Towards Visual Mega-Analysis of Voxel-based Measurement in Brain Cohorts

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Abstract

We present a visualization prototype for comparative analysis of factional anisotropy (FA) distributions constructed from three-dimensional (3D) brain diffusion tensor imaging (DTI) in brain cohorts. The prototype lets brain scientists examine meta-analysis (the pooled analysis of multiple smaller trials or multi-site studies) results for identifying differences in cohorts. Interactive side-by-side bar charts show multiple statistical results of FA comparisons in regions of interest (ROIs) defined by user-chosen atlas. An occlusion-free two-dimensional (2D) semantic merge tree further displays the global distribution of FA values. Two histograms on each tree arc reveal voxel-based FA distributions represented by that arc branch in cohorts. Interaction techniques support brushing-and-linking of local and global ROIs queries. ROIs can be defined from atlas or select through interaction. We report validation results in a case study and an interview.

1. Introduction

Recent large scale data gathering and analytics initiatives have advanced generalizable analyses and techniques by extracting and combining human brain imaging data from subjects collected worldwide regardless of imaging acquisition methods or population under study [TSM*14]. Some of the most important problems are related to methods to combine the cohorts (predefined population) to obtain pooled estimates through *meta-*(the pooled analysis of multiple smaller trials or multi-site studies) and *mega-analysis* (the pooled analysis of raw data to address subgroup differences and interaction) approaches to estimate the general additive contributions to the intersubject variance and to assist locate the affected brain regions due to pathological conditions.

The wealth of information is however far too rich for a brain scientist to take in at a single glance in the large imaging cohorts. Even when multiple trials are designed to address the same question, scientific conclusions may differ. Thus, visually communicating and comparing meta- and mega-analysis results could potentially assist interpretation of the analytical methods and offer novel possibilities for publications [GDL*11] One of the parameters frequently used in these analyses is fractional anisotropy (FA) extracted from diffusion tensor imaging (DTI) because FA values are sensitive to tracts integrity discovered in many brain disorders such as Alzheimer's disease (AD) [OMA*11] and schizophrenia [CHW*15]. We also make use of FA values in this work because

our collaborators are analyzing FA values to compare schizophrenia and control cohorts [JKN*14,KGW*16] as part of the ENIGMA project [TSM*14].

Communicating the cohort comparison visually is challenged by dense brain volume and computational solutions. Current approaches to displaying large-dense datasets of brain imaging focus on three solutions. The first is to center on the display hardware by increasing the display size and using immersion and stereo to augment human perceptual capabilities [CCAL12]. However, this approach is not often available in brain scientists' offices, where desktops are the usual environments. The second approach is to simplify the visualization to extract meaningful features such as topological structures [TKW08,STS07]. While this approach is powerful, it has the drawback that topology may not reflect critical brain *functions*, since it is derived using geometrical concepts. The third approach focuses on low dimensional representations and interactivity, i.e., using an embedding approach to yield 2D displays that can also show tract clusters [CDZ*09] or to optimize encoding to generate occlusion-free 2D visualizations [JDL09].

All these works have focused on visualizing a single dataset which is important to assess a particular mechanism which visualizations can be effective for. Studying cohorts requires one to show distributions and to support comparative data analysis.

