Title

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Journal

Brain Imaging and Behavior, 15(6)

ISSN

1931-7557

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Publication Date

2021-12-01

DOI

10.1007/s11682-021-00603-8

Peer reviewed

HHS Public Access

Author manuscript

Brain Imaging Behav. Author manuscript; available in PMC 2023 January 05.

Published in final edited form as:

Brain Imaging Behav. 2021 December ; 15(6): 2804–2812. doi:10.1007/s11682-021-00603-8.

Distribution and volume analysis of early hemorrhagic contusions by MRI after traumatic brain injury: a preliminary report of the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx)

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Author contributions

M.L.R., D.D. and A.T. conceived the work. M.L.R. and A.B. conducted the analyses and wrote the manuscript. E.G., E.R., F.W., L.Z. and P.V. collected the data. G.B., J.E., E.G., E.R., F.W., L.Z. and P.V. reviewed clinically the work. J.S. produced 3D animations. All authors M.L.R., G.B., A.B., R.G., J.E., E.G., D.M., E.R., J.S., F.W., L.Z., P.V, A.T. and D.D. analyzed the results, reviewed the manuscript, approved the final version to be published and agreed to be accountable for the integrity and accuracy of all aspects of the work.

Declarations

Consent to participate

All patients have consented for data to be deidentified and then analyzed.

Consent for publication

Not Applicable.

Availability of data and material

The data analyzed in this study is subject to the following licenses/restrictions: access to data must be requested and approved by the EpiBioS4Rx steering committee. Requests to access these datasets should be directed to epibiossteeringcommittee@loni.usc.edu.

Code availability

Data processing and analysis were performed with Oxford FMRIB Software Library (FSL) and R version 3.6.3 that are publicly available at the following links: https://www.r-project.org/, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki

Conflicts of Interest/ Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

We have no conflicts of interest to disclose.

Abstract

Traumatic brain injury (TBI) can produce heterogeneous injury patterns including a variety of hemorrhagic and non-hemorrhagic lesions. The impact of lesion size, location, and interaction between total number and location of contusions may influence the occurrence of seizures after TBI. We report our methodologic approach to this question in this preliminary report of the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx). We describe lesion identification and segmentation of hemorrhagic contusions by early posttraumatic magnetic resonance imaging (MRI). We describe the preliminary methods of manual lesion segmentation in an initial cohort of 32 TBI patients from the EpiBioS4Rx cohort and the preliminary association of hemorrhagic contusion and edema location and volume to seizure incidence.

Keywords

Traumatic brain injury; lesion segmentation; posttraumatic late seizures; lesion volume analysis

Introduction

Posttraumatic epilepsy (PTE) is a lifelong complication of traumatic brain injury (TBI). Risk factors for PTE include early posttraumatic seizure (PTS) occurrence (within 1 week post-injury) and high injury severity (Garner et al., 2019). Injury severity can be determined by Glasgow Coma Score (GCS) and a variety of brain lesion types including acute intracerebral hematoma, acute subdural hematoma, brain contusion, skull fracture and penetrating injury (Agrawal et al., 2006). Some studies have found an association between bilateral parietal lesions and later-onset PTE, and between frontal and temporal traumatic contusions and PTE (Mukherjee et al., 2020). Tubi et al. (2019) found that early seizure development was more likely in patients with temporal lobe injuries. These studies generally have limited impact since they use categorical presence or absence of brain contusions rather than using specific location and volume characteristics to predict PTE. To date, there have been few studies addressing the influence of contusion volume, with contradictory findings related to the influence of lesion volume and incidence of PTE (Raymont et al., 2010 Tomkins et al., 2008). While, rodent models suggest that larger lesions may be associated with epileptogenesis (Kendirli et al., 2014), the influence of contusion location, contusion volume, total lesion volume and the interaction of these three parameters and PTE have not heretofore been addressed in human subjects. In this work, we provide an initial exploratory methodological study of contusion volume, edema volume, their total volume and location in a prospective multicenter human cohort from the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx[1]) (Vespa et al., 2019). We describe and explore the preliminary methods determining the impact of the location and volume of hemorrhagic contusions and edema upon the incidence of late seizures.

[1] https://epibios.loni.usc.edu

Methods

Subjects and Data Acquisition

This is a prospective multicenter observational biomarker study of moderate-severe TBI patients and was approved by the UCLA Institutional Review Board and the local review boards at each EpiBioS4Rx Study Group institution. All patients have consented for data to be deidentified and then analyzed. Enrollment criteria for EpiBioS4Rx include age between 6–100, acute moderate to severe TBI with evidence of hemorrhagic contusion to frontal and/or temporal lobes on computed tomography (CT) imaging without continuous sedation at time of enrollment. Exclusion criteria included diffuse axonal injury in the absence of hemorrhagic contusions, skull fracture, isolated epidural hemorrhage that improved after evacuation, isolated anoxic brain injury, devastating cervical spine injury, and pre-existing neurological disorders, seizures, and dementia. Subjects were enrolled within 72 hours of TBI and were extensively monitored in the intensive care unit using clinical examination and continuous electroencephalography (EEG). MRI imaging was obtained within 33 days of TBI using a structured protocol at each center. MRI and clinical data were deidentified and uploaded to a central repository at USC (LONI Image Data Archive or IDA). The patients were followed clinically for up to two years after TBI and screened at designated time intervals for the incidence of PTS using a structured questionnaire (Ottman et al., 2010). At the time of this writing, patients were pending a formal determination of the diagnosis of PTE.

