Multimodal Patho-Connectomics of Brain Injury

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Abstract. The paper introduces the concept of *patho-connectomics*, an injury-specific connectome creation and analysis paradigm, that treats injuries as a diffuse disease pervading the whole brain network. The foundation of the "patho-connectomic" ideology of analysis is that no part of the brain can function in isolation, and abnormality in the brain network is a combination of structural and functional anomalies. Brain injuries introduce anomalies in this brain network that could affect the quality of brain tissue, break a pathway, and lead to disrupted connectivity in neural circuits. This in turn affects functionality. Thus, *patho-connectomes* go beyond the traditional connectome and include information of tissue quality and structural and functional connectivity, forming a comprehensive map of the brain network. Information from diffusion and functional MRI are combined to create these patho-connectomes. The creation and analysis of patho-connectomes are discussed in the case of brain tumors, that suffers from the challenges of mass effect and infiltration of the peritumoral region, which in turn affect the surgical and radiation plan, and in traumatic brain injury, where the exact injury may be difficult to determine, but the effect is diffuse manifesting in heterogenous symptoms. A network-based approach to analysis of both these forms of injury will help determine the effect of pathology on the whole brain, while incorporating recovery and plasticity. Thus, patho-connectomics with a broad network perspective on brain injuries, has the potential to cause a major paradigm shift in their research of brain injuries, facilitating subject specific analysis and paving the way for precision medicine.

Keywords: Diffusion MRI · fMRI · Connectomes · Free water · Tractography · Brain tumors · Neoplasms · Traumatic brain injury

1 Introduction

Brain injury can be organic as in brain tumors, incipient and developmental as in autism and psychopathology, or acquired as in traumatic brain injury. Traditionally, diffusion and functional magnetic resonance imaging (dMRI and fMRI) have been used for group-based statistical analysis and biomarker creation, in non-focal diseases, based on imaging features derived from the data. In injuries with focal anomalies like brain

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tumors, imaging has been used to localize pathology for focused treatment like surgery or radiation. However, the brain is a network, with no part that can truly be isolated.

dMRI offers a structural insight into the complex network architecture of the brain, based on the differential water diffusivity in tissue, with the white matter (WM) being highly organized and the cerebro-spinal fluid being pure water. It is therefore able to provide measures of tissue quality quantifying the anisotropy (directionality) and ease of diffusivity of water in tissue. Based on acquisition, dMRI can be fitted with a tensor model (as in Diffusion Tensor Imaging (DTI) [1, 2], with a short and clinically feasible acquisition) or a higher order model (as in high angular resolution diffusion imaging (HARDI) [3], with a longer and more research-oriented acquisition). Scalar measures of anisotropy and diffusivity derived from DTI [4], and invariants derived from HARDI [5] provide a characterization of tissue quality. Tractography, provides an insight into the fiber pathways in the brain [6], by tracking the directionality of water flow in tissue. Finally, by parcellating the brain into regions [7, 8], and tracking between them, we can create the structural connectome of the brain [9]. Resting state fMRI (rs-fMRI) provides information about the functional interaction between brain regions and can be used to create a functional connectome. Advances in dMRI and rs-fMRI analytics has enabled the systematic interrogation of the structural and functional networks of the brain, as well as the tissue and tractography maps, albeit, separately.

Brain injuries introduce anomalies in the brain's network. This could manifest as WM pathways being affected in the form of deteriorated quality, as well as a breakage in the pathway, leading to disrupted connectivity in neural circuits. This can in turn cause decrease or delay in functional activation. As brain regions are inter-connected, the effect of pathology on these measures is also inter-related, underlining further the need for a holistic approach to image analysis. This paves the way for a new philosophy of analysis, *patho-connectomics*, that goes beyond treating injuries as focal anomalies, but as a diffuse disease that is pervading the whole brain. A network-based approach to analysis will help determine the effect of pathology on the whole brain, while incorporating recovery and plasticity. This requires combining the information from structure and function, leading to a functionally guided structural network analysis of the brain. A *patho-connectome* therefore goes far beyond a traditional connectome, which is a simple map of connectivity, and its study involves a comprehensive analysis of the tissue quality, its connectivity, and the dynamics of the neural circuits in the face of plasticity. This has the potential to cause a major paradigm shift in the research of brain injuries, allowing a broader network perspective on them, as well as facilitating subject specific analysis and paving the way for precision medicine.