Most recently, Zhang et al. used semantic merge tree to compare and encode cohort datasets [ZKH*15]. That work contributes to the semantic overlay onto the topological representation. As an extension of the prior paper, this paper presents mega-analysis result
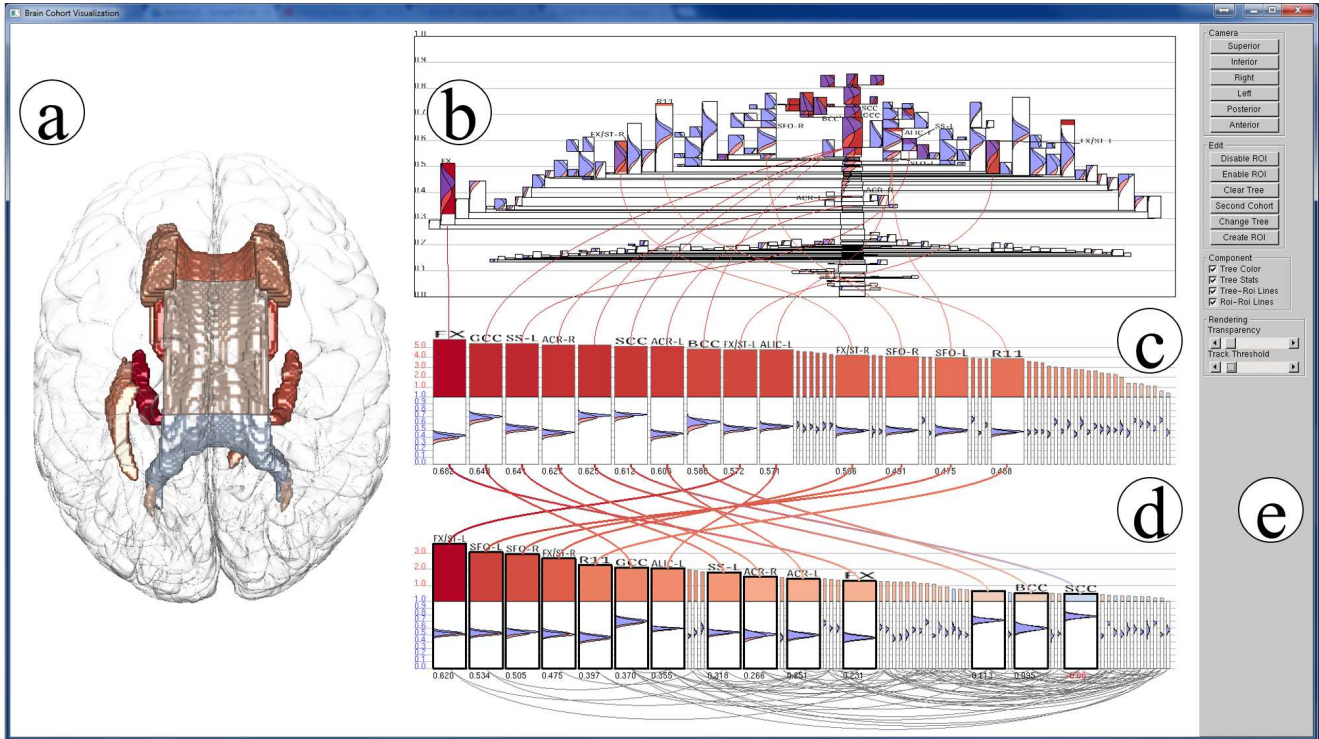

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Figure 1: Brain cohort comparison interface: (a) The spatial view shows the selected brain regions with the context of a transparent cortex mesh; (b) The merge tree constructed from average FAs in a cohort. (c) and (d) The regions of interest view to compare the control vs. patient cohorts. (e) The control panel.

comparisons with simple interactive bar-charts for between-cohort comparisons. We show the ability to visually convey both global and local FA value differences, which to the best of our knowledge is the first for a DTI cohort comparison. We also generate a condensed representation of a merge-tree to substitute the generic contour tree and make use of the merge-tree to select and add user-defined regions. Further more, a web version [ZKHC16] of this visualization tool is soon to be integrated with the ENIGMA project to be broadly disseminated to the brain imaging community to display cohort variances.

2. Background in Brain White Matter Analysis and Comparative Studies

Brain white-matter integrity is often measured using FA values derived from DTI. Brain scientists on our team are interested in understanding FA value changes in schizophrenia patients. Performing cohort-based analysis is important to demystify the results' differences in the brain science literature. While most recent advances in tensor field visualization focus on tensor field visualization with uncertainty by looking into local measurement and multi-level of details [AWHS16], ours focuses on synthesizing and communicating results from cohorts rather than showing local tensors from a set of individual measurements.