In this work, we focused on TBI patients consecutively enrolled who, at the time of this writing, completed two-year follow-up. The dataset used in this study includes 32 TBI patients: 11 patients with late seizures (patients who had at least a single seizure one week after the TBI) and 21 seizure-free patients (subjects who did not develop seizures within 2 years post-injury). For these subjects, a summary of clinical and demographic data including age, gender, group size, GCS, Glasgow Outcome Score Extended (GOSE) (Weir et al., 2012) is reported in the Table 1. Among late seizure-affected patients, only 5 had also had an acute seizure during the first week post-injury (Beghi et al, 2010). The brain injury mechanism for these TBI subjects included motor vehicle accidents, pedestrian versus automobile accidents, motorcycle accidents, cycling accidents, skateboard accidents, ground level falls, falls from height, gunshot and knife wounds, blow to head and head against object. Further clinical and demographic details broken-down by subject are reported in Figure S1 and Table S1 of the Supplementary Material. All the patients included in this study were placed on seizure prophylaxis in the acute phase of TBI for 7 days, and the prophylactic treatment included Levetiracetam in the majority of cases (Table S1). Additionally, 21 patients underwent a neurosurgical procedure in acute setting (Table S1), and 8 of them developed late seizures; 11 patients did not undergo any neurosurgical procedure (Table S1), and 3 of them developed late seizures.

In this study, we used high-resolution MRI scans acquired on 3T scanners and performed within 33 post-injury. MRI sequences used include 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE), 3D gradient echo / susceptibility weighted imaging (GRE/SWI) and 3D T2-weighted fluid attenuated inversion recovery (FLAIR). MRI

acquisition parameters were optimized across sites and scanner types to reduce inter-scanner variability. Additional information on the protocol used to acquire each MRI sequence is reported in Table S2 of the Supplementary Material. Each image used in this study passed through protocol compliance and quality control (QC) using the Laboratory of Neuro Imaging (LONI) QC System (Kim et al., 2019) in order to avoid using poor quality images with morphometric and signal alterations that could notably affect the normalization.

Lesion Segmentation

Parenchymal contusions and brain edema regions were manually segmented with ITK-SNAP (Yushkevich et al., 2006) from 3D T2-weighted FLAIR images acquired within 33 days after TBI. When edema and hemorrhagic contusion characterization were uncertain, the corresponding MPRAGE and SWI sequences were used to facilitate the identification of the two components on T2-FLAIR images. In accordance with research performed by Chang et al. (2006) and Iaccarino et al. (2014), brain contusion was defined as a lesion with abnormal signal intensity and hemorrhagic volume > 1 ml ; the perilesional edema was defined as an area surrounding or in the proximity of the contusion with hyperintense signal compared with the white matter signal on T2-FLAIR images. All segmentations were performed by a physician with 5 years of research experience in neuroradiology. In most cases, it was possible to clearly distinguish the contusion volume from the surrounding edema: in these cases, two different segmentation masks were obtained, one for each component (edema and hemorrhagic contusion). Segmentation validation was performed manually by a team of three neurologists familiar with characterizing hemorrhagic contusions versus edema. An example of segmentation is reported in Figure S2 of the Supplementary Material.

Statistical Analysis

Hemorrhagic contusion volumes, edema volumes and their total volume were expressed in cubic millimeters or voxels. Since the volumetric data are not normally distributed, the Wilcoxon rank-sum test was used to assess whether hemorrhagic contusion volume, edema volume and total volume were statistically different for seizure-free versus late seizure-affected patients. Then, we used the Kruskal-Wallis test to assess the statistical association between the lesion volumes and the first post-resuscitation GCS obtained when the patient was hospitalized. Statistical testing was carried out using R version 3.6.3 (R Core Team, 2013). An examination on how

Finally, for both clinical group (seizure-free and seizure-affected subjects), we investigated the anatomical brain regions most affected by contusions and edemas. For each subject, we mapped the total contusion and edema volume, from now on referred as lesion volume, in the same reference space (MNI 152 template) (Evans et al., 2012). Lesion volumes were affinely registered to the MNI template with the Linear Registration Tool (FLIRT) of the Oxford FMRIB Software Library (FSL) (Jenkinson et al., 2012) using the default parameter configuration. The anatomical regions affected by the lesions were identified using the Talairach atlas registered to the MNI template. Each label of this atlas provides information about hemisphere, lobe, gyrus, brain tissue type, and cell type (Talairach et al., 1988). We defined a region “affected” if more than 30% of its volume was occupied by contusions and/or edema. For each subject the lesion mask normalization was checked by a physician

with 5 years of research experience in neuroradiology to ensure that lesion locations in the MNI space and in the native space were consistent.

Results

Statistical inference for lesion volumes

We found that contusion volumes, edema volumes and total lesion volumes (including contusions and edemas) are statistically different for the seizure-free and late seizure-affected subjects with p-values equal to, 0.041, 0.009 and 0.015, respectively (with a statistical power greater than 0.8 and a Cohen's effect size greater than 1). Figure 1 shows the distributions of the total lesion volumes, contusion volumes and edema volumes for the seizure-free and the seizure affected groups. We did not find any significant association between the lesion volumes and the first post-resuscitation GCS when the patient was hospitalized.

