to 2.5 years) apart, MacKenzie et al. reported a longitudinal change in brain parenchymal volume of on average −4.16% (relative to −1.49% in healthy controls) and found greater volume loss in patients with initial loss of consciousness than in those without loss of consciousness (MacKenzie et al., 2002). However, in this study early and late atrophy were conflated since the time from injury to the first scan varied between 7 and 430 days. Recently, Trivedi et al. (2007) published a study applying SIENA (Smith et al., 2002) to evaluate global brain volume change between approximately 79 and 409 days post-TBI in 37 patients with TBI ranging from mild to severe. The authors found a change in brain volume of mean −1.43% (relative to +0.1% in healthy controls), with greater decline in brain volume being associated with longer duration of post-injury coma. However, relation to outcome was not reported.

Characterising quantitatively the regional distribution of late atrophy following TBI is challenging, especially because focal lesions often coexist with diffuse lesions, causing regional distortions in brain shape and intensity inhomogeneities which complicate procedures such as registration and tissue segmentation. Until recently, previous studies on TBI have been based on regions-of-interest (for a review, see Bigler, 2001) or on voxel-based morphometry (Gale et al., 2005; Tomaiuolo et al., 2005; Salmond et al., 2005; Bendlin et al., in press). However, recent advances in computational techniques for nonlinear image registration have allowed for an unbiased and more precise registration that does not necessarily rely on tissue segmentation, thus overcoming some of the major limitations of traditional volumetric approaches. One such approach is tensor-based morphometry (TBM), which determines the deformation field required to warp the early image to match the late image within subject (or in cross-sectional studies, the deformation field required to warp the image to a study-specific template). Regional volume change is quantified by taking the Jacobian determinant at each voxel (Ashburner et al., 2000). One cross-sectional TBM study on TBI was very recently published (Kim et al., 2008). The population consisted of 29 patients with moderate to severe TBI, scanned once at least 3 months (ranging between 4 months and 27.5 years) following injury. The authors found localized volume loss most prominently in the thalamus, the midbrain, the corpus callosum, the cingulate cortex, and the caudate. Significant volume increase was found mainly in the ventricles. However, as this study was not based on serial scans, and as the time from injury to MRI varied considerably between patients, no conclusions could be drawn about the time course of the structural changes.

In the present prospective longitudinal study, we examined the morphological changes occurring between two time points, approximately 8 weeks and 12 months post-injury, in 24 patients with severe TBI, comparing them to 14 healthy matched controls scanned with a similar time interval. We used SIENA to provide an estimate of global atrophy between scans, and TBM to investigate the regional distribution of late volume change. Additionally we used SIENAX (Smith et al., 2002) to estimate global atrophy occurring before the first scan time point, in order to compare this with the late atrophy. We hypothesized that the most pronounced late volume change would be found within regions susceptible to TAI (listed at the beginning of this introduction) as well as along the affected white matter tracts (as a consequence of secondary Wallerian degeneration). Further, we expected that the extent of global brain volume change from first to second scan would be larger in patients with longer duration of coma/post-traumatic amnesia and with poorer functional status and outcome.

Materials and methods

Subjects

Twenty-six adult patients with severe TBI were evaluated for this study. As two patients were subsequently excluded because of motion artefacts in the MR images, the final TBI group comprised 24 patients. Fourteen healthy control subjects were selected to match the patient group with respect to age, sex and education. Both patients and controls had two MR scans with an interval of 345±42 days (mean±SD). Group comparisons of age, sex, education and scan interval are listed in Table 1.

Patients were recruited from the Brain Injury Unit at Copenhagen University Hospital, Hvidovre, Denmark, to which they were admitted for subacute rehabilitation. Patients were referred from neuro-intensive units, and admitted for rehabilitation only if Glasgow Coma Scale score (GCS; Teasdale and Jennett, 1974) was still subnormal after cessation of sedation. Severe TBI was defined as a post-resuscitation GCS <8 measured within 24 h post-injury and prior to the initiation of paralytics or sedatives. Patients were excluded from the present study if they had any previous history of TBI or other neurological disorder, if contraindications to MRI or to sedation during MRI were present, or if the first MRI could not be performed within 12 weeks post-trauma for safety or practical reasons. Controls had no history of significant TBI or other neurological disorder.

The study was approved by the local Scientific Ethics Committee (KF 01-038/03), meeting criteria of the Helsinki Declaration. Informed consent was obtained from the participants or, for patients with impaired consciousness, from next of kin.

