Patient-tailored multimodal neuroimaging, visualization and quantification of human intra-cerebral hemorrhage

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ABSTRACT

In traumatic brain injury (TBI) and intracerebral hemorrhage (ICH), the heterogeneity of lesion sizes and types necessitates a variety of imaging modalities to acquire a comprehensive perspective on injury extent. Although it is advantageous to combine imaging modalities and to leverage their complementary benefits, there are difficulties in integrating information across imaging types. Thus, it is important that efforts be dedicated to the creation and sustained refinement of resources for multimodal data integration. Here, we propose a novel approach to the integration of neuroimaging data acquired from human patients with TBI/ICH using various modalities; we also demonstrate the integrated use of multimodal magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) data for TBI analysis based on both visual observations and quantitative metrics. 3D models of healthy-appearing tissues and TBI-related pathology are generated, both of which are derived from multimodal imaging data. MRI volumes acquired using FLAIR, SWI, and T_2 GRE are used to segment pathology. Healthy tissues are segmented using user-supervised tools, and results are visualized using a novel graphical approach called a 'connectogram', where brain connectivity information is depicted within a circle of radially aligned elements. Inter-region connectivity and its strength are represented by links of variable opacities drawn between regions, where opacity reflects the percentage longitudinal change in brain connectivity density. Our method for integrating, analyzing and visualizing structural brain changes due to TBI and ICH can promote knowledge extraction and enhance the understanding of mechanisms underlying recovery.

Keywords: magnetic resonance imaging, diffusion tensor imaging, brain injury, personalized medicine, multimodal brain imaging, visualization, connectogram

INTRODUCTION

Structural neuroimaging techniques have become invaluable in both clinical practice as well as biomedical research. In this context, multimodal neuroimaging broadly refers to the combination of data sets acquired with different types of instrumentation using various acquisition parameters. Magnetic resonance imaging (MRI) can provide static anatomical information as well as dynamic physiological insights through its functional counterpart, functional MRI (fMRI). Diffusion tensor imaging (DTI) is another MRI-based technique with the specific capability to map white matter (WM) connectivity based on patterns of diffusion anisotropy along the principal directions of water diffusion in the brain[1]. The clinical treatment of conditions such as traumatic brain injury (TBI) and intracerebral hemorrhage (ICH) often involves the use of these techniques to acquire knowledge of injury-related effects. In both conditions, a common goal is the identification of clinical biomarkers which can assist in the formulation of outcome prediction models. However, neuroimaging studies integrating multimodal data remain limited due to the challenges associated with data collection, storage, and availability of integration methodologies.

Acute TBI pathology comprises a spectrum of gross pathology types, including contusions, skull fractures, and (non-) hemorrhagic lesions. Although MRI is typically more sensitive for the detection of certain lesions compared to computed tomography (CT) – particularly at the sub-acute stage – standard T_1-weighted images alone may not sufficiently capture the gamut of lesion classes[1]. Comparatively, there are several, more-specialized MR modalities which are geared towards the detection of specific lesion properties. For example, fluid attenuated inversion recovery

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(FLAIR) and susceptibility weighted imaging (SWI) are MRI sequences which capture edema and cerebral micro-hemorrhages, respectively, more conspicuously.

In FLAIR images, edematous tissues appear as hyper-intensities in the WM, whereas hemorrhagic lesions are observed as hypo-intensities in SWI[2]. Thus, the observable qualitative differences among different imaging sequences suggest that a vital component of TBI neuroimaging involves the availability of multimodal datasets to aid in the process of pathology identification and characterization. One caveat is that discerning differences in voxel intensities is neither a comprehensive nor thorough approach to image analysis. Another complexity is that pathological changes may occur well below the threshold of visual inspection. Therefore, quantitative methods are more suitable for the purpose of objective image analysis and inspection.

Given the assortment of imaging sequences which are currently available, the integration of multimodal datasets provides greater versatility in computational analysis compared to the use of unimodal data. A consequent challenge is devising a framework which can fully leverage the benefits of both qualitative and quantitative observations. Because TBI and ICH often result in structural as well as functional changes, studies encompassing these aspects are critical for understanding degenerative processes as well as for improving patient rehabilitation. Here we propose a novel, patient-tailored approach to the multimodal analysis of TBI and ICH via integration of structural MRI with DTI and with the field of brain connectomics.

