A COMPUTATIONAL DIFFUSION MRI FRAMEWORK FOR BIOMARKER DISCOVERY IN A RODENT MODEL OF POST-TRAUMATIC EPILEPTOGENESIS

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ABSTRACT

Epilepsy is a debilitating neurological disorder that directly impacts millions of people and exerts a tremendous economic burden on society at large. While traumatic brain injury (TBI) is a common cause, there remain many open questions regarding its pathological mechanism. The goal of the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) is to identify epileptogenic biomarkers through a comprehensive project spanning multiple species, modalities, and research institutions; in particular, diffusion magnetic resonance imaging (MRI) is a critical component, as it probes tissue microstructure and structural connectivity. The project includes in vivo imaging of a rodent fluid-percussion model of TBI, and we developed a computational diffusion MRI framework for EpiBioS4Rx which employs advanced techniques for preprocessing, modeling, spatial normalization, region analysis, and tractography to derive imaging metrics at group and individual levels. We describe the system's design, present characteristic results from a longitudinal cohort, and discuss its role in biomarker discovery and further studies.

***Index Terms*—** diffusion MRI, traumatic brain injury, epilepsy, tractography, neuroinformatics

1. INTRODUCTION

Epilepsy is a debilitating neurological disorder that directly impacts millions of lives and exerts a tremendous economic burden on society at large [1]. While traumatic brain injury (TBI) is a common cause, post-traumatic epilepsy (PTE) cases are often heterogeneous and symptoms may appear years after the primary insult, [2], making it difficult to study the pathomechanisms of the disease and to identify acute biomarkers. Despite this, the discovery and use of non-invasive imaging biomarkers of TBI and PTE pathology are technically feasible because imaging is routinely acquired in acute patient care settings. The goal of the Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) is to identify such epileptogenic biomarkers through a comprehensive project spanning multiple species, modalities, and research institutions [3] [4], and in this paper, we focus on the diffusion MRI component used in the rodent TBI model.

Diffusion magnetic resonance imaging (MRI) is a well established tool for probing brain tissue microstructure and structural connectivity [5] that has been widely adopted in TBI studies [6]. In recent years, diffusion tensor imaging (DTI) has enabled the detection of structural plasticity following injury [7] and the evaluation of diffuse axonal injury [8] [9]. However, conclusive DTI findings related to disease progression and subsequent outcome remain open due to some inconsistent findings [10].

Advanced diffusion MRI modeling techniques have been used to go beyond DTI analysis, including track-density and track-weighted imaging [11], apparent fiber density imaging [11], multi-compartment imaging [12], and spherical deconvolution tractography [11]. These advanced approaches provide potentially greater specifity in their parameter maps, and they can better resolve crossing fibers and other partial volume effects, paving the way for accurate and reproducible quantification of white matter architecture in induced models of TBI. Another way to better understand the tissue changes that underlie diffusion effects is to compare imaging data with histology. For example, ex-vivo studies of white matter have found imaging correlates of axonal loss and iron accumulation in key white matter tracks – the corpus callosum, angular bundle, and internal capsule – six months after lateral fluid percussion injury [7], and gray matter tissue correlates of diffusion changes have been found in the hippocampal dentate gyrus up to 79 days post injury following induced status

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epilepticus. [13] [14]

The approach we report here combines both standard and more advanced approaches to develop a computational diffusion MRI framework for biomarker discovery in the rodent model of post-traumatic epilepsy (PTE) in EpiBioS4Rx. Our framework includes components for quality assessment, artifact correction, multi-compartment modeling, tensor-based spatial normalization, region-analysis, and tractography. These elements are assembled to derive group-level representations of anatomy in aggregate form, as well as individual-level measures to enable fine-grained analysis. We describe the system's design, present characteristic results from a longitudinal cohort, and discuss its role in biomarker discovery and further studies.

2. METHODS

The overall goal of our framework is to provide an automated and reproducible pipeline for obtaining imaging metrics for biomarker discovery. To accomplish this, we implemented a workflow that includes stages for preprocessing to produce robust diffusion parameter maps, and subsequently, to produce data representations at group and individual levels. The motivation for making this distinction is that the group level data may inform population level changes, for example to find what is consistent at a given timepoint after injury; in contrast, individual level data can provide the specificity necessary for deriving biomarkers, as they may depend closely on a specific configuration of anatomical parameters, and they are necessary for eventual translation to personalized medicine solutions for clinical care. We used several software packages, including FSL [15], QIT [16][1], DTI-TK [17], and the LONI Pipeline [18] in our workflow, which is illustrated in Fig. 1 and described as follows.