Clinical assessments

For all patients, clinical data were documented in medical files, and ratings were performed by trained staff, neurologists, and neuropsychologists. Cause of trauma was either motor vehicle accident (n=16), fall (n=7) or assault (n=1). Accidents with any direct involvement of a motor vehicle (including pedestrian or bicyclist hit by car) were classified as motor vehicle accident. Neurosurgery was defined as surgery that involved craniotomy, excluding insertion of ICP monitoring devices. The number of days from TBI until GCS >8 was registered as a measure of coma duration, and the Galveston Orientation and Amnesia Test (Levin et al., 1979) was repeatedly applied to establish duration of post-traumatic amnesia (PTA). Both were regarded as measures of injury severity. The Functional Independence Measure (FIM; Granger et al., 1986) was documented regularly, including at both scan time points (sum score ranging from 18 indicating “total assist”, to 126 indicating “complete independence”). Functional outcome at ~12 months post-TBI was evaluated using the 8-point Glasgow Outcome Scale Extended (GOS-E; Wilson et al., 1998), ranging from 1=dead to 8=good recovery (upper). For dichotomized outcome, the commonly used division into unfavourable outcome (GOS-E=1–4) and favourable outcome (GOS-E=5–8) was applied, distinguishing whether or not patients were able to live independently.

Image acquisition

All patients and controls were scanned on the same 1.5 T MRI scanner (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany) using a standard circular-polarized head coil. During the study period, MRI sessions for patients and controls were interleaved in time, and no major upgrades were carried out on the scanner during the study.

A 3D sagittal T1-weighted sequence (MPRAGE, TR/TE/TI=13.5/7/100 ms, flip angle 15°, isotropic 1 mm resolution) was acquired in all

Table 1
Group comparisons of demographics and scan interval

	Patients (n=24)	Controls (n=14)	Group differences
Age, at scan 1 (years) [mean (SD)]	33.2 (13.5)	31.2 (8.1)	$P>0.5$[a]
Sex: M/F	18/6	9/5	$P>0.7$[b]
Education (years) [mean (SD)]	13.3 (3.1)	13.7 (2.7)	$P>0.6$[a]
Scan interval (days) [mean (SD)]	343 (47)	348 (30)	$P>0.6$[b]

[a] Independent-samples t-test.
[b] Fishers Exact test.

subjects at both scan time points. For patients, additional conventional sequences included: axial T2-weighted images (spin-echo, TR/TE=5400/99 ms, 27 contiguous, 5 mm thick slices, 0.5×0.5 mm in-plane resolution), coronal T2*-weighted gradient-echo images (TR/TE=544/15 ms, 34 contiguous, 5 mm thick slices, 0.9×0.9 mm in-plane resolution), axial and sagittal FLAIR (TR/TE/TI=9000/110/2500 ms, 34 contiguous, 5 mm thick slices, 0.9×0.9 mm in-plane resolution). All the structural images were evaluated by a neuroradiologist (M.H.) for identification and classification of lesions.

All patients were referred for the first MRI for clinical purposes. The majority of patients (n=19) were sedated for this scan, since they were unable to cooperate due to decreased level of consciousness or cognitive impairment. Intravenously administered propofol was used for sedation, and patients were monitored by anaesthesiology staff. Oxygen supply and mechanical ventilation were provided when necessary.

For the follow-up scan, subjects were repositioned as close as possible to their position in the previous scan. For ethical reasons patients were sedated only if a follow-up MRI was requested for clinical purposes and patients were unable to cooperate for MRI. While 4 patients were sedated for the follow-up MRI, 20 were fully cooperative without sedation. Two additional non-sedated patients were excluded from this study due to motion artefacts in the follow-up images. All the remaining images were judged of good quality.

Image processing

Preprocessing: global volume changes

The 3D T1-weighted images were first reoriented manually to the anterior–posterior commissure (AC–PC) orientation, and resliced to 1 mm^3 voxels. Intensity normalisation within and between scans was performed using N3 and MRI Normalise from the MNI toolbox (www.bic.mni.mcgill.ca).

We used SIENA, available in the FSL 3.3 toolbox (www.fmrib.ox.ac.uk/fsl), to evaluate global brain volume change between the two scan time points for each subject. Additionally we applied SIENAX (also within FSL) for an estimation of brain parenchymal volume, normalized for head size, at the first scan time point. These methods have been described in detail elsewhere (Smith et al., 2001; Smith et al., 2002). In brief, SIENA starts by extracting brain and skull images from the two-timepoint whole-head input data. The two brain images are then aligned to each other (using the skull images to constrain the registration scaling); both brain images are resampled into the space halfway between the two. (This intermediate result was later entered into the TBM analysis, see below). Then segmentation is carried out in order to find brain/non-brain edge points. Perpendicular edge displacement, between the two time points, is estimated at these edge points, and the mean edge displacement is converted into a global estimate of percentage brain volume change (%BVC) from first to second scan. Measurement error of %BVC is reported to be approximately±0.20% (Smith et al., 2002).