Lesion location

Figure 2 shows, for each group, an overview of the regions affected by lesions with an occurrence greater than the 98th quantile of the occurrence distribution. In the seizure-affected group the brain area that is most frequently affected by lesions is the right sub-lobar extra-nuclear white matter (WM): the lesion occurrence in this region is 91%. In the seizure-free group, the region that is most often affected by lesions, with an occurrence of 68%, is the left sub-lobar Extra-Nuclear WM. These findings suggest that the seizure-free group has a more heterogeneous distribution of the lesions in the brain compared with late seizure-affected subjects. Indeed, the percentage of seizure-free patients that have lesions in the same regions does not exceed 68% and is lower than in seizure-affected patients ($p < 0.01$ obtained with the Wilcoxon rank-sum test). Moreover, in most of the seizure-affected subjects, the lesions are located in the right hemisphere, whereas in most of the seizure-free subjects the lesions are in the left hemisphere. We tested with Fisher's statistical test the dependence of the subjects' clinical status from the hemisphere in which the lesions are located and we found a 1% significance ($p= 0.002$).

Lesion overlap

For the seizure-affected group, the highest percentage of subjects who have lesions in the same voxels is 46% (5 subjects out of 11) whereas in the seizure-free group it is 29% (6 subjects out of 21). In Figure 3, for each clinical group, the map of the anatomical areas in which most of the subjects have lesions is reported. In Table 2, a list of the brain areas showing maximum lesion overlap across subjects is reported for each clinical class. For both groups, there is maximum lesion overlap in the temporal and frontal sub-gyral WM, the inferior, middle and medial frontal gyrus in the frontal lobe, and the anterior cingulate gyrus in the limbic lobe. For the seizure-free group the maximum lesion overlap is in the left hemisphere, whereas for the seizure-affected group, the maximum overlap is in the right hemisphere and only occurs in the right superior frontal gyrus and in the right parahippocampal gyrus. Two 3D renderings of the brain areas in which different percentages of seizure-free subjects and seizure-affected subjects have lesions are respectively reported in Video S1 and Video S2 of the Supplementary Material.

Discussion

In this paper, we manually segmented and automatically processed lesions seen on MRI in patients with TBI enrolled into the EpiBioS4Rx study to explore the link between lesion volume and site to late PTS onset. We found that, in TBI patients with late seizures, total lesion volume, contusion volume, and edema volume are significantly greater ($p< 0.05$) than in TBI seizure-free patients. Therefore, these severity factors could be potentially used to identify patients with increased seizure susceptibility and potentially increased risk of developing epilepsy after TBI. This finding is in agreement with Raymont et al. (2010) stating that larger lesions resulted in a higher seizure frequency. Temporal lobe volume reduction, which may be attributed to greater lesion volumes, has also been reported as a possible risk factor for PTE (Tubi et al., 2019). Raymont et al. (2010) found a relationship between late PTS and total brain volume loss as well. Similar to lesion volume, increased edema volumes have also been related to injury severity and, therefore, to late PTS (Shear et al., 2011; Garner et al., 2019). Increased edema volume has been studied as a risk factor in other seizure disorders (Herrick et al., 2018), but has not yet been identified as a risk factor for PTE. Our results suggest that peri-contusional edema may play a role in late seizure formation after TBI.

The fact that we did not find an association between lesion volume and GCS suggests that GCS, although useful to assess the state of a person's consciousness for initial treatment, does not provide an exhaustive description of injury severity, and might not be a predictor of epilepsy after TBI. A similar conclusion was also reported by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2015). In our cohort, we found that lesion location is right lateralized in seizure-affected patients and left lateralized in seizure-free subjects with a 1% statistical significance ($p<0.01$). This lesion lateralization in epilepsy after TBI is not reported in the literature, thus it necessitates further investigation. In accordance with the inclusion criteria, most of the lesions in this sample were found in the temporal and frontal lobes. Analysis of the occurrence of the regions affected by the lesions in each clinical group showed that seizure-affected patients have lesions concentrated in specific brain regions whereas seizure-free subjects have lesions distributed more heterogeneously along various regions of the temporal, limbic, and frontal lobes. In seizure-affected patients, the region affected by the lesions with the highest occurrence is sub-lobar extra-nuclear WM. Analysis of lesion overlap in this sample highlighted that seizure-affected subjects have a higher percentage (46%) of subjects with the lesions in the same area compared with seizure-free subjects (29%). In particular, only the seizure-affected group has maximum lesion overlap in the right superior frontal gyrus and in the parahippocampal gyrus.

These findings are consistent with those reported by Gupta et al. (2014) who suggested that PTE can be categorized into multiple subtypes based on lesion location and who found that the majority of patients had focal epilepsy in the frontal or temporal lobe. Further, a comparison of lesion location between patients with and without PTE showed that the PTE group was less likely to have diffuse axonal injury (Tubi et al., 2019). This supports our findings that seizure-free subjects have heterogeneously distributed lesions throughout different parts of the brain as opposed to the seizure-affected patients. Our results further the

idea proposed by Tubi et al., (2019) that seizure onset may be attributed to disruptions of specific neural networks. Lesion location and the consequential disruptions to these neural networks should be further studied.

