Multiclass semantic segmentation and quantification of traumatic brain injury lesions on head CT using deep learning: an algorithm development and multicentre validation study

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Summary

Background CT is the most common imaging modality in traumatic brain injury (TBI). However, its conventional use requires expert clinical interpretation and does not provide detailed quantitative outputs, which may have prognostic importance. We aimed to use deep learning to reliably and efficiently quantify and detect different lesion types.

Methods Patients were recruited between Dec 9, 2014, and Dec 17, 2017, in 60 centres across Europe. We trained and validated an initial convolutional neural network (CNN) on expert manual segmentations (dataset 1). This CNN was used to automatically segment a new dataset of scans, which we then corrected manually (dataset 2). From this dataset, we used a subset of scans to train a final CNN for multiclass, voxel-wise segmentation of lesion types. The performance of this CNN was evaluated on a test subset. Performance was measured for lesion volume quantification, lesion progression, and lesion detection and lesion volume classification. For lesion detection, external validation was done on an independent set of 500 patients from India.

Findings 98 scans from one centre were included in dataset 1. Dataset 2 comprised 839 scans from 38 centres; 184 scans were used in the training subset and 655 in the test subset. Compared with manual reference, CNN-derived lesion volumes showed a mean difference of 0·86 mL (95% CI –5·23 to 6·94) for intraparenchymal haemorrhage, 1·83 mL (–12·01 to 15·66) for extra-axial haemorrhage, 2·09 mL (–9·38 to 13·56) for perilesional oedema, and 0·07 mL (–1·00 to 1·13) for intraventricular haemorrhage.

Interpretation We show the ability of a CNN to separately segment, quantify, and detect multiclass haemorrhagic lesions and perilesional oedema. These volumetric lesion estimates allow clinically relevant quantification of lesion burden and progression, with potential applications for personalised treatment strategies and clinical research in TBI.

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Introduction With an estimated global incidence of more than 60 million cases per year, traumatic brain injury (TBI) is the leading cause of mortality in young adults and a major cause of morbidity worldwide.13 CT is the imaging modality of choice to assess the extent and distribution of injury, provide input to prognostic models, and assess the requirement for surgery.1 Being able to automatically and accurately quantify lesion load and its progression would provide a more objective basis than qualitative assessment by visual inspection for medical and surgical treatment decision making.

A substantial focus of TBI research has been to refine the current classification schemes into more therapeutically meaningful categories by incorporating information on a patient’s genetic, blood, and cerebrospinal fluid biomarkers along with clinical and neuroimaging data.14 Hence, being able to reliably and efficiently differentiate lesion types and compute their spatial distribution, number, and volumes would enable optimised and more individualised treatment strategies. Such automated assessment would also facilitate the analysis of large imaging datasets, which are emerging as an essential research resource. Finally, by far the greatest burden of TBI is in low-income and middle-income countries,2 where radiological expertise is likely to be less easily available. Having automatic CT analysis algorithms would be of particular benefit in such contexts.2

Substantial inter-centre variability and discordance by radiologists exists when reporting CT scan results from patients with TBI.5 Automating such quantitative measurements would, in theory, circumvent interobserver
variability and allow for analysis of large-scale imaging datasets. Until recently, attempts to automate acute intracranial haemorrhage segmentation on CT have relied on techniques such as intensity thresholding and active contouring, which still require some degree of manual input, and have only been applied to small datasets, raising concerns about the robustness and generalisability of these models.10–12 Little past success in this context probably reflects two challenges in working with this patient population. First, the heterogeneity of radiographic phenotypes in TBI makes the development of accurate segmentation rules challenging. Second, the diffuse nature of the injury in a large proportion of patients with TBI renders the manual annotations required to establish a ground truth reference dataset difficult and time consuming.

Convolutional neural networks (CNNs) have emerged as a powerful tool for image segmentation, with the ability to learn complex non-linear mappings between the input image and segmentation.13 Previous deep learning studies for segmentation of TBI lesions have focused on the segmentation of undifferentiated haemorrhagic lesions, with no attempts to differentiate pathoanatomical lesion types.14 Although such binary image-level detection of abnormalities might prove useful for triaging patients in need of urgent medical attention, it has little value for analysis of lesion progression and predictive modelling.