2.1. Preprocessing

Our preprocessing stage included steps for quality control and enhancement using QIT, as well as diffusion model fitting using FSL. We first convert Bruker data to NIfTI using Bru2Nii [2] and harmonize subject identifiers and volume filenames [19]. We perform quality control by visually inspecting mosaic image plots, by estimating the global noise characteristics, and by inspecting boxplots depicting the entire cohort to detect outliers. We perform artifact correction by first normalizing the signal to have a mean baseline intensity of one, applying non-local means filtering to reduce noise, and then performing intra-subject linear registration to reduce motion artifact. We performed skull stripping by applying FSL BET to the average baseline scan. Lastly, we estimate diffusion tensors using FSL DTIFIT and multi-tensor models (ball-and-sticks) using FSL BEDPOSTX [20].

[1] http://cabeen.io/qitwiki

[2] https://github.com/neurolabusc/Bru2Nii

2.2. Group-level Analysis

Our group-level analysis uses a deformable template-based approach to obtain population averaged data for comparison across timepoints and for a point of reference in later analyses. We used the tensor-based diffeomorphic registration algorithm in DTI-TK to create a population averaged DTI dataset. We also created population averaged multi-tensor data using a model-based kernel regression framework for fiber orientation mixtures [21]. This allowed us to inspect population averaged maps of DTI parameters such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), as well as the fiber orientations and volume fractions of the multi-tensor model. We further can delineate population-averaged white matter fiber bundles using streamline tractography of the average multi-tensor data.

2.3. Individual-level Analysis

Our individual-level analysis included three approaches: z-score mapping, region-based analysis, and tractography modeling. For z-score analysis, we aimed to locally measure how each TBI case differed from sham cases in a statistical sense; for this, we computed mean and standard deviation maps for sham cases, and measured the absolute z-score from each TBI case. For region-analysis, we aimed to quantify microstructure properties of gray matter areas, for which, we deformed a gray matter template to our study template, and then summarized the average FA, MD, AD, and RD in each region [22]. For tractography analysis, we used a bundle-specific approach. First, a prototypical example of each bundle was extracted from the average multi-tensor sham data using manually guided seeding, inclusion, and exclusion [21]. For each bundle, we then computed tract orientation maps (TOM) and inclusion masks for the bundle starting and ending points. These were deformed to native space of each scan, and we selected only the closest compartment to the TOM from the subject multi-tensor data and performed streamline tractography with the deformed inclusion mask. We summarized the bundles with mean FA, MD, RD, AD, and total volume.

3. EXPERIMENTS

3.1. Datasets

EpiBioS4Rx includes data collected across multiple research centers and species, and here we present characteristic results of our framework using rodent imaging data collected with ethics approval at the University of Eastern Finland in Kuopio [19]. Adult, male Sprague-Dawley rats were scanned longitudinally at two days, nine days, 30 days, and five months post-injury with left lateral fluid percussion experimental model of TBI and with a sham injury. A total of 204 scans were included in the analysis. Diffusion MRI data were acquired