METHODS

Here we demonstrate the combined use of multimodal data for TBI analysis based on both visual observations and quantitative metrics. In this approach, the primary step is the generation of 3D models of healthy-appearing tissues and TBI-related pathology, both of which are derived from multimodal imaging data. This process comprises tissue segmentation, which is the classification of voxels from MRI volumes into relevant tissue types so that geometric properties can be calculated. MRI volumes acquired using FLAIR, SWI, and T_2-weighted gradient recalled echo (GRE) sequences are used to segment hemorrhagic lesions and edematous tissue. Edemas are coded as hyper-intensities in FLAIR images, and (micro-) hemorrhages are coded as hypo-intensities in GRE and SWI sequences, respectively.

Before any analysis is performed, both MRI and DTI volumes are co-registered and image processing is performed using the LONI Pipeline environment (pipeline.loni.usc.edu), which accommodates operations such as bias field correction, skull stripping and volume co-registration. A brain mask is first created using FSL to eliminate extra-cerebral noise. Bleeds are segmented from MRI volumes which obviate hemorrhages well (e.g. SWI) and CSF-perfused tissues are segmented from T_2 and FLAIR volumes. Edematous tissues which do not contain hemorrhages are identified from T_2-weighted GRE images and from FLAIR. Both healthy-appearing and gross pathology-affected tissues are segmented using user-supervised tools available within 3D Slicer, a freely available software environment for image processing. The same software package is used to generate 3D models and pathology visualizations.

FreeSurfer 6.0 is used to co-register WM surface models to pathology models, to segment healthy-appearing WM, grey matter (GM) and cerebrospinal fluid (CSF). One advantage of using DTI volumes is that they allow diffuse axonal injuries (DAI) to be identified using connectomic analysis. Two software packages for DTI processing, namely TrackVis and Diffusion Toolkit, are used to reconstruct fiber tracts via deterministic tractography. TrackVis is then employed to reconstruct and to render fiber tracts, and these tracts are subsequently loaded and viewed in 3D Slicer.

The quantitative measures which are extracted include metrics of cortical atrophy such as the bifrontal index, the bicaudate index, Evan's index, the ventricular index, and Huckman's index[3]. The bifrontal index is the ratio of the maximum width of the anterior horns of the lateral ventricles (HLV) to the inner skull diameter at HLV level. The bicaudate index is the ratio of the minimum width of the lateral ventricles (MLV) to the width of the inner skull at that level. Evan's index is the ratio of the HLV to the maximum inner skull diameter. The ventricular index is the ratio of the MLV to the HLV. Huckman's index is the sum of the MLV and HLV.

RESULTS

Figure 1 illustrates a novel approach to incorporating DTI with multimodal MRI, as well as the visual mapping of longitudinal WM changes due to TBI and ICH. The added dimensionality of connectivity data emphasizes the relationship between TBI lesion profiles and neurophysiological outcomes based on the severity of pathology-related connectivity loss. Our paradigm combines DTI metrics with cortical parcellation to generate whole brain connectomic representations of WM atrophy. In other instances, WM fiber integrity with relation to lesion size and location lesion are also useful. Figure 1B displays a representative case where the CST is visualized in a case of ICH.