In this study, we report quantitative multiclass segmentation results using a convolutional neural network (CNN) for intraparenchymal haemorrhage, extra-axial haemorrhage, intraventricular haemorrhage, and perilesional oedema. We show that these lesion types can be detected and measured with high accuracy. These attributes are relevant for image-based diagnosis, assessment of injury type, quantification of injury burden, and measurement of lesion progression, both for clinical care and research. We have made the algorithm freely available to facilitate future research.

Implications of all the available evidence

CNN-based processing of CT images in TBI can be used to quickly and accurately detect the type, distribution, and extent of injury after TBI. Such algorithms are likely to be of use in research studies, facilitate clinical radiology workflows by flagging scans that require urgent attention, aid reporting in resource-constrained environments, and help to detect pathoanatomically relevant features for prognostication and characterisation of lesion progression.
A complete ethics statement, which contains a comprehensive list of sites, ethical committees, and approval numbers, is available online. For development and internal validation, we use two datasets from CENTER-TBI: dataset 1 and dataset 2. We used a two-step process to acquire a large number of annotated scans (appendix p 4). The scans in dataset 1 were annotated manually in a bespoke segmentation tool (ImSeg, version 1.9, BioMedIA, London, UK) by trained personnel (FM and KA) and checked by two other experts (VFJN and TD). These segmentations were used to develop the initial segmentation model and then excluded from any subsequent training or evaluation to avoid skewing the analysis of results. With the model developed on dataset 1, we did automatic lesion segmentation on dataset 2. These automatic segmentations were refined manually by trained personnel (FM and KA) using ITK-SNAP.
improve visualisation. Axes are plotted on different scales across plots for clarity. Absolute volume errors are shown in the appendix (pp 9–10).

Figure 2: Bland-Altman plots for lesion volume estimation
The solid horizontal lines are means and the shaded regions are 95% CIs. The x-axes are on a logarithmic scale to maximise the number of scans for training and testing under the constraint of finite resources for expert annotations.

Evaluation metrics were computed and stratified by lesion class and volume. A virtual lesion class (any lesion) consisting of the combined lesion map that merged all lesion types into one was created to allow for evaluation in terms of lesion versus non-lesion.

To assess the performance of the algorithm, we used the Dice similarity coefficient (DSC), which measures the agreement between manual and automatic segmentation. Since the mean DSC is sensitive to lesions with small volumes or scans on which lesions are not present, we report DSC scores for lesions above several volume thresholds. DSC is a well accepted metric for assessing accuracy in image segmentation. However, it is not meaningful when assessing performance with respect to clinical utility (appendix pp 2–3). For a clinically relevant assessment, we have provided additional metrics such as lesion volume estimates and receiver operating characteristic (ROC) curves for lesion detection and lesion volume classification.

To assess the accuracy of the algorithm at estimating lesion volume, we extracted lesion volumes from the manual and predicted segmentations to calculate volume error, which we summarised in Bland-Altman plots. We also assessed the accuracy of the algorithm at quantifying lesion progression. To obtain the error in volume change, we calculated the true volume difference and predicted volume difference between repeat scans for patients in the test set who had repeat scans for which both manual and predicted segmentations were available.

For the study algorithm see https://github.com/biomedia-mira/blast-ct (version 3.8.0-beta), and the corrections were reviewed by two experts (VFJN and TD) to provide high-quality, accurate ground truth lesion segmentations. The refined segmentations contained four lesion types: intraparenchymal haemorrhage; extra-axial haemorrhage, which includes subdural haematoma, extradural haematoma, and traumatic subarachnoid haemorrhage; perilesional oedema (hereafter referred to as oedema); and intraventricular haemorrhage. Small petechial haemorrhages, which probably arise from diffuse vascular injury and are thought to be a surrogate for accompanying diffuse axonal injury, were classified as intraparenchymal haemorrhage.

To establish whether the semi-automatic annotation procedure of dataset 2 provided adequate reproducibility, we did repeat manual segmentation on 20 scans by a single expert (FM) to assess intra-rater reproducibility, and on 25 scans by a second expert (DW) to assess inter-rater variability.