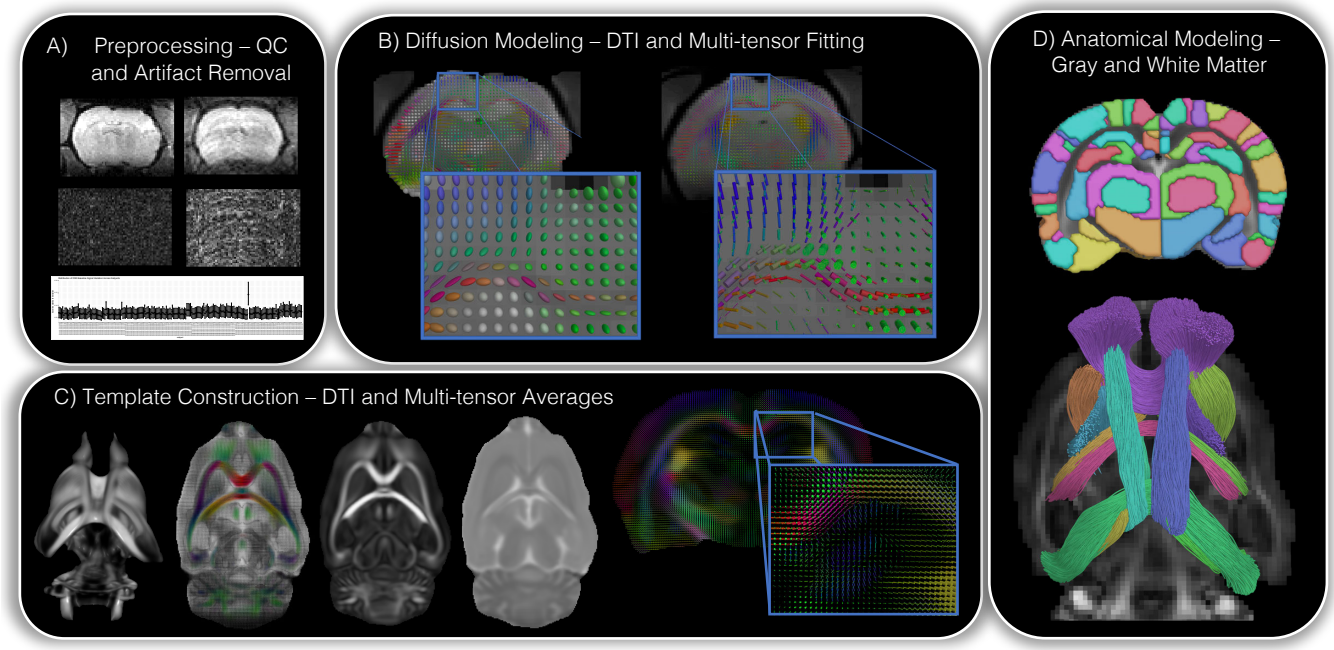

Fig. 1. An illustration of our computational diffusion MRI framework, which includes steps for preprocessing (A), diffusion modeling (B), spatial normalization (C), and anatomical modeling (D), which is done at group and individual levels.

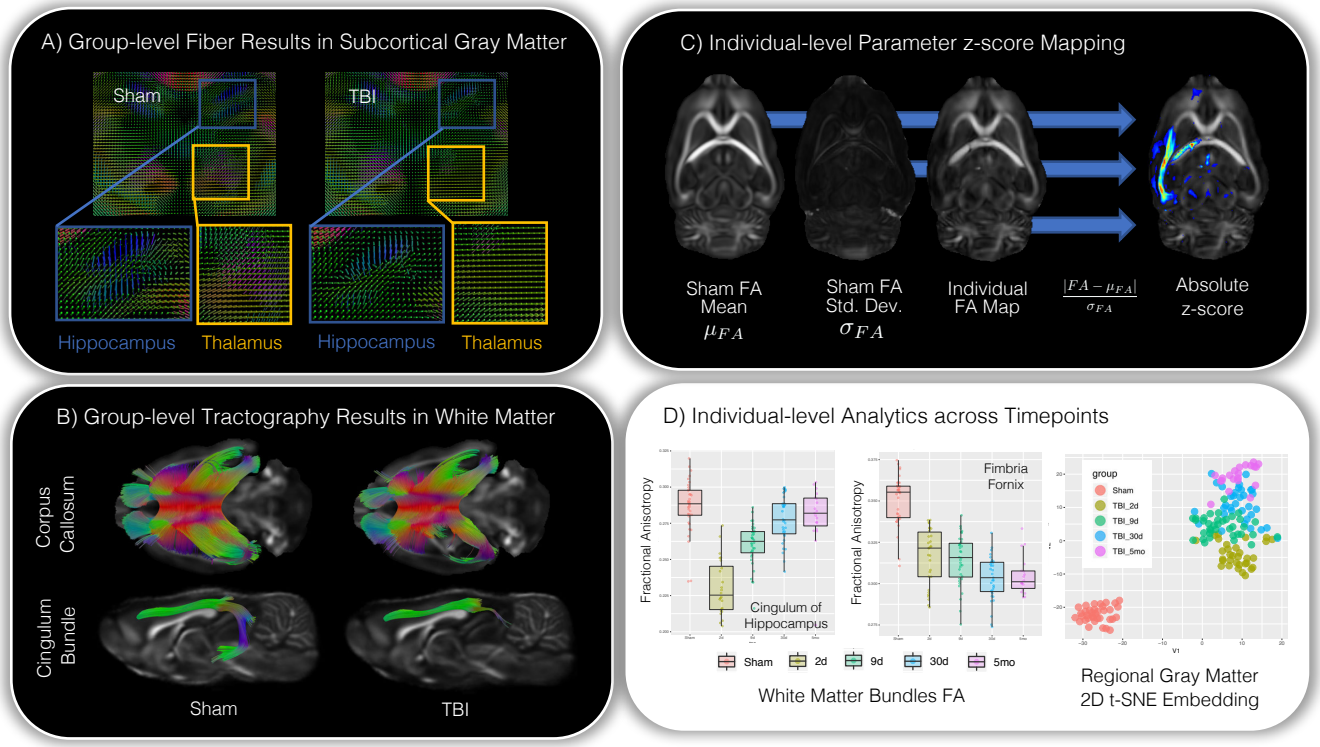

Fig. 2. Shown on the left are group level results comparing sham and TBI cases, including gray matter (A) and white matter (B). Shown on the right are individual level results, including voxelwise z-scores (C) and variation across timepoints (D).

using a Bruker BioSpin MRI GmbH with a dtiEpiT SpinEcho sequence [4] and included four b-zero scans and 42 diffusion-weighted scans with a b-value of 3000 s/mm^2.