In SIENAX, brain and skull images are extracted, and the brain image is affine-registered to an MNI standard template (using the skull image to determine registration scaling, to be used as a normalisation for head size). Next, segmentation with partial volume estimation is carried out in order to calculate the total volume of brain tissue: normalised brain parenchymal volume (BPV).

Preprocessing: regional volume changes

We used TBM to evaluate the regional distribution of brain volume change between the two scan time points. Following the intensity

Table 2
Clinical characteristics and global brain volume results for the 24 patients

Patient no.	Age at scan1 (years)	Sex	Cause of trauma	Neurosurgery	Duration of coma (days)	Duration of PTA (days)	TBI to scan1 (days)	TAI grade[a]	Focal lesions[b]	FIM at scan1	FIM at scan2	GOS-E at ~1 year	BPV at scan1	%BVC
1	23	F	Fall	−	>FU	>FU	58	2	−	18	18	2	1406	−9.42
2	21	F	MVA	+	12	39	64	2	+	79	117	4	1536	−5.29
3	34	M	MVA	−	126	>FU	81	3	−	18	30	3	1471	−8.80
4	40	F	Fall	+	9	>FU	64	2	+	18	20	3	1263	−7.02
5	40	M	Assault	−	4	88	50	0	−	87	122	6	1405	−1.16
6	60	M	Fall	+	21	>FU	46	2	+	34	35	3	1543	−7.21
7	28	M	MVA	−	24	66	69	3	−	122	125	8	1595	−4.08
8	54	M	Fall	−	14	119	45	2	+	60	125	5	1429	−1.80
9	23	M	MVA	+	18	47	81	2	+	117	124	6	1584	−2.56
10	24	M	MVA	−	1	39	36	1	−	93	125	5	1549	−0.62
11	65	M	Fall	−	3	39	42	1	+	116	120	6	1449	−2.60
12	31	M	MVA	+	7	48	40	2	+	38	102	5	1609	−6.28
13	37	M	MVA	+	14	40	69	1	+	117	122	7	1535	−2.74
14	22	M	MVA	−	7	31	55	2	−	120	125	7	1587	−1.78
15	19	M	MVA	−	2	23	37	1	−	113	124	7	1673	−1.28
16	41	F	MVA	+	10	65	41	2	+	55	113	5	1537	−3.73
17	26	M	MVA	−	22	65	77	1	+	106	124	6	1500	−1.87
18	22	M	MVA	−	9	178	79	2	−	18	103	4	1543	−2.45
19	23	M	MVA	−	11	107	55	3	+	23	111	4	1515	−5.58
20	18	F	MVA	−	15	66	62	3	+	24	105	4	1443	−2.69
21	40	M	Fall	+	10	84	48	2	+	100	117	5	1484	−1.63
22	53	M	Fall	+	5	171	39	3	+	18	111	5	1443	−6.80
23	27	M	MVA	−	10	77	47	2	−	49	113	5	1498	−2.98
24	26	F	MVA	−	4	58	29	2	−	59	126	8	1557	−4.75

MVA = motor vehicle accident; >FU = exceeds ~1 year follow-up; PTA = post-traumatic amnesia; FIM = functional independence measure; GOS-E = Glasgow outcome scale, extended; BPV = brain parenchymal volume; %BVC = percent brain volume change. See text for details.
[a] According to location of microhaemorrhages on T2*-W images (0=none, 1=subcortical only, 2=callosal, 3=brainstem).
[b] Parenchymal lesions excluding TAI (mainly contusions).

normalisation and initial registration steps from SIENA, described above, we then applied the high dimensional warping available in the SPM2 'Deformation toolbox' (www.fil.ion.ucl.ac.uk/spm) to these images. This TBM analysis estimates the deformation field that would warp the early T1 image to match the late T1 image within each subject (Ashburner et al., 2000). From this deformation field the amount of regional expansion or contraction is extracted by taking the Jacobian determinant at each point, thus generating a Jacobian determinant map in alignment with the late image. Following logarithmic transformation of the Jacobian determinant values (Leow et al., 2007) regional contraction corresponded to positive values and regional expansion to negative values. The non-skull-stripped follow-up T1 images were then normalized in SPM2 to the MNI standard space, and this transformation was applied to the log-transformed Jacobian determinant maps. Finally, these images were smoothed with an 8 mm Gaussian kernel.

Statistical analysis: global volume changes

The outputs from SIENA and SIENAX, %BVC and BPV respectively, were analysed group-wise using the non-parametric Mann Whitney *U*-test. Correlation analyses with clinical and conventional imaging variables were performed using the Spearman's rho. Prediction of functional status at follow-up by BPV and FIM at the first scan and % BVC was assessed using linear regression.