For the subsequent analyses, we split dataset 2 into a training and test set. Different scans from the same patient were placed together in either the training or the test set to avoid the correlation between repeat scans biasing the results. Only scans with more than 1 mL of lesion load were included in the training set to ensure that there was enough training signal for the CNN.

For the segmentation method, we used DeepMedic, a three-dimensional CNN with three parallel pathways that process the input at different resolutions. Details on the model and image pre-processing are provided in the appendix (p 2). To facilitate its use in future studies, our algorithm is available online.

For external validation, we used the CQ500 dataset, a publicly available, anonymised, TBI CT dataset provided by the Centre for Advanced Research in Imaging, Neurosciences and Genomics, New Delhi, India. This dataset provides image-level labels as opposed to voxel-wise segmentations. However, it is the largest labelled TBI cohort available publicly, and no other dataset provides voxel-wise segmentations.

Outcomes
The primary outcome was the quantification of lesion volume. The secondary outcomes were lesion detection and the assessment of lesion progression.

Statistical analysis
Statistical analysis was done in Python 3.6.8 (appendix p 3). Classic sample size calculation is not directly applicable to CNN-based segmentation. The sample sizes in this work followed the common principle in current deep learning research whereby more data tends to yield better results. Thus, we attempted to maximise the number of scans for training and testing under the constraint of finite resources for expert annotations.

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The output of the segmentation algorithm can be used for lesion detection and lesion volume classification. We used the true lesion volume to set a classification target (eg, target is positive if the true volume is greater than 1 mL and negative otherwise). We then used the predicted lesion volume as the score on which a threshold was varied to calculate ROC curves. We addressed three key lesion detection and lesion volume classification problems to assess the clinical applicability of the model: (1) ability to detect lesions, which is equivalent to classifying lesions with a volume greater than 0 mL; (2) classification of lesions with a volume greater than 1 mL, to enable comparison with findings from datasets that did not contain small lesions; and (3) classification of lesions with a volume greater than 25 mL, equivalent to Marshall grade V/VI, which may indicate lesions requiring surgical intervention.

For each curve, we computed the area under the curve (AUC), its 95% CI using the Hanley and McNeil approach, the sensitivity and specificity of the two operating points (sensitivity at a specificity of 0.90 and vice versa), and their 95% CIs using the Clopper-Pearson method.

We used our algorithm to segment the scans in the CQ500 dataset and to calculate lesion volumes. These are used as the classification score to compare with the ground truth image-level labels provided. This dataset was used only at the end for final validation, never during development. This approach validated the lesion detection performance of our algorithm on an external, independent dataset from a different patient population. CQ500 was not annotated for oedema, and so instead of our summed any lesion class we report on intracranial haemorrhage, which includes all haemorrhage classes in our analysis: intraparenchymal haemorrhage, extra-axial haemorrhage, and intraventricular haemorrhage.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Dataset 1 consisted of 98 different CT scanning sessions from 27 patients from one centre (Cambridge University NHS Foundation Trust, Cambridge, UK). Data from this centre were available first as part of a preliminary proof-of-concept study. Dataset 2 consisted of 839 different CT scanning sessions from 512 patients and 38 different centres from which data were available at the time of the study, including Cambridge NHS Foundation Trust. The procedure of semi-automatic segmentation enabled the creation of a much larger dataset (839 vs 98 scans) without a commensurate increase in resource requirements. Table 1 shows the cohort characteristics of both datasets, representing the broad spectrum of TBI.

dataset 2, 184 scans were included in the training subset and 655 scans were included in the test subset. Consistent with the known heterogeneity of TBI, 744 (89%) of 839 scans did not contain all four lesion types. The distribution of lesions is available in the appendix (p 8).

Figure 1A shows qualitative results for five different cases from our test set, showing the visual agreement between the true and predicted segmentations. Figure 1B shows DSC boxplots. The median DSC for the any lesion class was 36-0% (IQR 0-0–63-4) when including all 599 scans (469 with lesions plus 130 with no lesions but where our model predicted a lesion). In addition to calculating DSCs using all the test scans, we chose the following preplanned thresholds to address different performance levels: 0 mL, 1 mL, and 5 mL (appendix p 9).