3. A Two-Stage Approach for Cohort Comparison

This section presents our contributions for comparative visualization of mega-analysis results and merge tree construction of FA values. We also present the interface design for data exploration.

3.1. Mega-Analysis in Cohorts

3.1.1. Analytical Approaches

The goal in mega-analysis is to merge ROIs and compare ROI differences in brain cohorts. We have followed the automatic approaches in Kochunov et al. [KGW*16] to perform the mega-analysis. We first construct ROI-based statistics using template-based white matter volume deformation analysis [KLT*01] and then compare these regions in cohorts using voxel-based statistical comparison of FA values.

A common skeleton mask is generated and every subject's deformed volume is sampled through the skeleton mask to provide FA value for each ROI using atlas-based approach. Our tool supports the JHU atlas [WJNP*04]. This process is followed by using the mapped skeletonized volume data in the cohorts to conduct tract-based spatial statistics (TBSS) [SJJB*06] and compute aggregated measurements-to-skeleton mapping [JKS*13]. Global whole-brain and regional FA values were extracted using the ENIGMA-DTI protocols and statistics were modeled to study tract-specific measures of FA values.

3.1.2. Visualization of Mega-Analysis Statistics

Brain scientists perform comparative analysis from different anatomical regions in cohorts. These analyses often present different results due to different empirical study approaches and parameter settings etc. While showing the details will lead to answering questions why study results may differ, here we present the first step to visualize the value distribution in interactive bar charts. Brain scientists can directly compare results to locate the import brain regions and find differences.

Figure 1 (c and d) show the ROI statistics from two data collecting sites; each data site includes one control and one diseased cohorts. Within each cohort, we use two rows of bar-chart to encode the sorted p-values or other statistical measures (e.g., effect size) from high to low. Each bar represents an ROI derived from that atlas in that cohort or defined by the user (see Section 3.3).

The top bars encode the effect size with a diverging color scheme [Mor09], where positive effect size (when control cohort has higher average FA, and vise versa) is mapped to red and negative is mapped to blue. The effect size is encoded using saturation. The more saturated colors represent larger effect size. The bottom bars are the normal distribution plots of regional FA values for control (blue) and diseased (red) cohorts.

Because regional connectivity can aid brain scientists to identify regions of interest, these connectivities between regions are shown as links (at the bottom of the ROI bar charts in Figure 1(d)) filtered by the ratio of common tracts shared between regions measured by the Jaccard index.

3.2. Semantic Merge Tree

The purposes of creating merge tree are two-fold. The first is to generate an occlusion-free representation for showing FA value distributions. The benefit is for the ease of exploration of the complicated 3D brain volume. The second goal is to let the user select interesting regions based on FA values. The purpose of this display is not to study the functional aspects of the brain imaging.

3.2.1. Construction and Space-Saving Layout

We have constructed a merge tree [BWT*11] to create a more compact representation than the contour tree in Zhang et al. [ZKH*15]. The split tree in the generic contour tree is not necessary because ROIs are associated with higher local FA values and these values can be sufficiently represented using upper arcs in the join tree. A benefit of excluding the split tree is that the final tree does not contain any downward arcs and is thus edge-crossing free [GGT96]. Our merge tree is computed using the averaged skeletonized data from the control cohort. The arcs are arranged vertically and an arc's vertical position encodes the range of the FA values. Trees are also pruned to reduce the number of contour branches. The semantic mapping on these arcs follow Zhang et al. [ZKH*15].