The lesion occurrences found in the right superior frontal gyrus are also supported by several studies that describe a correlation between late PTS and lesions in the frontal or temporal lobe (Angeleri et al., 1999; Gupta et al., 2014). While lesions in the sub-lobar regions are common after TBI (Schönberger et al., 2009), these lesions have not been carefully studied in patients with late PTS. Our results suggest that further studies should investigate sub-lobar extra-nuclear WM lesions as a risk factor for late PTS. In fact, changes in WM volumes, functional connectivity, and structural connectivity have been found in patients with epilepsy in similar locations to those we identified as having the most involvement in seizure-affected cases (Rodríguez-Cruces, 2015; Pell et al., 2008; Peng, 2017; Riazi et al., 2012). This suggests a possible relationship between these regions and seizure onset after TBI. Reductions in sub-lobar extranuclear WM have been linked to patients with childhood absence epilepsy (Chan et al., 2006). Interestingly, WM abnormalities have been associated with temporal lobe epilepsy (Rodríguez-Cruces & Concha, 2015). Both WM and T2 signal abnormalities in the right superior frontal gyrus are often connected to temporal lobe epilepsy (Pell et al., 2008). Further, functional connectivity changes in extra-nuclear WM have been found in patients with seizures originating near the mesial temporal lobe region (Peng, 2017). Similarly, significant connectivity changes in WM tracts have been reported in the sub-lobar extra-nuclear regions in patients with medial temporal lobe epilepsy (Riazi et al., 2012). This suggests that lesions, and consequently, functional connectivity differences in the extra-nuclear WM are important for epileptogenesis, which is consistent with our findings. In medial temporal lobe epilepsy patients, functional and structural connectivity differences were also found in WM tracts of the parahippocampal and superior frontal gyrus (Riazi et al., 2012). In the seizure-affected patients, we found these regions were also affected by lesions. It has also been stated that PTE often arises from mesial structures in the temporal lobe, which includes the parahippocampal gyrus (Gupta et al., 2014). There is also other evidence of parahippocampal involvement in temporal lobe epilepsy (Bernasconi et al., 2003). PTE has been indicated as a heterogeneous condition (Gupta et al., 2014), therefore, specific lesion location studies may have important implications in determining distinct subtypes of PTE, which could facilitate more targeted treatment.

Although this work demonstrates the potential value of manual segmentation for relating lesion characteristics to seizures after TBI, it is important to note that patients who are seizure-free after two years still have an approximately 20% chance of developing seizures later (Ding et al., 2016) and that at the time of this writing, patients were pending a formal determination for the diagnosis of PTE. Therefore, in the future, it will be interesting to perform these analyses including PTE patients who have received a formal diagnosis. Moreover, despite in this study similar types of medical and neurosurgical treatments are performed both in the seizure-free and in the seizure-affected groups during the first week after TBI, we cannot completely exclude that the type of anti-epileptic prophylaxis and the neurosurgical intervention might at least partially influence the results of our analysis.

Conclusion

Manual segmentation of brain lesions in TBI patients can be very promising in the elucidation of mechanisms underlying epileptogenesis. We found that total lesion volume, contusion volume and edema volume are significantly higher in TBI patients with late seizures compared with seizure-free patients. Furthermore, lesion location evaluation for each clinical class suggests that limbic parahippocampal gyrus, sub-lobar extra-nuclear and sub-lobar insula may be critical to the formation of late PTS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data used in the preparation of this article were obtained from the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) database (https://epibios.loni.usc.edu). EpiBioS4Rx was funded by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) in 2017. EpiBioS4Rx is a large, international, multi-site Center without Walls (CWOW) which has been collecting longitudinal EEG, imaging, and blood data from human patients and an animal model with the primary goal to identify biomarkers of epileptogenesis after a traumatic brain injury and then provide therapies and treatments that may stop the development of posttraumatic epilepsy. EpiBioS4Rx is the result of efforts of many investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 30 sites across the world. EpiBioS4Rx data are disseminated by the Laboratory of Neuro Imaging at the University of Southern California.

We would like to acknowledge the following EpiBioS4Rx investigators and collaborators: Agoston, Denes, Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences; Au, Alicia K., Critical Care Medicine, University of Pittsburgh Medical Center; Bell, Michael, Critical Care Medicine, Children's National Hospital DC; Churn, Ben, NINDS, National Institute of Health; Claassen, Jan, Neurology, Columbia University; Diaz-Arrastia, Ramon, Neurology, University of Pennsylvania; Foreman, Brandon, Neurology and Rehabilitation Medicine, University of Cincinnati Medical Center; Galanopoulou, Aristea, Neurology, Albert Einstein College of Medicine; Hunn, Martin, Neurosurgery, The Alfred/Monash University; Jette, Nathalie, Neurology, Icahn School of Medicine at Mount Sinai; Morokoff, Andrew, Surgery, Royal Melbourne Hospital/The University of Melbourne; Moshé, Solomon L., Neurology, Albert Einstein College of Medicine; O'Brien, Terence, Neurology, The Alfred/Monash University/The University of Melbourne; Laing, Joshua, Neurology, The Alfred/Monash University; Perucca, Piero, Neurology, The Royal Melbourne Hospital/ Monash University; O'Phelan, Kristine H., Neurology, University of Miami; Pitkanen, Asla, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland; Courtney Real, Neurosurgery, University of California Los Angeles; Ellingson, Ben, Radiology, University of California Los Angeles; Jesus E. Ruiz Tajeda, University of California Los Angeles; Buitrago Blanco, Manuel, Neurology, University of California Los Angeles; Correa, Daniel, Neurology, Montefiore Medical Center; Harrar, Dana, Pediatrics, Children's National Hospital DC; Bleck, Thomas P., Neurology, Northwestern University; Burrows, Brian, Phoenix Children's Hospital; Appavu, Brian, Neurology, Phoenix Children's Hospital; Struck, Aaron, Neurology, University of Wisconsin; Allen, Baxter, Neurology, Weill Cornell; Keselman, Inna, Neurology, University of California Los Angeles Health; Kennedy, Jeff, Neurology, University of California Davis Medical Center; Ferastraoaru, Victor, Neurology, Albert Einstein College of Medicine; Yoo, Ji Yeoun, Neurology, Icahn School of Medicine at Mount Sinai.