Limiting the analysis to the 469 scans with lesions increased the median DSC to 49-4% (IQR 21-5–67-1), and the exclusion of lesions of 1 mL or smaller further increased the DSC to 59-3% (42-6–73-1, n=328). A similar relationship between lesion volume and DSC was noted for individual lesion classes (figure 1B). For lesions with a volume greater than 1 mL, the median DSC was 65-2% (IQR 30-6–77-8, n=167) for intraparenchymal haemorrhage, 55-3% (39-1–71-0, n=262) for extra-axial haemorrhage, 44-8% (15-5–64-1, n=208) for oedema, and 47-3% (38-1–60-3, n=21) for intraventricular haemorrhage; for lesion volumes greater than 5 mL, these numbers increased to 72-6% (58-1–81-6, n=90) for...

Figure 3: Bland-Altman plots for lesion progression
The solid horizontal lines are means and the shaded regions are 95% CIs. The x-axes are on a logarithmic scale to improve visualisation. Axes are plotted on different scales across plots for clarity. Absolute volume change errors are shown in the appendix (pp 9–10).
intraparenchymal haemorrhage, 67·5% (52·5–78·2) for extra-axial haemorrhage, and 54·6% (32·0–68·1, n=137) for oedema. To compare with previous literature, we combined intraparenchymal haemorrhage and extra-axial haemorrhage and obtained a median DSC of 72·0% (59·2–80·1, n=210) for lesion volume greater than 5 mL.

Table 2 shows Bland–Altman plots of the agreement between the true and predicted lesion volumes. The mean difference was 0·86 mL (95% CI −5·23 to 6·94) for intraparenchymal haemorrhage, 1·83 mL (−12·01 to 15·66) for extra-axial haemorrhage, and 67·5% (52·5–78·2) for oedema. For lesions with a volume greater than 5 mL, the median absolute error was 3·57 mL (IQR 1·96 to 7·97, n=90) for intraparenchymal haemorrhage and 4·57 mL (0·12 mL to 1·71) for extra-axial haemorrhage. The mean difference was 0·46 mL (95% CI −0·37 mL to 1·30) for intraparenchymal haemorrhage, −0·37 mL (−5·42 to 4·69) for extra-axial haemorrhage, and 0·68 mL (−9·03 to 10·39) for oedema, and −0·12 mL (−1·48 to 1·13) for intraventricular haemorrhage.

For further discussion regarding absolute volume error see the appendix (p 3). Regarding the reproducibility of the manual annotation procedure, for intra-rater reproducibility (n=20) and inter-rater variability (n=25), we obtained agreements in the range of 0·90–1·00 for all lesion types (appendix p 8).

98 patients in the test set who had repeat scans for which both timepoints could be established (196 scans) were included in the calculations of true and predicted volume difference. Figure 3 presents Bland–Altman plots of the agreement between the true and predicted lesion volume change. The mean difference was 0·46 mL (95% CI −4·04 to 4·97) for intraparenchymal haemorrhage, −0·37 mL (−5·42 to 4·69) for extra-axial haemorrhage, 0·68 mL (−9·03 to 10·39) for oedema, and −0·12 mL (−1·48 to 1·13) for intraventricular haemorrhage.

In the appendix (p 3), we show that our algorithm enables localisation of lesions (ie, the quantification of lesion volume by brain region).

Table 2 and figure 4 show the results of lesion volume classification and lesion detection for the external validation dataset CQ500.
On the external validation set, we reported an AUC of 0.83 (95% CI 0.79–0.87) for the intracranial haemorrhage class, 0.90 (0.86–0.94) for the intraparenchymal haemorrhage class, 0.80 (0.75–0.85) for the extra-axial haemorrhage class, and 0.95 (0.89–1.00) for the intraventricular haemorrhage class.