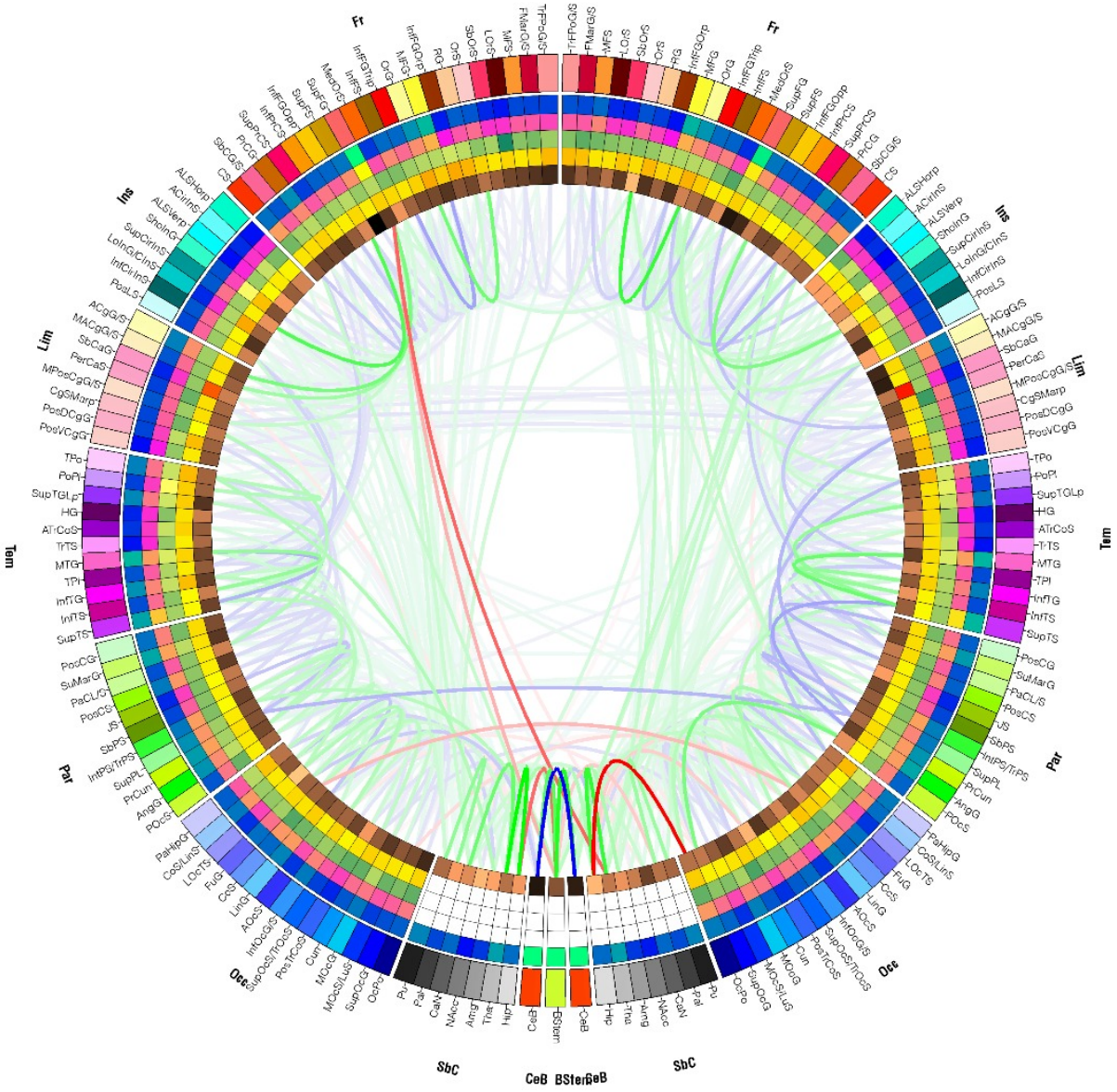

Figure 1. Visualization of longitudinal GM and WM changes due to TBI and ICH. The brain was first segmented and parceled into 164 regions, and WM connectivity strength was represented by fiber density based on DTI data. Results are depicted using a graphical approach which we name a 'connectogram', in which brain connectivity information is depicted within a circle of radially aligned elements. Each circular wedge element represents a specific cortical region which is positioned on either side of the vertical axis, corresponding to the left or right hemisphere, respectively. Inter-region connectivity and connectivity strength are represented by links of variable opacities drawn between regions, where opacity reflects percentage changes in connectivity density.