Statistical analysis: regional volume changes

For statistical analysis of TBM results, we used a permutation test (Randomise, available in FSL). Unlike the general linear model, permutation tests do not rely on the assumption that data are normally distributed (Nichols and Holmes, 2001). To compare patients and controls, a design matrix was constructed that included the nuisance variables age, sex, education and scan interval. Calculations were performed voxel-wise with 10,000 permutations, and a whole-brain correction for multiple comparisons was applied using a false discovery rate (FDR) of 0.05. Clusters with a radius of <2 mm (volume <33.5 mm^3) were rejected for display purposes. Anatomy atlas tools available in FSL were used to help identify anatomical regions.

Results

Global volume changes

Already at the first scan time point ~8 weeks post-trauma, normalized BPV, derived from SIENAX, was 8.4% lower in patients

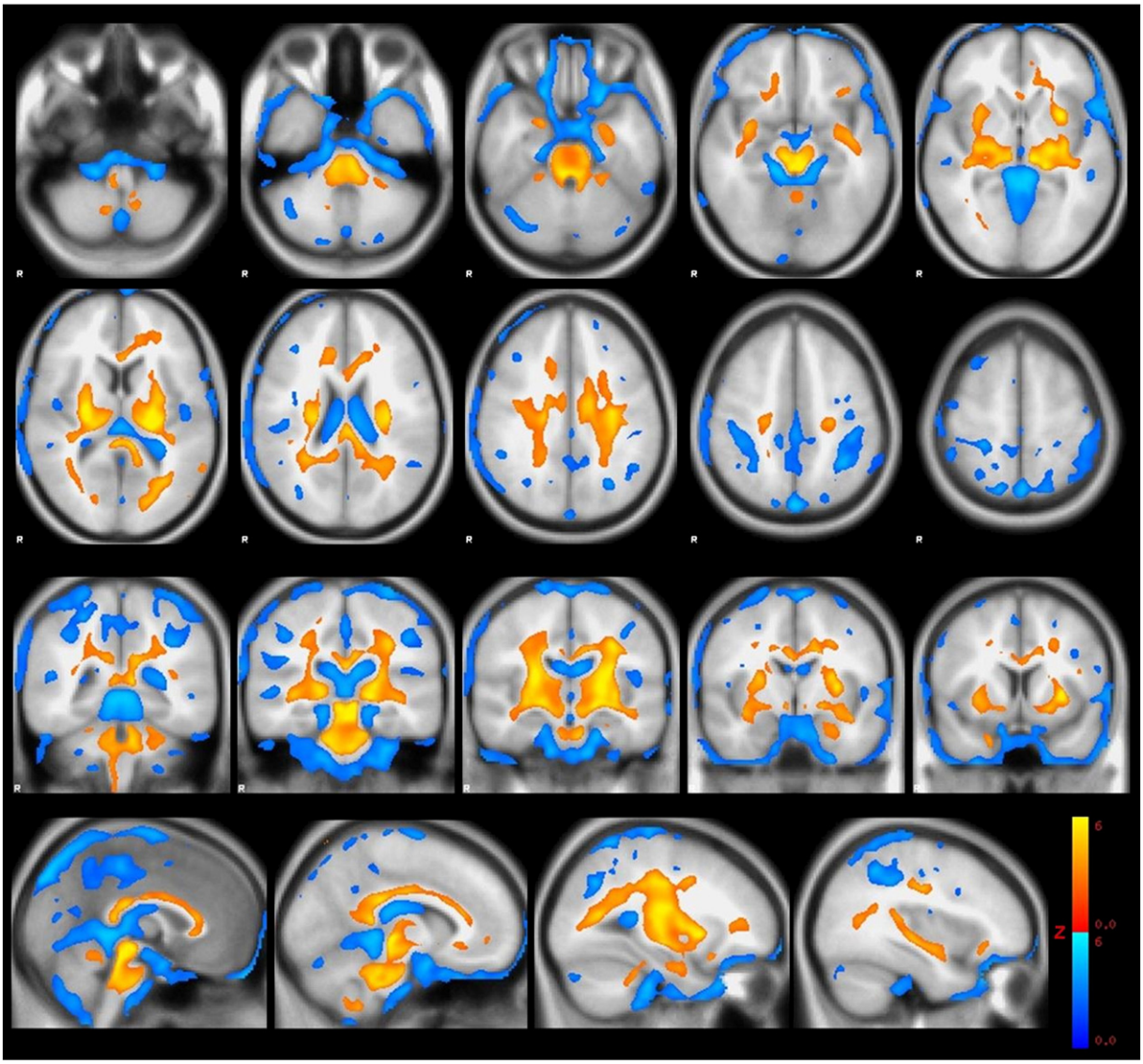

Fig. 1. Regions of significant volume changes in TBI patients between ~8 weeks and ~12 months post-injury, as compared to controls, thresholded at false discovery rate (FDR) 0.05 (clusters of <33.5 voxels rejected). Longitudinal volume reduction is coded red/yellow, volume expansion is coded blue. Results are overlaid onto the MNI standard template.

than controls (mean±SD: 1506 ml±85 ml vs. 1645 ml±85 ml, $P<0.0001$, Mann–Whitney U-test).