This study was conducted with the support of the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) under award number U54 NS100064 (EpiBioS4Rx).

Funding

This study was conducted with the support of the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) under award number U54 NS100064 (EpiBioS4Rx).

Ethics approval

This work was approved by the UCLA Institutional Review Board (IRB# 16-001 576) and the local review boards at each EpiBioS4Rx Study Group institution. Assent and written consent was obtained from the legal representative as per state law.

References

Agrawal A, Timothy J, Pandit L, & Manju M. (2006). Post-traumatic epilepsy: an overview. Clinical neurology and neurosurgery, 108(5), 433–439. [PubMed: 16225987]

Angeleri F, Majkowski J, Cacchio G, Sobieszek A, D'acunto S, Gesuita R, ... & Salvolini U. (1999). Posttraumatic epilepsy risk factors: one-year prospective study after head injury. Epilepsia, 40(9), 1222–1230. [PubMed: 10487184]

Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, ... & Hauser WA (2010). Recommendation for a definition of acute symptomatic seizure. Epilepsia, 51(4), 671–675. [PubMed: 19732133]

Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, & Arnold DL (2003). Mesial temporal damage in temporal lobe epilepsy: a volumetric MRI study of the hippocampus, amygdala and parahippocampal region. Brain, 126(2), 462–469. [PubMed: 12538412]

Centers for Disease Control and Prevention (CDC). Report to Congress on Traumatic Brain Injury Epidemiology and Rehabilitation [Internet]. Atlanta: National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention; 2015

Chan CH, Briellmann RS, Pell GS, Scheffer IE, Abbott DF, & Jackson GD (2006). Thalamic atrophy in childhood absence epilepsy. Epilepsia, 47(2), 399–405. [PubMed: 16499767]

Chang EF, Meeker M, & Holland MC (2006). Acute traumatic intraparenchymal hemorrhage: risk factors for progression in the early post-injury period. Neurosurgery, 58(4), 647–656. [PubMed: 16575328]

Ding K, Gupta PK, & Diaz-Arrastia R. (2016). Epilepsy after traumatic brain injury. In Translational research in traumatic brain injury. CRC Press/Taylor and Francis Group.

Evans AC, Janke AL, Collins DL, & Baillet S. (2012). Brain templates and atlases. Neuroimage, 62(2), 911–922. [PubMed: 22248580]

Garner R, La Rocca M, Vespa P, Jones N, Monti MM, Toga AW, & Duncan D. (2019). Imaging biomarkers of posttraumatic epileptogenesis. Epilepsia, 60(11), 2151–2162. [PubMed: 31595501]

Gupta PK, Sayed N, Ding K, Agostini MA, Van Ness PC, Yablon S, ... & Diaz-Arrastia R. (2014). Subtypes of post-traumatic epilepsy: clinical, electrophysiological, and imaging features. Journal of neurotrauma, 31(16), 1439–1443. [PubMed: 24693960]

Herrick JA, Maharathi B, Kim JS, Abundis GG, Garg A, Gonzales I, ... & Cysticercosis Working Group in Peru. (2018). Inflammation is a key risk factor for persistent seizures in neurocysticercosis. Annals of Clinical and Translational Neurology, 5(5), 630–639. [PubMed: 29761125]

Iaccarino C, Schiavi P, Picetti E, Goldoni M, Cerasti D, Caspani M, & Servadei F. (2014). Patients with brain contusions: predictors of outcome and relationship between radiological and clinical evolution. Journal of Neurosurgery, 120(4), 908–918. [PubMed: 24506250]

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, & Smith SM (2012). Fsl. Neuroimage, 62(2), 782–790. [PubMed: 21979382]

Kendirli MT, Rose DT, & Bertram EH (2014). A model of posttraumatic epilepsy after penetrating brain injuries: effect of lesion size and metal fragments. Epilepsia, 55(12), 1969–1977. [PubMed: 25470332]

Kim H, Irimia A, Hobel SM, Pogosyan M, Tang H, Petrosyan P, ... & Toga AW (2019). The LONI QC system: a semi-automated, web-based and freely-available environment for the comprehensive quality control of neuroimaging data. Frontiers in neuroinformatics, 13, 60. [PubMed: 31555116]

Mukherjee S, Arisi GM, Mims K, Hollingsworth G, O'Neil K, & Shapiro LA (2020). Neuroinflammatory mechanisms of post-traumatic epilepsy. Journal of neuroinflammation, 17(1), 1–11. Boysen, G. A., Kelly, T. J., Raesly, H. N., & Casner, R. W. (2014). [PubMed: 31900165]

Ottman R, Barker-Cummings C, Leibson CL, Vasoli VM, Hauser WA, & Buchhalter JR (2010). Validation of a brief screening instrument for the ascertainment of epilepsy. Epilepsia, 51(2), 191–197. [PubMed: 19694790]

Pell GS, Briellmann RS, Pardoe H, Abbott DF, & Jackson GD (2008). Composite voxel-based analysis of volume and T2 relaxometry in temporal lobe epilepsy. Neuroimage, 39(3), 1151–1161. [PubMed: 18042496]

Peng SJ, & Hsin YL (2017). Altered structural and functional thalamocortical networks in secondarily generalized extratemporal lobe seizures. NeuroImage: Clinical, 13, 55–61.