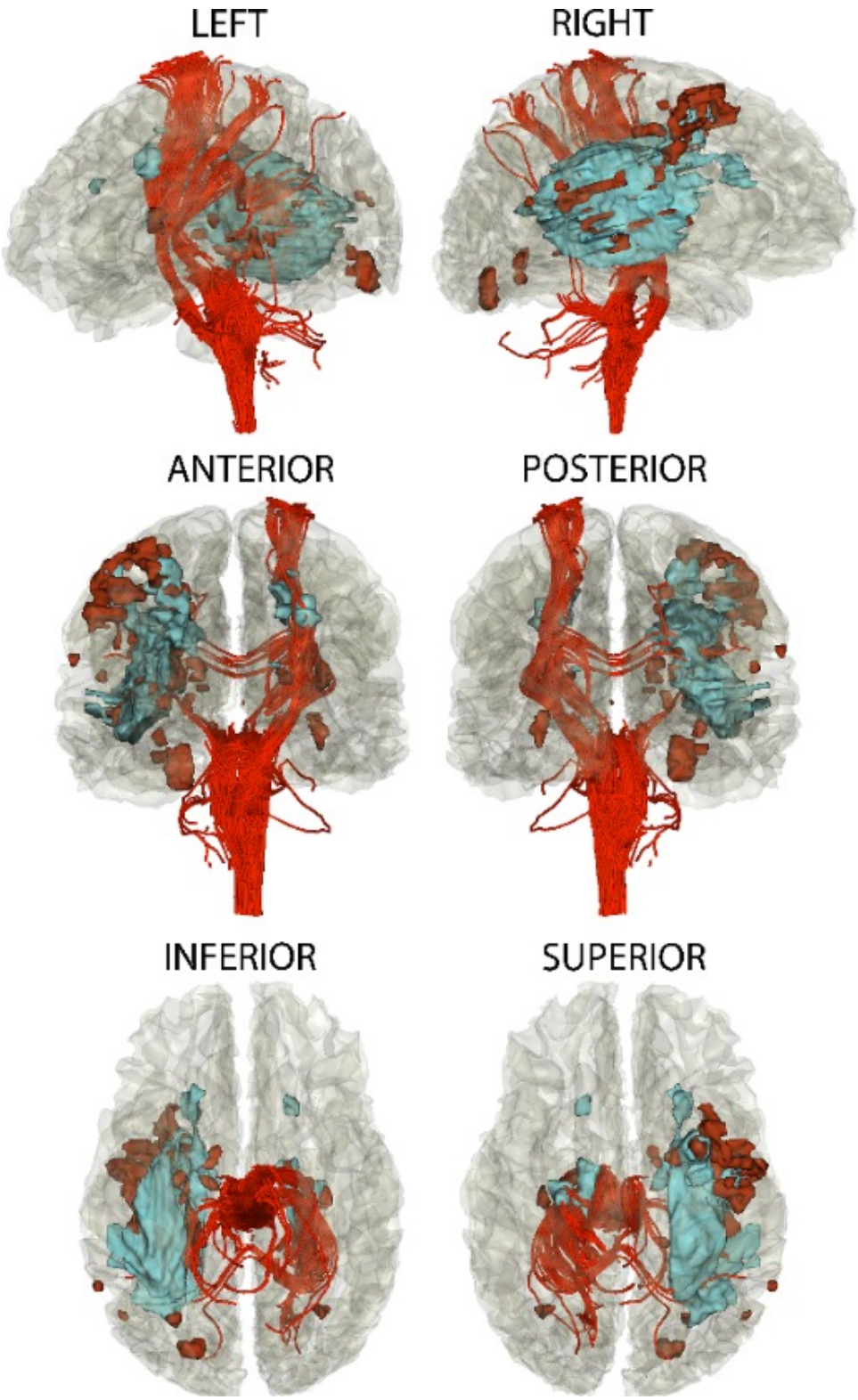

Figure 2. Example of explicit modeling of the CST (displayed in red). Hemorrhagic lesions appear in dark red, whereas edematous tissue appear in cyan. The WM reconstruction is displayed in the background, with reduced opacity for illustrative purposes.