3.2. Experiments

Our experiments applied the framework described above to characterize the cohort. We investigated group-level differences between average multi-tensor data from the sham and two day post-TBI rodents as follows: first, we examined voxel-wise multi-tensors models in the gray matter of the hippocampus and thalamus, and we performed population averaged tractography of the corpus callosum and cingulum bundle. We investigated individual level effects by computing z-score maps of each TBI case and plotting data to assess changes in white matter across TBI timepoints. We also created 2D t-Distributed Stochastic Neighbour Embedding (t-SNE) plots of the gray matter regional metrics, which were labeled according to TBI after embedding.

3.3. Results

Our results are shown in Fig. 2. Our group-level tests in gray matter showed loss of fiber populations in subregions of hippocampus and thalamus, ipsilateral to the injury (Fig. 2A). Our group-level tractography analysis showed ipsilateral disruptions in the hippocampus portion of the cingulum bundle and corpus callosum (Fig. 2B). The corpus callosum also showed changed in contralateral connectivity somewhat anterior to the frontal level of the injury site. Our individual-level analysis demonstrated the ability to detect fine-grained tissue abnormalities using z-score mapping (Fig. 2C). It also showed that analysis of white matter pathwas enables the detection of distinct responses to injury, for example the cingulum showed recovery of baseline FA, while the fimbria pathway showed progressive decline (Fig. 2D, left). The embedding plots showed that gray matter metrics can be used to derive a low-dimensional summary of differences among TBI timepoints in an unsupervised manner.

4. DISCUSSION AND CONCLUSIONS

We have presented a diffusion MRI framework designed for characterizing rodent brain structure after experimental traumatic brain injury, and our results demonstrate a variety of potential routes for biomarker discovery for post-traumatic epilepsy. Our multi-tensor approach was important for detecting gray matter changes, which were evident in crossing fiber regions; furthermore, our population-averaged tractography approach showed the framework's potential for directly visualizing structural changes following TBI. In contrast, our individual analysis was able to characterize anatomically specific differences among cases using z-score mapping, region-based analysis, and bundle-specfic modeling. These may help build multivariate approaches to biomarker discovery, and our t-SNE results show that they can depict anatomical changes following injury with a low-dimensional representation.

Regarding possible limitations, our analysis depends in part on accurate spatial alignment among cases. We chose tensor-based alignment and created a study-specific template to help address possible issues with regard to registration quality. The deformable registration algorithm in DTI-TK is well-suited to this task, as it uses the principal orientation of the tensor for alignment, and consequently, it may be less sensitive to changes in image contrast due to lesions than other algorithms. A review of the coregistered DTI data provided some support for this reasoning, as they exhibited good registration quality. Furthermore, we used a multi-compartment multi-tensor approach with the ball-and-sticks model; and while many approaches have instead used spherical deconvolution fiber orientation distribution imaging, the ball-and-sticks model has several advantages in our study. First, it has been shown to have good performance with single shell and low b-value data, and second, the inclusion of a ball compartment can perhaps better account for signal from factors that may confound tissue properties, such as the presence of lesions and changes in cerebro-spinal fluid.

Finally, this framework was designed to include advanced techniques that provide both group-level and individual levels of analysis. These two views on the data may help guide the biomarker discovery process, as they can lead EpiBioS4Rx researchers to form hypotheses in a coarse-to-fine manner, which can compromise between comprehensively considering brain areas for the search and considering a feasible subset of potential markers that can be evaluated with the necessarily limited amount of behavioral data at hand. Our experiments focused on data from University of Eastern Finland, primarily to demonstrate the capabilities of the system; however, EpiBioS4Rx has already collected similar data across imaging centers, and our harmonization pipeline enables our framework to be applied similarly across data collected across other EpiBioS4Rx sites at UCLA, University of Melbourne, and Albert Einstein College of Medicine. Beyond the present study, our framework may be more broadly extended to other preclinical rodent imaging studies for discovering biomarkers or evaluating therapeutic interventions.

5. REFERENCES

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