Discussion

In this study, we found that the voxel-wise segmentation produced by a CNN can be used for volumetric quantification and detection and classification of multiclass TBI lesions in head CT, as well as for the assessment of lesion progression. We were able to accurately quantify and detect lesions on an external, independent dataset. To our knowledge, this is the largest study so far to use a ground truth reference of manually annotated and manually corrected automatic segmentations of CT scans. The size and diversity of this multicentre dataset provide insights into the performance of deep learning in a real-world clinical scenario. We extend findings from previous studies by providing quantitative volumetric results separately for intraparenchymal haemorrhage, extra-axial haemorrhage, intraventricular haemorrhage, and perilesional oedema.

The CNN provided a well-calibrated prediction of lesion volume since differences between the true and predicted volumes were small when compared with the overall lesion volume. The funnelling observed can be explained by lesions being predicted where there were none and vice versa, which mostly occurs for smaller lesions. For comparison, previous work reported a median absolute error of 8.83 mL (n=39) for intraparenchymal haemorrhage and extra-axial haemorrhage lesions combined while considering only lesions with a volume greater than 5 mL. In our analysis, we did fine-grained segmentation of these two classes individually and validated our CNN on a larger dataset. For lesions with a volume greater than 5 mL, our median absolute error was smaller than that reported previously for intraparenchymal haemorrhage and extra-axial haemorrhage.

The potential clinical applicability of the volume estimates is further confirmed by our results on lesion progression. Such progression of intracranial lesions represents a major target for therapies in the acute phase. For example, cerebral contusions are common after TBI, occurring in up to two-thirds of patients admitted to hospital, and progression of such lesions is common, occurring in up to half of patients within the first 24–48 h. The ability to automatically monitor lesion progression offers key opportunities to improve patient stratification, guide and monitor management, and investigate potential causes and risk factors for lesion progression in large cohort studies such as CENTER-TBI. Until now, the identification of factors that predict or cause contusion progression, or both, has been hampered by the need to estimate lesion volume and change manually, restricting analyses to small sample sizes.

Regarding the underlying lesion segmentation, the DSC increased with lesion volume, illustrating that the DSC is sensitive to small or non-existent lesions, which is a limitation of the metric. The median DSC of 73.0% (n=39) reported previously for large intraparenchymal haemorrhage and extra-axial haemorrhage lesions combined (lesion volume >5–5 mL) is similar to that found in our study.

The algorithm performed less well at quantifying perilesional oedema, and by extension mixed density lesions. However, the ability to undertake such quantification has not been reported previously; hence, we are unable to benchmark it against previous work. Although detection and delineation of high-intensity haemorrhagic lesions are straightforward, precise delineation of hypointense oedema can be challenging, even for radiologists. The ability of our algorithm to do this task, in addition to quantifying other lesion types, may be important for prognostication, aid detection and avoidance of secondary injury, the evaluation of neuroprotective measures, and as an intermediate biomarker for clinical

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trials aimed at the reduction of cerebral oedema and contusion growth.11

The accuracy of our CNN was lower in segmenting small haemorrhagic lesions. From a clinical perspective, however, this reduced accuracy is mitigated by the fact that the volume of these small lesions is less important in terms of prognostication or deciding on therapy. These small lesions are typically microhaemorrhages associated with diffuse vascular injury and are clinically used as a surrogate marker for diffuse axonal injury. Consequently, their clinical significance is dependent on number and distribution, rather than volume of individual lesions.17

Although our model was not designed for classification specifically, as a byproduct of the segmentation algorithm, it is able to do so with comparable performance to state-of-the-art methods developed solely for detection.12 On the CQ500 dataset, previous work12 reported an AUC of 0.94 (95% CI 0.92–0.97) for intracranial haemorrhage, 0.95 (0.93–0.98) for intraparenchymal haemorrhage, 0.95 (0.91–0.99) for subdural haematoma, 0.97 (0.91–1.00) for extradural haematoma, 0.97 (0.92–0.99) for traumatic subarachnoid haemorrhage, and 0.93 (0.87–1.00) for intraventricular haemorrhage.12 Apart from the intraventricular haemorrhage class, the AUCs we report on the same data are lower. However, our algorithm also has the ability to quantify lesion volume, shape, and location, which can be used to extract other radiological features of potential interest. Additionally, our results are not directly comparable with the previous work by Chilamkurthy and colleagues12 because they used certain rules to select the optimum scan per patient processed by their algorithm and we were not able to determine those rules for comparison. Instead, we processed all available scans for each patient (up to eight) and calculated the mean predicted volume for subsequent classification. Using a selected set of scans, as done in previous work, is likely to improve our results.