R Core Team. (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Raymont V, Salazar AM, Lipsky R, Goldman D, Tasick G, & Grafman J. (2010). Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology, 75(3), 224–229. [PubMed: 20644150]

Riazi AH, Soltanian-Zadeh H, & Hossein-Zadeh GA (2012). Feature-based approach to fuse fMRI and DTI in epilepsy using joint independent component analysis. In 2012 19th Iranian Conference of Biomedical Engineering (ICBME) (pp. 209–212). IEEE.

Rodríguez-Cruces R, & Concha L. (2015). White matter in temporal lobe epilepsy: clinico-pathological correlates of water diffusion abnormalities. Quantitative imaging in medicine and surgery, 5(2), 264. [PubMed: 25853084]

Schönberger M, Ponsford J, Reutens D, Beare R, & O'Sullivan R. (2009). The Relationship between age, injury severity, and MRI findings after traumatic brain injury. Journal of Neurotrauma, 26(12), 2157–2167. [PubMed: 19624261]

Shear DA, Lu XCM, Pedersen R, Wei G, Chen Z, Davis A, ... & Tortella FC (2011). Severity profile of penetrating ballistic-like brain injury on neurofunctional outcome, blood–brain barrier permeability, and brain edema formation. Journal of neurotrauma, 28(10), 2185–2195. [PubMed: 21644814]

Talairach J. & Tournoux P. (1988). Co-planar stereotaxic atlas of the human brain-3-dimensional proportional system. New York: Thieme Medical Publishers Inc.

Tomkins O, Shelef I, Kaizerman I, Eliushin A, Afawi Z, Misk A, ... & Friedman A. (2008). Blood–brain barrier disruption in post-traumatic epilepsy. Journal of Neurology, Neurosurgery & Psychiatry, 79(7), 774–777. [PubMed: 17991703]

Tubi MA, Lutkenhoff E, Blanco MB, McArthur D, Villablanca P, Ellingson B, Diaz-Arrastia R, Van Ness P, Real C, Shrestha V, Engel J Jr, & Vespa PM (2019). Early seizures and temporal lobe trauma predict post-traumatic epilepsy: A longitudinal study. Neurobiology of disease, 123, 115–121. [PubMed: 29859872]

Vespa PM, Shrestha V, Abend N, Agoston D, Au A, Bell MJ, ... & Duncan D. (2019). The epilepsy bioinformatics study for anti-epileptogenic therapy (EpiBioS4Rx) clinical biomarker: Study design and protocol. Neurobiology of disease, 123, 110–114. [PubMed: 30048805]

Weir J, Steyerberg EW, Butcher I, Lu J, Lingsma HF, McHugh GS, ... & Murray GD (2012). Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale?. Journal of neurotrauma, 29(1), 53–58. [PubMed: 22026476]

Xia M, Wang J, & He Y. (2013). BrainNet Viewer: a network visualization tool for human brain connectomics. PloS one, 8(7), e68910.

Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, & Gerig G. (2006). User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage, 31(3), 1116–1128. [PubMed: 16545965]