2 Patho-Connectomics of Tumors

Primary and secondary neoplasms may result in structural and functional impairment in the brain. Structurally, WM fiber pathways are displaced by tumor mass effect and disrupted by cancer infiltration. The functional framework in the brain is damaged by several mechanisms including the pathophysiological exchange in ion channels [10] and the presence of angiogenesis [11]. Traditionally, a combination of surgical

resection, chemotherapy, and radiation therapy are used, in order to resect and restrict the tumor with the aim of increasing survival. However, the prognosis remains poor, largely because the etiology of brain neoplasms continues to be poorly understood, especially of primary tumors. Also, despite increased survival, the quality of life may deteriorate as a result of the resected WM. Hence, there is an urgent need for a "patho-connectomic" global view of treating neoplasms, that can predict global effects of local changes, as well as the behavioral deficits associated with a pathologic, surgical, or therapeutic change in connectivity. Such a connectomic approach will revolutionize the oncological protocol: (1) in surgical planning where a better characterization of the peritumoral region, and non-invasive markers that identify infiltration will aid in maximal resection with minimal deficit; and (2) in treatment monitoring by determining the effect of WM removal mediated and compensated by plasticity, enabling a better quality of life.

2.1 Characterizing Peritumoral Tissue

A characterization of the peritumoral tissue will aid in determining the extent of infiltration, as well as potential for recurrence. As tumor growth may be associated with several abnormal processes like leaking blood-brain barrier, change in the tissue due to infiltration, inflammation, increased permeability of blood vessels, etc., various MR imaging contrasts provide information about the edema (dMRI and FLAIR), vasculature and blood flow (perfusion, dynamic contrast enhanced imaging), metabolic tissue properties (spectroscopic imaging), and molecular water mobility within the tissue (diffusion and magnetization transfer imaging). It is expected that a multimodal radiomic marker characterizing the peritumoral tissue will aid in determining tumor type, malignancy grade, and the potential for recurrence, thereby replacing an invasive biopsy and shaping the treatment procedures. Peritumoral tissue has traditionally been characterized by the dMRI measures of fractional anisotropy (FA) and mean diffusivity (MD). However, as dMRI is representative of water diffusivity in tissue, and edema and infiltration pertain to variable water content and ease of diffusion, the characterization of these regions will gain from multicompartment tissue modeling. Maps of various compartments, especially free water volume fraction, have the potential to provide additional information about the tissue microstructure associated with edema and tumor infiltration, and can characterize changes associated with different tumor types as well as their genetic underpinnings.

Infiltration of tumor in the peritumoral region suggests a tissue type different from healthy tissue and edema and would gain from a specific modeling of this compartment. However, research in multi-compartment modeling is limited to healthy tissue without incorporating pathology as a compartment. Additionally, most of the microstructural modeling is on long acquisitions infeasible in the clinic. Models based on single shell clinical acquisitions [12] use initializations tuned for the healthy tissue. We have developed a free water elimination method based on the bi-compartment modeling of clinically feasible dMRI acquisitions [13]. As can be seen in Fig. 1, it estimates both the unhealthy peritumoral and the healthy regions well. Such a characterization of tissue microstructure should be able to distinguish tumor types, which till now needed an inclusion of information from various modalities. The variation in

water content in the peri-tumoral regions between primary (glioblastoma multiforme (GBM)) and secondary (metastatic)) tumors is captured by the free water volume fraction maps, as the former has infiltration and the latter is mostly pure water. A statistical analysis comparing 87 GBMs and 54 metastatic tumors shows a significant difference between their volume fraction maps, as well as the extent of change in fractional anisotropy induced by the free water correction (Fig. 2).