The ability to distinguish between different lesion types is important to aid understanding of pathophysiology and to implement personalised care. The heterogeneity of TBI is well described, encompassing a wide spectrum of pathologies, from axonal injury to focal contusions and extracranial bleeding. The large annotated dataset used in this study is representative of this clinical spectrum. The CENTER-TBI study14,15 allowed a large variety of vendors and acquisition protocols to be used. Images in this analysis were contributed from 38 centres. Consequently, the performance is not manufacturer or acquisition dependent. The ability to generalise is supported by validation on an external, independent dataset from a different continent, for which the results for lesion validation on an external, independent dataset from a different continent, for which the results for lesion classification were comparable with the results obtained on internal data.

Adding the ability to distinguish the different types of extra-axial haemorrhage is important, particularly given that extradural haematomas portend a better prognosis, and the presence of traumatic subarachnoid haemorrhage is a marker for worse outcomes in prognostic models.26,27,32 Furthermore, expanding on the capability of lesion localisation may help answer key research questions and support clinical reporting of scans.

Future work needs to focus on the optimal incorporation of such algorithms into clinical practice, which must be accompanied by a rigorous assessment of performance, strengths, and weaknesses. Such algorithms will find clear research applications, and, if adequately validated, may be used to help facilitate radiology workflows by flagging scans that require urgent attention, aid reporting in resource-constrained environments, and detect patho-anatomically relevant features for prognostication and a better understanding of lesion progression.

Contributors

MM, VFJN, DKM, and BG conceived and designed the study. MM did implementations, analysed data, and co-wrote the manuscript with VFJN. MM, VFJN, DKM, and BG revised and finalised the manuscript. VFJN, FM, KA, and DW did the manual and semi-automatic segmentation of the scans or provided broader clinical input, or both, K, EF, and BG provided feedback on the development of the model. TD provided specialist neuroradiological oversight of image analysis. VFJN, DR, DKM, and BG secured the funding. All authors read and approved the final manuscript.

Declaration of interests

VFJN reports an Academy of Medical Sciences/The Health Foundation Clinician Scientist Fellowship, during the conduct of this study; and a grant from Roche Pharmaceuticals and honoraria from Neuronom, outside the submitted work. DR has received grants from EU Horizon 2020, during the conduct of this study; and personal fees from IXICO, Heartflow, and Circle Cardiovascular Imaging, outside the submitted work. DKM reports grants from GlaxoSmithKline and personal fees from NeuroTraumaSciences, Pfizer, Calico, PressuraNeuro, Luntzmanner, Integra Neurosciences, Gyrophon, and Cortizo, outside the submitted work. BG has received grants from European Commission and UK Research and Innovation Engineering and Physical Sciences Research Council, during the conduct of this study; and is Scientific Advisor for Kheiron Medical Technologies, Advisor and Scientific Lead of the HeartFlow-Imperial Research Team, and Visiting Researcher at Microsoft Research. All other authors declare no competing interests.

Data sharing

The data and algorithm are available at the time of publication. Data access is conditional to an approved study proposal; there are no end dates to the availability. The CENTER-TBI dataset used in this study is available to researchers who provide a methodologically sound study proposal that is approved by the CENTER-TBI management committee to achieve the aims in the approved proposal. Proposals may be submitted online to CENTER-TBI. A data access agreement is required, and all access must comply with regulatory restrictions imposed on the original study. No patient-identifiable information is made available, and all data have been anonymised. Study protocols and additional information for CENTER-TBI about data collection, recruitment, and participating centres is available online. The anonymised CQ500 data used for the external validation of our algorithm can be accessed and downloaded online. The source code of our algorithm together with pre-trained models and usage instructions are available online. An archive of the version used for the experimental validation in our paper is also available online.

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