During the ~11 months scan interval %BVC, derived from SIENA, ranged between −0.6% and −9.4% (mean −4.0%, median −2.9%) in patients, compared to between −0.9% and +0.3% (mean −0.18%, median −0.13%) in controls (patients vs. controls: $P<0.000001$, Mann–Whitney U-test).

For each patient, Table 2 lists BPV and %BVC together with selected demographic, clinical and conventional imaging variables. There was a significant correlation between BPV and %BVC when all subjects were considered ($r=0.57$, $P<0.001$, Spearman's rho); however this correlation was not significant for either patients or controls separately. No significant correlations were found between %BVC and scan interval, age or gender. All but one patient had microhaemorrhages on T2*-weighted images, indicating TAI. Graded according to location (Graham et al., 2002), TAI grade correlated with %BVC ($r=-0.59$, $P<0.01$, Spearman's rho), but not with BPV.

To check for the robustness of SIENAX for these traumatized brains, we also applied SIENAX on the follow-up scans, again comparing to controls, and calculated the differences (in %) between BPV at the first and second scan (data not shown). These values were roughly comparable to the %BVC derived from SIENA, indicating that the estimates from SIENAX were reliable, at least as rough estimates of BPV.

Regional volume changes

TBM, with whole-brain correction for multiple comparisons, identified regions with significant volume loss or volume expansion over time in patients as compared to controls. Fig. 1 shows the differences between patients and controls using an FDR of 0.05. At this threshold, a large coherent cluster of volume loss extended from the brain stem and cerebellar peduncles and bilaterally through the thalamus, internal capsule, external capsule, putamen, inferior and superior longitudinal fasciculus, corpus callosum (genu, body and splenium) and corona radiata. Small clusters of significant volume loss were also found, mainly in the cerebellum and in the frontal lobes. Significant longitudinal volume expansion in patients compared to controls was found in the ventricles and scattered in the subarachnoidal space (with a large cluster at the fundus of the intraparietal sulcus). In general the pattern of volume loss as well as volume expansion was relatively symmetric. The statistical strength of volume loss, reaching its maximum in the tectum mesencephali ($Z=6.86$), exceeded that of volume expansion (maximum $Z=5.07$). Details of significant volume loss are found in Table 3.

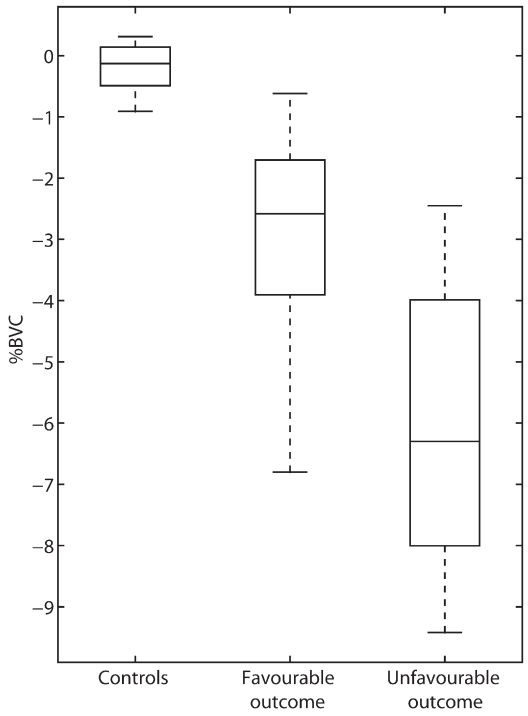

Fig. 2. Box and whiskers plot of %BVC in patients with favourable ($n=16$) and unfavourable ($n=8$) outcome ($P<0.01$, Mann–Whitney U-test). Control values ($n=14$) are displayed for comparison. %BVC = percent brain volume change.

Correlation with clinical variables

Injury severity

BPV at the first scan correlated significantly with duration of PTA ($r=-0.59$, $P<0.01$, Spearman's rho), however not with duration of coma. Both duration of coma and PTA correlated significantly with % BVC between the two scan time points ($r=-0.45$, $P<0.05$ and $r=-0.53$, $P<0.01$, respectively, Spearman's rho).

Functional status and outcome

BPV at the first scan correlated significantly with concomitantly evaluated FIM ($r=0.46$, $P<0.05$, Spearman's rho). Also %BVC between the two scan time points was significantly correlated with FIM evaluated both at the first and at the second scan time point ($r=0.62$, $P=0.001$ and $r=0.68$, $P<0.001$ respectively, Spearman's rho).