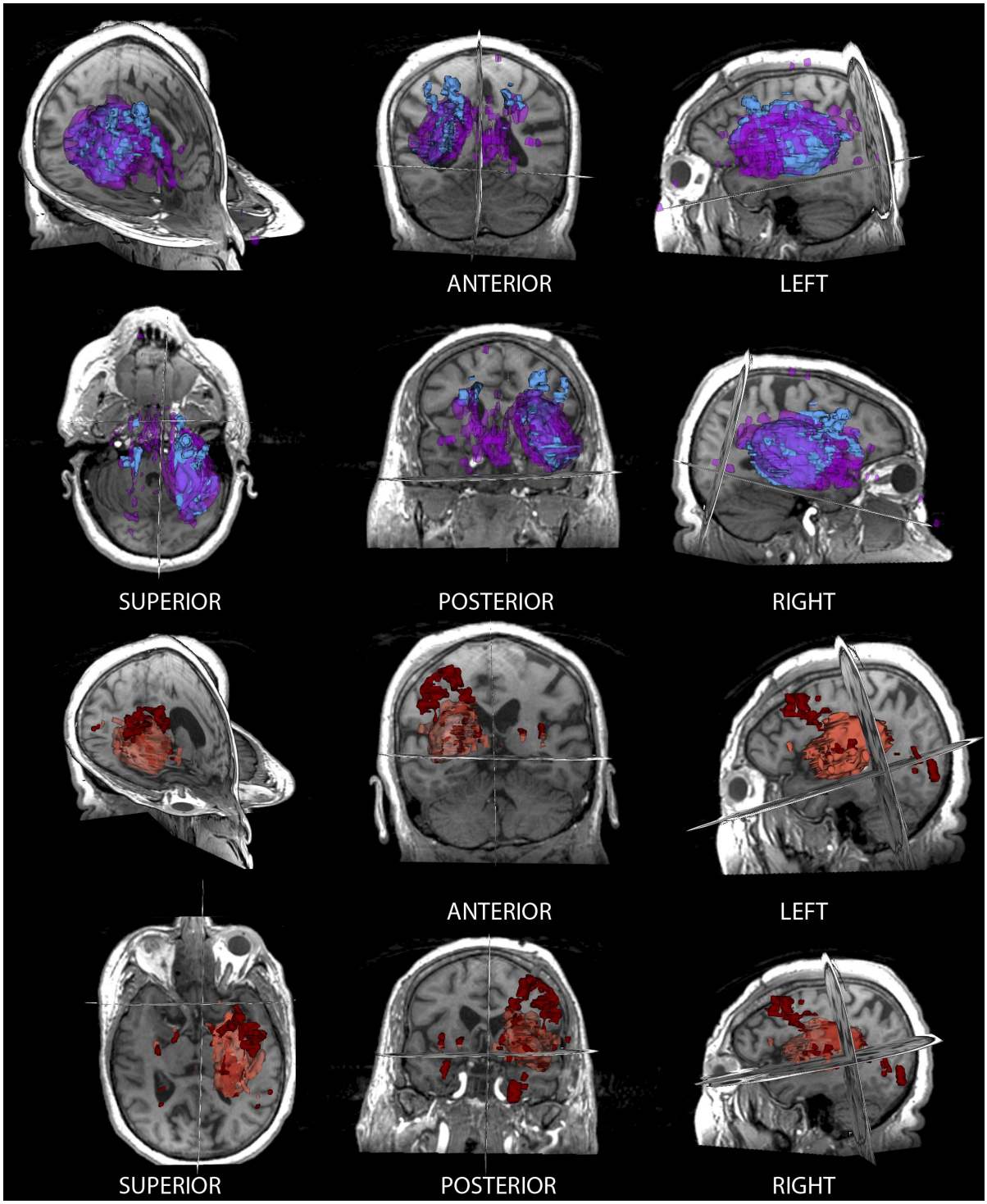

Figure 3. Longitudinal trajectory of lesion volume in a sample ICH patient. The top two rows show the extent of gross pathology several days after injury; the bottom two rows show its extent two weeks after injury. At the first time point, edema is shown in purple and bleeding is shown in blue. At the second time point, edema is in light red and bleeding is in dark red.