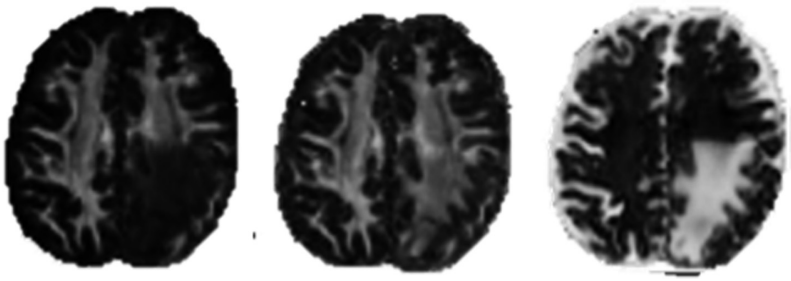

Fig. 1. Effect of Free Water (FW) Correction on tissue quality measures: FA map pre-FW correction shows decrease in edema (left), which is restored after correction (middle), with the FW map capturing the water and infiltration (right).

Thus, dMRI offers imaging contrasts that could permit more uniform sampling than heterogeneous biopsies and can be applied repeatedly to monitor therapy and facilitate a comprehensive diagnosis of brain tumors. Currently, clinical protocols comprise multiple modalities, and it may be possible to lower these by using different contrasts from DTI. Modeling the infiltrated tissue as a separate compartment, is the next big step in this area, that will revolutionize cancer research, by providing an alternate to invasive biopsy. However, obtaining ground truth in the form of biopsy of peritumoral tissue is difficult, as there is high heterogeneity in that region as the tissue could be a mix of edema, cancer and healthy tissue. With brain shift and swelling, pin pointing the exact location is difficult. Thus, the validation of such a tissue compartment remains the biggest challenge to this research.

2.2 Better Mapping of Structural Pathways

Optimal surgical resection or radiation planning of brain tumors hinges on the knowledge of the spatial extent of the tumor, the displacement and infiltration of fiber pathways, as well as a characterization of the peritumoral edema to obtain better delineation of fiber pathways. DTI is used in pre-surgical planning for the purposes of creating maps of eloquent tracts using tractography techniques, that will enable the surgeon to plan maximal resection with minimal damage. fMRI is used to provide additional evidence of presence of tracts. Tractography is based on the diffusion parameter of FA which is adversely affected by edema, as well as infiltration, which alter the tissue quality and hence these measures of diffusion, leading to potentially erroneous tracking. With the free water modeling of the peri-tumoral tissue, the

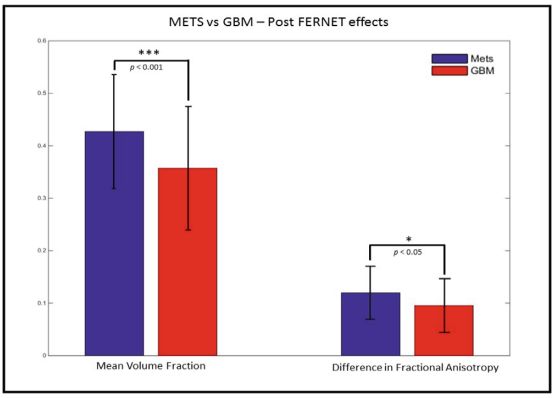

Fig. 2. Characterization of the peri-tumoral region using free water correction is able to distinguish tumor types: there is a significant difference between free water volume fraction maps (left) and difference in corrected FA (right) of GBMs and metastatic tumors.

corrected tissue shows improved tracking in peri-tumoral region (Fig. 3), irrespective of the type of tractography and length of tract. Manual identification of tracts for surgical planning is very challenging due to displaced and broken tracts, leading to the development of several automated tract segmentation algorithms. Most of these are based on geometric and shape features [14] that fail for displaced and broken tracts. This paved the way for a fiber clustering algorithm [15, 16] that is based on encoding the tracts based on their connectivity signatures, and subsequent clustering them using an atlas. The method is able to capture tumor and subject-wise variability, underlining its importance for precision medicine. A combination of the edema invariant tractography with this connectivity-based tract clustering will make the fiber extraction robust to disruption due to infiltration and displacement as a result of mass effect caused by the tumor. The biggest challenge of research projects in fiber tracking and clustering, is the validation. Animal models with similar pathology are hard to find, tracer-based results are an unfair comparison to tracking done on clinical resolution, and cortical stimulation is challenging to perform on deep white matter, and on tracts like language tracts.