Table 3
Clusters of significant volume loss in patients compared to controls at false discovery rate (FDR) 0.05

	Anatomical region	Tissue type	Side	MNI coordinates of voxel of maximum significance			PeakZ	Cluster size (voxels)
				x	y	z		
1	Large coherent cluster in the brain stem and cerebellar peduncles, extending bilaterally through internal capsule, thalamus, putamen, external capsule, inferior and superior longitudinal fasciculus, corpus callosum, corona radiata	WM+GM	L/R	−1	−31	−16	6.86	129013
2	Cerebellum	GM	L	−8	−50	−54	4.06	963
3	Frontal orbital cortex	GM	L	−29	18	−18	3.54	736
4	Cerebellum	GM	R	10	−62	−52	3.74	508
5	Frontal orbital cortex	GM	R	9	20	−21	3.04	301
6	Cerebellum	GM	R	25	−53	−23	3.05	212
7	Frontal lobe, subcortical WM	WM	L	−43	10	18	3.13	178
8	Frontal lobe, cortex/subcortical WM	WM+GM	L	−42	29	2	3.77	148
9	Middle temporal gyrus	GM	L	−60	−56	10	3.40	122
10	Superior corona radiata	WM	R	23	8	38	2.72	110
11	Lateral occipital cortex	GM	L	−50	−77	13	3.06	61

Coordinates of each cluster maximum are reported. Cluster maximum for cluster 1 corresponds to tectum mesencephali.
GM = grey matter; WM = white matter; L = left; R = right.

With respect to 1-year outcome, BPV at the first scan did not differ significantly between favourable and unfavourable outcome groups (Mann–Whitney *U*-test). However, BPV correlated significantly with the full scale GOS-E ($r=0.48$, $P<0.05$). Late volume change (%BVC between the two scan time points) was significantly different between outcome groups (Fig. 2; $P<0.01$, Mann–Whitney *U*-test) and also correlated significantly with the full scale GOS-E ($r=0.55$, $P<0.01$).

In a linear regression model with FIM at the follow-up scan as the dependent variable, FIM at the initial scan significantly predicted late FIM, as one would expect ($P<0.001$). Adding BPV at the first scan did not improve the model. However, adding %BVC to the model improved prediction of late FIM (increment $F=4.7$ and parameter estimate $P<0.001$ for %BVC), with pronounced late atrophy predicting lower FIM at follow-up, and vice versa.

Discussion

We studied late atrophy occurring between ~8 weeks and ~12 months following severe TBI, using TBM to evaluate the regional distribution of volume change and SIENA to estimate individual global atrophy. Additionally, SIENAX was used to estimate global atrophy occurring prior to the first time point. In patients, as compared to controls, significant atrophy during the scan interval was found in: a large coherent cluster in the brain stem and cerebellar peduncles extending bilaterally through the thalamus, internal capsule, external capsule, putamen, inferior and superior longitudinal fasciculus, corpus callosum and corona radiata; and in smaller clusters mainly in the cerebellum and the frontal lobe. At ~8 weeks post-injury brain volume was already reduced by mean 8.4% in patients as compared to controls, but an additional mean 4.0% (median 2.9%) volume loss occurred in patients during the scan interval. The magnitude of this late volume loss was significantly correlated with injury severity (duration of coma and PTA), with FIM at both scan time points, and with 1-year GOS-E.

Global volume changes

We found a highly significant decline in brain volume during the late subacute and chronic phases of TBI. This is in agreement with the recent study by Trivedi et al. also using SIENA (Trivedi et al., 2007). While our patient population represented very severely injured survivors of TBI (Engberg et al., 2006), Trivedi studied a population of mixed injury severity ranging from mild to severe TBI. This probably explains why we found a greater decline in brain volume (mean −4.0%, median −2.9%) compared to their study (mean −1.43%). However, part of this difference may also be due to the fact that the time from TBI to the first scan was slightly shorter in our study (55 days, range=29–81 days compared to 79 days, range=39–109 days).

All but one patient in the present study had microhaemorrhages on conventional T2*-weighted images, indicating the presence of TAI. In accordance with the view that general atrophy post-TBI is mainly caused by TAI, we found that TAI grade, as evaluated on T2*-weighted images, correlated with %BVC. However, a similar correlation could not be found for initial atrophy estimated by BPV.