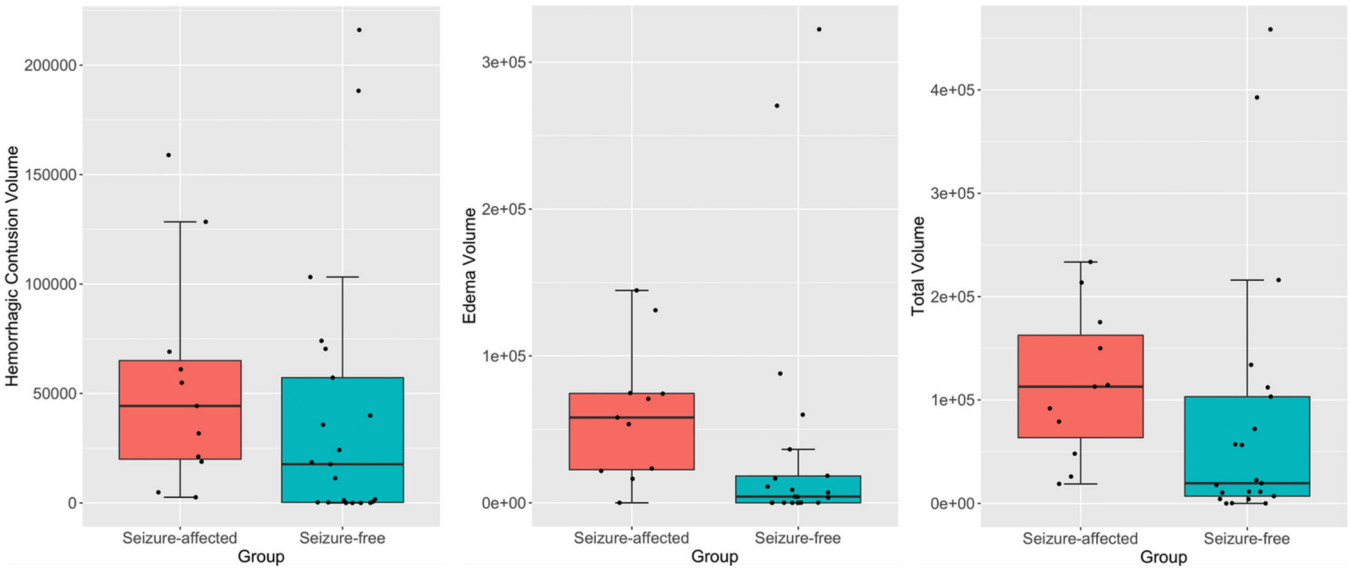

Figure 1.

Boxplots of the distributions of the total lesion volumes, contusion volumes, and edema volumes for the late seizure-affected subjects (salmon boxplot) and the seizure-free subjects (cyan boxplot). Seizure-affected group includes TBI subjects who had at least a single seizure one week after the TBI.

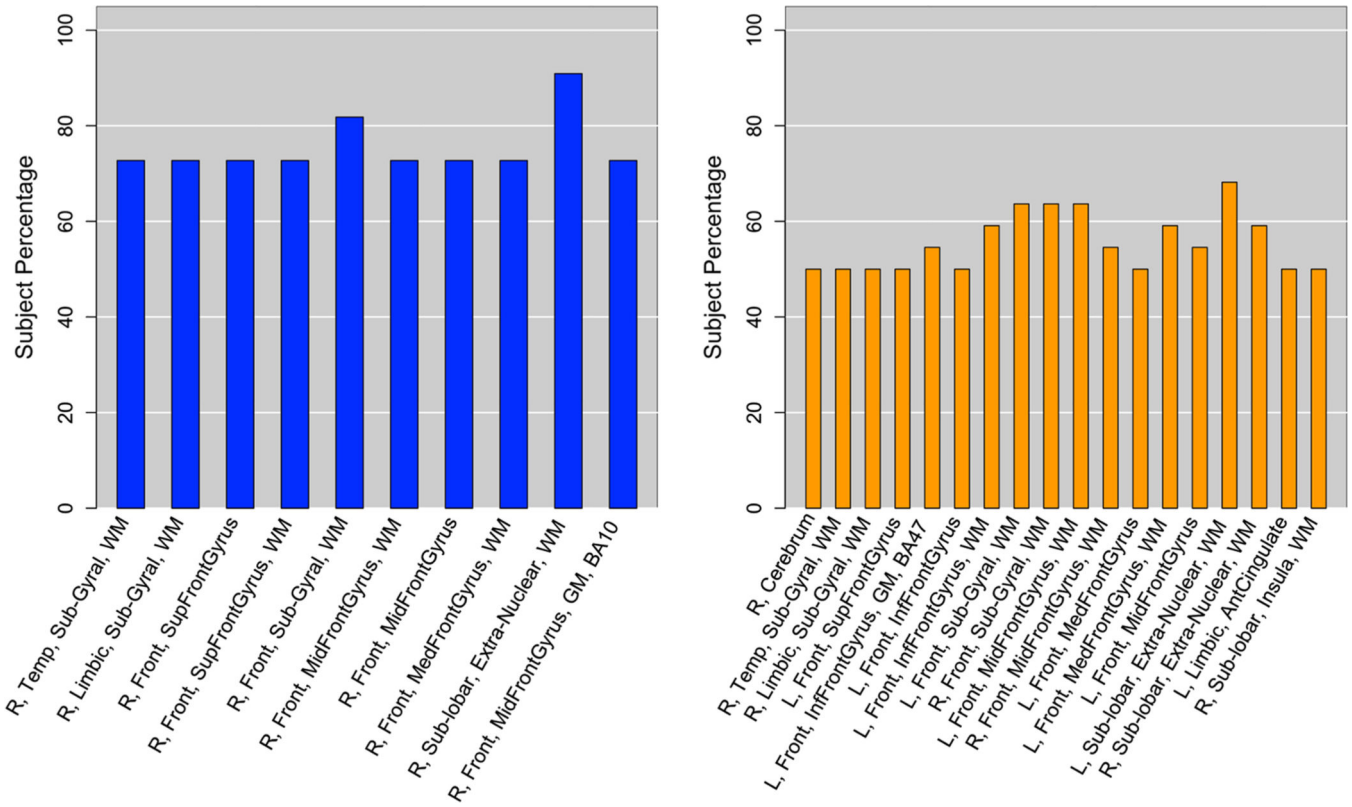

Figure 2.

Histograms indicating occurrence percentage of the anatomical brain regions that are affected by lesions in most TBI subjects (occurrence greater than the 98th quantile of the occurrence distribution). Region occurrences are reported for two clinical groups: late seizure-affected subjects (blue histogram and seizure-free subjects (gold histogram). L and R indicate left and right, WM and GM indicate white matter and gray matter, BA indicate Brodmann area, Temp, Front, Sup, Lat and Ant stand for temporal, frontal, superior, lateral and anterior, respectively.