3 Patho-Connectomes of Traumatic Brain Injury

dMRI has been used in traumatic brain injury (TBI) [17], mostly to demonstrate differences at the group level using measures of tissue quality like FA and MD, which are representative of anomalies in the axonal and myelin structure. Additionally, a few connectivity studies have revealed abnormalities [18–21] in the structural connectome. However, studies showing resting state fMRI abnormalities in brain injury [22], suggest that both structure and function are affected, and that TBI studies will gain from their combination.

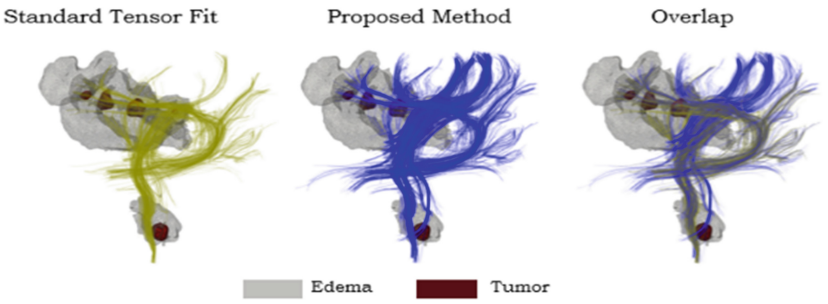

Fig. 3. Tracking incorporating free water correction of the peritumoral region: Tracking coverage in peri-tumoral regions increases with free water correction (middle), in comparison to the standard tensor fit (left). The overlap (right) shows the additional fibers (blue) that are tracked after free water correction. (Color figure online)

3.1 Measures on Injury in TBI

Due to the diffuse effect of TBI on WM, a large number of studies have used measures of tissue quality like FA and MD, as measures of injury in TBI. In most chronic TBI cases, there is an increase in FA and a decrease in MD. However, the results, and their interpretations have varied across studies due to the small sample sizes and high heterogeneity of the effect of trauma, even within the groups of mild, moderate and severe TBI. Higher order dMRI, have the ability to provide other measures called invariants [5], but long acquisition times and sequences that are clinically not viable, have hindered the popularity of higher order schemes. Due to the extent of knowledge provided by these invariants, it is expected that with the advent of deep learning, and with advanced acquisition in recent studies, these invariants will provide more sensitive measures of injury. Diffuse axonal injury in traumatic brain injury may be a combination of swelling (inflammation) and axonal disruption in the chronic stages, that presents itself in the form of changes in the free water. Figure 4 shows the extent of free water differences as a result of trauma to the brain, in a group of TBI patients, as compared to controls. The extent of free water may be a measure of damage and indicative of future cognitive decline.

In addition to the measures of tissue quality, connectomes, provide a wealth of information that can be used to derive measures to quantify injury post trauma [19]. However, measures devised in the literature are generic and their interpretability is difficult. Ideally, a measure should incorporate the vulnerability of the different parts of the brain, mediated by the amount of injury that causes a disruption in the connectivity of the brain. In that vein, we have developed a disruption index [18], that captures the extent of injury, in correlation with clinical and cognitive scores. Although the measure has been used to evaluate the extent of injury in TBI, the same can be used to determine the effect of surgery or radiation planning on the brain, as the extent of change can be determined, along with the vulnerability of the nodes with regard to a population of healthy controls. Future work involves extending this to functional connectomes.

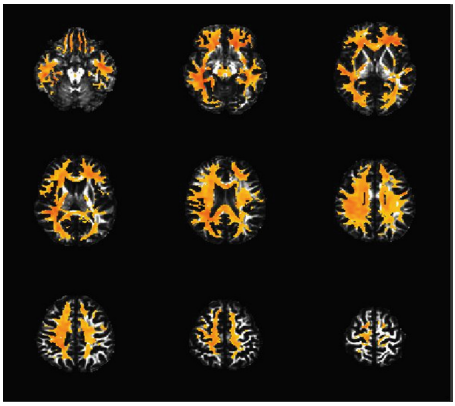

Fig. 4. Free-water increased in TBI brains as compared to healthy controls. These are the results of voxel-based analysis, when TBI patients are compared to controls. The colored voxel indicates significant differences relative to healthy controls.