To relate longitudinal decline in brain volume to the early atrophy occurring between the time of injury and the first scan time point (the first ~8 weeks post-injury), we used SIENAX, comparing brain volume in patients at the first scan time point to that of the controls. With SIENAX we found that BPV in patients at the first scan time point was on average 8.4% smaller than BPV in controls. While this should be regarded as a fairly rough estimate (see subsection Limitations), it clearly indicates that the rate of decline in brain volume is much higher in the acute/early subacute phase post-trauma than at later stages. Obviously our study does not allow further conclusions to be made about the time course of atrophy following TBI, as we cannot know whether the late atrophy occurred gradually during the whole scan interval, or whether the degenerative process ended already after a few months. However, animal studies suggest a gradual volume decrease up to at least 1 year post-trauma (Rodriguez-Paez et al., 2005). Future human studies with multiple scan time points should be conducted to better characterize the time course of the progressive atrophy following TBI.

Regional volume changes

The pattern of late atrophy observed in patients as compared to controls corresponds well to those regions known from neuropathological and biomechanical studies to be susceptible to TAI or to consequences of TAI (Graham et al., 2002; Maxwell et al., 1997). The continuous involvement of the corticospinal tract from the corona radiata through the posterior limb of the internal capsule, crus cerebri and pons is likely to represent Wallerian degeneration secondary to TAI. These results suggest that the progressive atrophic process following TBI is a direct consequence of TAI. The highest level of significance was found for the tectum mesencephali, which is one area particularly susceptible to TAI.

The results of the present study are mainly in agreement with the findings of the single available TBM study on TBI (Kim et al., 2008). When comparing these two studies, one should bear in mind that while we investigated the regional distribution of late atrophy only, the study by Kim et al. was not longitudinal and therefore did not distinguish between early and late atrophy. In both studies, the statistical strength of volume loss was generally higher than that of volume expansion. As concluded by Kim et al. this suggests that using ventricular enlargement to indirectly measure atrophy is not the most sensitive measure. Like in the study by Kim et al. we found significant volume loss (at FDR 0.05) in the brainstem, thalamus, corpus callosum, putamen and cerebellum. However, the volume loss was more widespread in our study and included the entire corticospinal tract from corona radiata to pons as one coherent cluster. Additionally we found significant volume loss in the external capsule, inferior and superior longitudinal fasciculus and in the cerebellar peduncles. Unlike Kim et al. we did not find volume loss in the caudate. While in both studies significant volume expansion was found in CSF, Kim et al. also found apparent volume expansion in some white matter areas including the internal capsule, which they interpreted as secondary to heavy atrophy of surrounding areas.

Some of the discrepancies between the present study and the study by Kim et al. are likely to be due to differences in injury severity, as Kim et al. included patients with both moderate and severe TBI. It is possible that there are also some differences in the regional distribution of the atrophy occurring in the acute/early subacute phase compared to the late atrophy in the late subacute/chronic phase. One should also bear in mind the somewhat random nature of the injuries in the individual TBI patients, which inadvertently is another source of variability between studies. Finally, discrepancies may also be related to methodological differences in the two studies. Importantly, in the cross-sectional study by Kim et al., every brain was warped to a population-specific template based on both controls and patients, while in our longitudinal study warping was performed within subject.

In a very recent longitudinal study, Bendlin and co-workers (Bendlin et al., in press) measured regional volume changes in patients with moderate TBI using voxel-based morphometry (VBM). Their study design is somewhat similar to ours, but differs in some key elements. Firstly, there is a difference in injury severity of the TBI patients. Secondly, as opposed to VBM, TBM is based on intra-subject volume change. Thirdly, VBM relies on segmented white matter and grey matter maps, whereas our TBM analysis has the advantage of not relying on tissue segmentation (in our dataset tissue segmentation tended to misclassify focal lesions, see subsection Limitations). Despite these differences, our results are largely in agreement with the findings of Bendlin et al. who reported longitudinal volume losses

in corona radiata, corpus callosum, internal and external capsules, superior and inferior longitudinal fascicules, cingulum, inferior fronto-occipital fasciculus, corticospinal tract, cerebellar peduncles, thalamus, and pallidum, as well as small areas with volume loss in the cerebellar white matter, right post-central and precentral gyri, supplementary motor area, and putamen.

Clinical significance of progressive atrophy

One of the advantages of the prospective longitudinal design used in this study is that it allowed us not only to scan the patients with a uniform time interval, but also to collect clinical data at predefined time points, including outcome evaluation about 1 year post-injury. We found several correlations between clinical variables and the degree of late global atrophy. In agreement with the study by Trivedi et al., we found a significant correlation between duration of coma and %BVC, although duration of coma was defined slightly differently in the two studies. Another indicator of injury severity, duration of PTA, also correlated significantly with %BVC in our study. These findings are not surprising given that the extent of TAI is likely to be a major determinant of %BVC as well as of the severity of impairment of consciousness reflected by duration of coma or PTA.