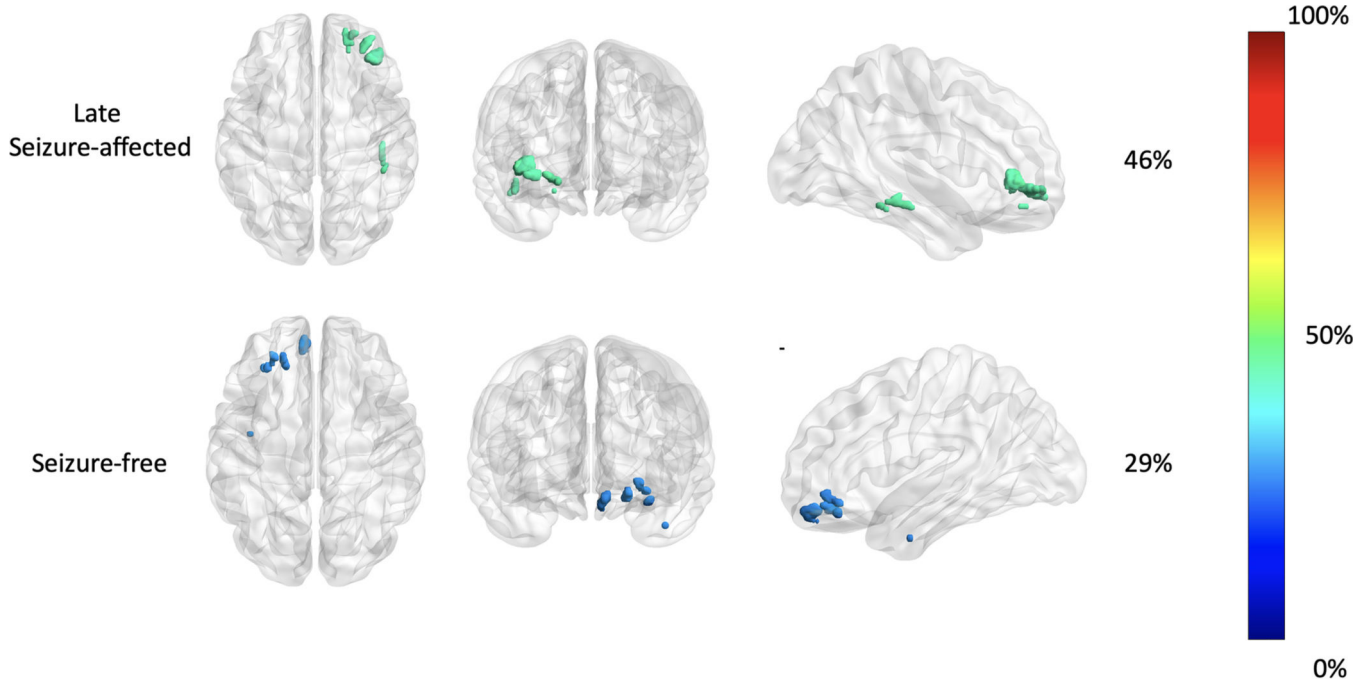

Figure 3.

Axial, coronal, and sagittal view of the brain areas in which the highest percentage of TBI subjects with late seizures (top row) and without seizures (bottom row) have lesions. Each colormap represents the percentage of subjects in each TBI group who have lesions in that area according to the color code reported in the figure. This figure was obtained with BrainNet Viewer (Xia et al., 2013).

Table 1

Group size, gender, age, initial GCS and GOSE at the time of the paper are reported by group. Age and GCS are given as mean and standard deviations. No statistically significant differences between the two classes were found with respect to age, GCS, GOSE and gender. Statistical evaluations were performed with a Wilcoxon rank-sum statistic test except for the gender, for which a Chi-square test was used.

Groups	Sample Size	Age	GCS	GOSE	Male/Female
Seizure-free	21	37.86 ± 22.43	10.24 ± 3.83	5.71 ± 1.55	18/3
Late seizure affected	11	42.73 ± 19.27	7.82 ± 4.31	4.46 ± 2.38	6/5

Table 2

Within each clinical group, the lesion areas shared by the highest percentage of subjects is reported. For the seizure-free group the highest percentage of subjects who have lesions in the same brain areas is 29%, for the seizure-affected group 46%. L and R stand for left and right, WM and GM stand for white matter and gray matter, BA stands for Brodmann area, Temp, Front, Sup and Ant stand for temporal, frontal, superior and anterior. In this table, each label is composed of five levels: hemisphere, lobe, gyrus, tissue type, and cell type.

Seizure-free group	Seizure-affected group
L, Temp, Sub-Gyral, WM	R, Temp, Sub-Gyral, WM
L, Front, Inf Front Gyrus, WM	R, Front, Sup Front Gyrus, WM
L, Front, Sub-Gyral, WM	R, Front, Inf Front Gyrus, WM
L, Front, Mid Front Gyrus, WM	R, Front, Sub-Gyral, WM
L, Front, Med Front Gyrus	R, Front, Mid Front Gyrus, WM
L, Front, Med Front Gyrus, WM	R, Front, Med Front Gyrus, WM
L, Limbic, Ant Cingulate, WM	R, Limbic, Ant Cingulate, WM
L, Limbic, Ant Cingulate	R, Front, Inf Front Gyrus, GM, BA46
L, Limbic, Ant Cingulate, GM, BA32	R, Limbic, Parahippocampal Gyrus, WM
L, Front, Med Front Gyrus, GM, BA10	