Because fiber integrity is extrapolated through diffusion anisotropy, areas in which fibers are not fully resolved imply the involvement of hemorrhagic or edematous lesions. As illustrated in Figure 2, the right CST is substantially impacted by the lesions and therefore could not be reconstructed up to the somatosensory cortex. Comparatively, the left CST exhibits pathology of lesser severity, and tractography was more successful in this case. One point of significance involves the correlations between stroke recovery and resolution of pathological factors. For example, rapid recovery is associated with factors such as peri-lesional edema or inflammation, whereas slow (but functionally positive) recovery is associated with brain plasticity[4]. Kwon et al. suggested that the former scenario can be attributed to the preservation of the CST over the course of the injury, whereas the latter can be attributed to CST recovery[5].

The complexity of the dynamics of brain recovery after ICH is made clear in Figure 3, where the spatial extent of lesions is followed over a two-week period. Although there is a clear overall reduction in total lesion volume over this period, what is obviated by this figure is the fact that there can be continued damage to the brain in regions which do not appear to be affected at all at the earliest time point. For example, many of the brain regions affected by hemorrhage at the second time point in Figure 2 do not seem to be bleeding at the first time point. This point suggests that the changes in brain shape and lesion morphology which occur after ICH are difficult to model using a classic differential geometry model of diffeomorphisms, and that the presence of non-diffeomorphic components in the shape analysis of ICH is a major hurdle to be overcome as shape analysis algorithms for the study of brain pathology mature.

DISCUSSION

The novelty of our work is partly due to the fact that (a) the 3D Slicer environment allows a variety of sequence types to be utilized simultaneously, and (b) previous studies have correlated quantitative measures with clinical outcome measures. The benefit to clinicians thus comprises both informatics-related (integration of datasets) and patient-tailored (systematic correlations) components. The level of characterization illustrated by these results would not be feasible via structural MRI alone, where voxel intensities are affected by lesion class, and segmentation of WM/GM is dependent upon voxel intensities. Notably, integrated DTI and MRI analysis encompasses both visual and quantitative dimensions. Fractional anisotropy (FA) measures recorded from diffusion imaging provide quantifiable descriptors of WM tracts that can be assessed across time points. Comparatively, conventional structural volumes provide measures on pathology size, resolution, and GM/WM volume loss.

TBI and ICH can have both focal as well as diffuse effects upon cortical circuitry; because higher-level cerebral functions are mediated by their corresponding neural networks, changes in WM connectivity patterns after TBI or ICH can adversely affect neuropsychological outcomes[6, 7]. Given these complex dynamics, quantitative structural evaluation may not be sufficient for outcome prognosis due to inconsistent correlations between volume changes and neuropsychological outcomes[8]. Additional damage outside the areas of primary injury is difficult to detect, as in the case of diffuse axonal injury (DAI)[8]. The acquisition and incorporation of DTI data proposed here provide an understanding of WM connectivity and loss thereof after TBI/ICH which is substantially more comprehensive than in previous approaches.

In spontaneous ICH, hematoma expansion is exhibited in approximately one third of patients who receive a follow-up CT within 3 hours of injury onset. Although CT measurements have predictively correlated hemorrhage volume with patient mortality, morbidity within the context of motor outcome is not consistently reflected due to the fact that neural fibers are highly susceptible to mass effect[9, 10]. Thus, in the representative case of the corticospinal tract (CST), even slight mechanically-induced extensions of the CST may induce debilitating neural deficits. The integration of DTI with structural MRI therefore provides insights on fiber integrity, with the possibility of also resolving fiber displacement resulting from mechanical deformations. This novel mode of integration is demonstrated here, where multimodal neuroimaging volumes provide the basis for modeling hemorrhagic and edematous pathology, whereas acquired DTI scans are processed to explicitly reconstruct the CST.

CONCLUSION

In the past decade, the rate of neuroimaging data collection has increased exponentially, and current methodologies for their analysis do not sufficiently facilitate integrative studies. A prevalent challenge, for instance, is the considerable manual effort needed to bridge compatibility gaps between the various software environments which are typically employed by researchers. The methods described here account for only a few of the many ways in which meaningful and clinically useful information can be extracted from neuroimaging datasets. Next-generation, informatics-informed data processing strategies must therefore address the need for integrative workflows, with the specific aim to reduce the number of software environments required, as well as to minimize the amount of time and effort devoted to the manual customizations of tools across environments. Such integration would promote knowledge extraction and, moreover, enhance the understanding of mechanisms underlying successful brain recovery.

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