3.2 Creation of Injury Connectome

The creation of the injury score from a traditional connectome underlines the potential of a whole brain map in quantifying the injury burden. Despite their glory, traditional connectomes are limited in that, they encode only pairwise connectivity information of the regions which is taken from a single imaging modality, overlooking much of the information that can be obtained from the network structure of the brain. These limitations can be overcome by introducing an enhanced injury connectome that includes regional features in addition to connectivity information, that are obtained from various modalities. This can further be supported by tools to discover similarity among such structures at various levels, from individual regions up to the whole network. Considering connectomes as annotated graphs and establishing similarity measures between them, that account for network wide connectivity as well as local features of regions, provide ways to obtain such an injury connectome.

As the first step along these lines, we evaluated structural and functional connectomes as weighted graphs and proposed using a novel similarity measure based on graph matching, enabling comparison across subjects in [20]. The main idea with this form of connectome matching is that, regions with similar connectivity signatures should get mapped to each other, with mismatches indicating an anomaly of connectivity (Fig. 5). In analyzing a TBI dataset consisting of structural and functional MRI of patients at three time points post injury, we observed significant group differences between patients and controls longitudinally. We also observed that, our graph matching based similarity measure correlates well with the clinical scores of patients, indicating the ability of the approach to capture underlying changes in pathology. This study lays the foundation for the analysis of structural and functional plasticity as it provides the means to measure connectomic similarity at various levels.

Taking a further step towards obtaining an injury connectome in [21], we further enriched the traditional connectome with graph theoretical measures such as node

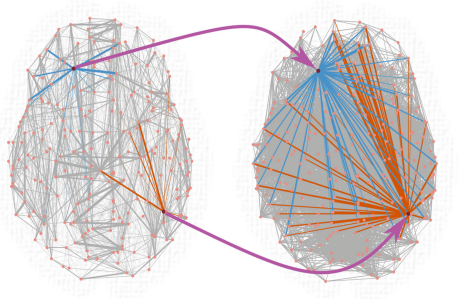

Fig. 5. Graph matching establishes a one-to-one mapping between nodes of two connectomes based on nodal connectivity patterns. Mismatches indicate dissimilarity between corresponding nodes across subjects arising from an altered network, possibly due to pathology. Hence, graph matching is a viable method to distinguish patients from controls as well as identifying brain regions that differ across groups or in individual subjects.

degree, strength, and centrality, in addition to the connectivity signature of nodes with respect to the rest of the network. We also extended our graph matching based similarity metric to enriched connectomes. When applied to a dataset with TBI patients on a classification task, we found that the enriched connectome along with the similarity measure outperforms traditional connectome in distinguishing patients from controls (Table 1). Our results further indicate that, graph theoretical features and the connectivity signature of nodes complement each other in classification, highlighting the importance of enriching the connectome with extra nodal information.

Table 1. Comparison of classification accuracy of TBI patients and controls between traditional and enriched connectomes (EC)

Scenario	Accuracy (%)
Traditional connectome	66.7
EC with graph theory measures alone	42.03
EC with edge weights alone	62.32
EC with graph theory measures and edge weights	72.46

A future direction will be to investigate different communication models in the brain, that could explain the functional changes related to the structure and can aid in incorporating the concept of plasticity better. Traditionally, all the analysis is carried out with the assumption that the brain adopts the “shortest path” mode of communication. But that does allow for the concept of “delayed” processing in the brain, that can occur as a result of injury. It is also difficult to explain the rewiring of the brain that must occur due to plasticity. This presents an exciting direction of future research.

3.3 Applying Injury Connectomes to Tumors

Creating an injury connectome for tumors will revolutionize neuro-oncology. An enriched connectome with information from tissue quality and fMRI, goes beyond the traditional use of fMRI which is used in surgical planning to compliment the extracted tracts from dMRI. It will enable the surgeon to take a connectomic approach to surgery in which the effect of the resection of tumor and healthy tissue leading to tumor region, can be known beforehand, enabling maximal resection with minimal current and future deficit, structurally, functionally and behaviorally. Such a connectome will help understand the mechanism of plasticity as the tumor grows, as well as after surgery, suggesting therapeutic prospects. This is expected to improve the quality of life considerably. However, creating such a connectome in the presence of tumors is challenging. The creation of a connectome requires the parcellation of the brain into regions, which has traditionally been achieved by registering an atlas to the brain. However, registration algorithms fail in the presence of a tumor, or at least in the vicinity of it as the layout of regions and the pathways connecting them are altered. The methods that avoid registration to an atlas by obtaining subject specific parcellation [7], still fail around the tumor. Hence, doing tracking based on edema invariant tractography, using it to create a connectivity map of the brain, and finally obtaining a parcellation is an open area of research. Success of graph matching in identifying anomalies in TBI [20, 21], suggests it as a promising tool to overcome the registration problem through mapping regions from a healthy brain into a brain with tumor. Figure 6 demonstrates how graph matching could be used for registration.