Furthermore, we found significant correlations between %BVC and functional status (as evaluated by FIM) at both scan time points, and between %BVC and 1-year GOS-E. These findings, however, do not necessarily imply that late volume loss *per se* is a determinant of functional status and outcome. It might be that the extent of TAI is the major determinant of both %BVC and clinical function including long-term clinical outcome. The consequences of TAI may involve cellular processes other than atrophy, which also might account for some of the clinical consequences following TAI.

Using linear regression, we determined which parameters predicted functional status at the follow-up scan. We found that inclusion of %BVC dramatically improved upon the predictive performance offered by the ~8 week FIM values alone. Thus, a higher rate of volume loss during the scan interval was associated with poorer functional status at follow-up, controlling for the degree of functional impairment present at the first scan time point. It should be noted, however, that the four most severely injured patients (patient no. 1, 3, 4 and 6 in Table 2, who all had PTA >1 year) stood out from the rest, causing the correlation between %BVC and FIM at ~12 months to be driven mainly by these subjects. Larger studies are clearly needed to confirm the observed relationship between atrophy and functional impairment.

For the majority of patients, decline in brain volume occurred concurrently with remarkable clinical improvement, as for example reflected in the median FIM-value which increased from 60 (18–122) at the time of the first scan to 117 (18–126) at the second scan. This apparent paradox indicates that some regenerative processes must occur despite the macroscopic degeneration. From animal studies evidence is accumulating that neuroplastic changes, such as axonal sprouting and synaptic reorganization, accompany functional recovery following TBI (reviewed e.g. by Levin 2003; Albensi and Janigro 2003, Dancause 2006) and may even be enhanced by pharmacological procedures (see e.g. Priestley 2007). In humans, using diffusion tensor imaging, we recently found that diffusion abnormalities following severe TBI, supposedly reflecting disruption of axonal micro-architecture, partly normalise during clinical recovery, particularly in patients with good outcome (Sidaros et al., 2008). Metabolite abnormalities, as measured by MR proton spectroscopy, also have been found to recover over time to near normal levels in good outcome patients (Holshouser et al., 2006; Signoretti et al., 2008).

Limitations

The use of SIENAX is based on the assumption that brain volume of the patients prior to injury was comparable to that of the controls. Since the groups were matched with respect to age, sex and education, this may be a reasonable approximation. Even if it had been feasible to acquire another MRI in the very acute phase following trauma, oedema would have greatly confounded longitudinal volume comparisons.

In principle, clearing of brain oedema between scans could be responsible for an apparent loss of brain volume over time. However, we found no radiological evidence of oedema at the first MRI (evaluated on T2-weighted and FLAIR images), consistent with the experience that oedema resolution usually occurs within the first four weeks post-injury, i.e. before the first scan time point of this study. Furthermore, the fact that BPV was found to be substantially lower in patients than controls at the first scan time point, strongly argues that oedema had resolved at that point and thus did not mediate the observed longitudinal decline in brain volume.

Grey matter/white matter segmentation tended to misclassify focal lesions as grey matter, regardless of original tissue type. This prevented us from studying grey and white matter atrophy separately. However, lesioned tissue was never misclassified as CSF, and the sum of grey matter and white matter volume estimates, derived from SIENAX, were therefore regarded as valid estimates of BPV.

One limitation related to voxel-wise morphometric approaches such as TBM is that the sensitivity to areas with high anatomical variability between subjects, such as cortical gyri and sulci, is less than to areas exhibiting little inter-subject variability. In a TBI population, the correct warping of cortical areas is even further complicated by the occurrence of focal lesions, which are often cortical in location. Therefore, we cannot exclude the possibility that the observed relative sparing of cortical areas, in terms of late atrophy, could be a false-negative result. On the other hand, we did not expect cortical atrophy to be a prominent feature in comparison with white matter atrophy, because local cortical atrophy due to focal lesions would vary in location between patients and thus be unlikely to emerge as significant in a voxel-wise group analysis. The possibility of more widespread cortical thinning, e.g. secondary to TAI with retrograde degeneration, would probably be below the limit of detection by TBM. Future studies, using for example cortical thickness mapping, might elucidate a possible cortical involvement in the degenerative process following TBI.

Finally, another limitation of our study is that we did not acquire MRI at more than two time points. Future studies using multiple data acquisitions at shorter time intervals would allow for a more detailed description of the time course of atrophy following TBI.

Conclusions

In this prospective longitudinal study of late volume changes following severe TBI we have demonstrated that the most pronounced atrophy is found in regions susceptible to TAI or to consequences of TAI, suggesting that TAI is a major factor responsible for late degeneration. We have further shown associations between the extent of global atrophy and clinical parameters, including duration of coma and PTA, functional status and 1-year outcome. Interestingly, in most patients these long-term degenerative changes occurred concurrently with functional improvement, suggesting that macroscopic tissue loss is less important than supposedly microscopic neuroplastic processes in determining clinical function.

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