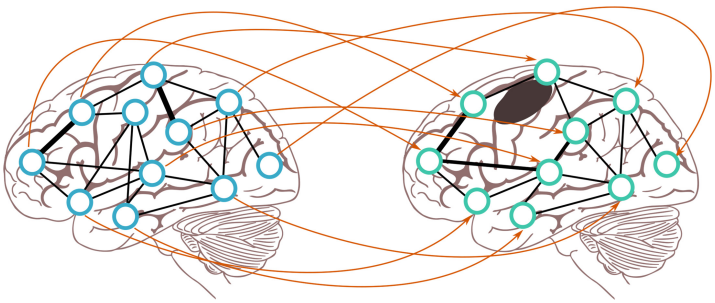

Fig. 6. Matching networks between brains, post- (left) and pre- (right) tumor resection: Using graph matching to overcome the registration problem in the presence of tumor, by finding a mapping between the nodes of a resected brain with nodes of brain with tumor.

Once such a connectome is created, measures of injury like the one described above, can be used to quantify the effect of WM removal, and that of radiation on the rest of the brain. In a longitudinal study on the effect of radiation on brain connectivity, we saw a decreased efficiency of the brain with increased dosage (Fig. 7). Analysis at the subnetwork level of eloquent (motor, visual and language) and behavioral (executive functioning, working memory and other cognitive networks) subnetworks will pave the way of quantifying cognitive changes temporally. Surgical and radiation

planning will improve with such a connectome, as it will be possible to know how the surgical path will affect the brain post-surgery, as well as determine a radiation plan that is least invasive. This "patho-connectomic" view of surgery will therefore enrich therapeutic care, and subsequently the quality of life.

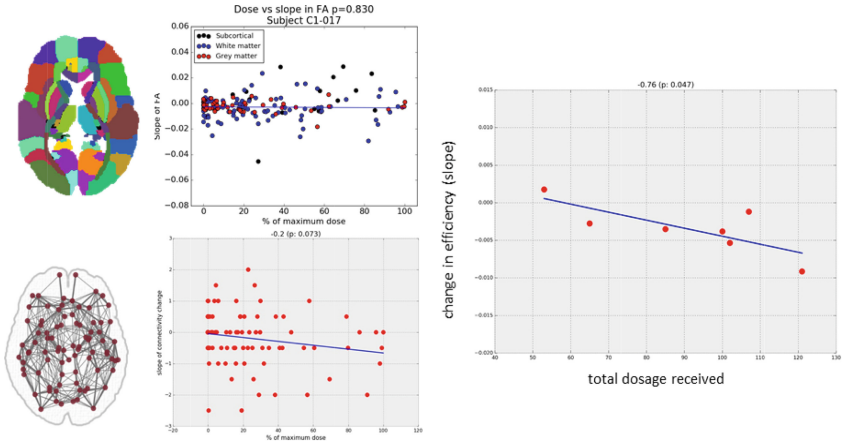

Fig. 7. Effect of radiation on local measures of tissue quality (left: top) and connectivity (left: bottom) does not show any changes with dosage. The global measure of efficiency of brain network shows a decrease with increasing dosage (right).

3.4 Conclusions

Connectomics [9, 23] has revolutionized brain research in the past decade, enabling research in sex differences [24, 25], development [26] and psychopathology [27]. However, despite its tremendous potential, traditional connectomics falls short in the analysis of brain injury and has not translated to the clinic. In this paper, we enumerated some of the major limitations of traditional connectomics in brain injury, highlighting the need for *patho-connectomics,* an injury specific connectomic paradigm, that would enable a multi-modal analysis of injured brains, both at the population level for creating biomarkers, but also at the individual level paving the way for precision medicine.

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