We have optimized the tree layout using a branch-based method in order to generate a more compact layout than that in Zhang et al. [ZKH*15]. A branch rooted at an arc is defined to be the path from this arc to one of the leave arcs that has the highest vertical coordinate. Zhang et al.'s layout algorithm works on the subtree level:

each subtree will be allocated space equals to its bounding box, resulting in larger horizontal span in the bounding box corners. Our method saves space by laying out on the branch level: an arc can be placed *within* the bounding box of the adjacent subtree. Figure 2a illustrates a case where the blue subtree is moved to the side of the green subtree to improve the space utilization.
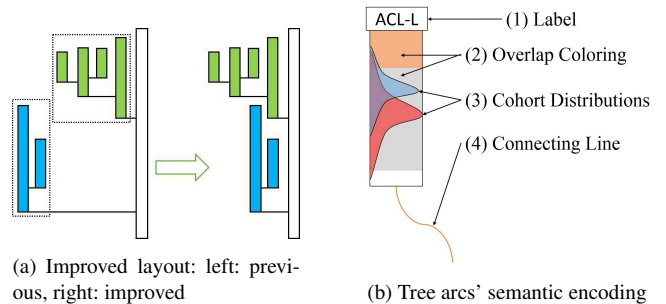

(a) Improved layout: left: previous, right: improved

(b) Tree arcs' semantic encoding

Figure 2: Space-saving merge tree construction and FA distribution and location encoding

3.3. User-Defined ROIs

Since the merge tree can display the FA value distribution where regions of similar FA values can be easily selected, we have allowed the user to select interesting FA values and to generate user-defined ROIs associated with these FAs. The user-defined ROI can also be inserted into the bar-chart ROI maps created from atlas. Subsequent statistical analysis for the newly generated ROI can also be performed and compared between cohorts 3a.

3.4. Visualization Interface

The user interface consists of a multiple view display and a control panel (Figure 1) Panel-a is a 3D spatial view of selected ROIs, generated using the isosurface tracking algorithm [CSvdP04]. We render a transparent brain cortex mesh in the spatial view as a spatial context. The mesh has its alpha modulated with $\alpha = (1 - |\vec{n} \cdot \vec{e}|)^c$, where $\vec{n}$ and $\vec{e}$ are the normalized normal direction and viewing direction respectively. This method preserves the curvatures of the gyrus and sulcus [PTKK03]. Panel-b contains the merge tree visualization of FA distributions; Panels-c and -d are the ROI statistics visualizations of two datasets. Panel-e contains a control panel for adjusting rendering and filtering parameters. The interface was implemented using GLUI [RS16] and the web-version [ZKHC16] was implemented in WebGL.

Brush-and-link interactions are provided to select ROIs. Selecting a ROI in one view will highlight the corresponding ROIs in all other views. The user can also expand or squeeze any ROIs to fit their analytical needs. Those regions that are not of current interests are shown in thinner bars to kept in context and can be expanded.

4. Validation of Our Mega-Analysis Toolkit

This section reports preliminary validations using a case study and an interview. Below we first show a case study executed by a brain scientist named Lucy.

4.1. Case Study: Mega-analysis of Regional Differences in Two Cohorts

Lucy has obtained two datasets from two different labs, where the the first dataset consists of 122 control and 127 schizophrenia patients and the second contains 62 control and 81 schizophrenia patients. She is interested in learning effect size significances between patient and control cohorts in these two datasets.

Lucy begins her study right away to confirm the data analysis results. She first loads the first datasets; the JHU atlas is automatically applied to show her analysis results of those regions, such as fornix (FX), genu of corpus callosum (GCC), left of sagittal stratum (SS-L), right and left of anterior corona radiata (ACR-R and ACR-L), splenium of corpus callosum (SCC), and body of corpus callosum (BCC). These regions are shown with saturated red indicating patient-control differences: the white matter (WM) deficits are significant in these regions, in consistent with literature in schizophrenia [FKS*09, FRLA*11].

Lucy is interested in examining if the same pattern presents in the second dataset obtained in a different lab. When she clicks to add the second dataset, another ROI dual-row bar charts reveal the FA values in these 62 controls and 81 patients. She sets the significance level of the effect of the *effect size* to $p < 0.01$ to accommodate for the smaller sample size in this dataset. She sees that the bar-charts views gets updated where the four most important ROIs which meet the significance level constraint are expanded to the full-width bars. These four regions are the left and right regions of both FX/ST (Fornix (cres) and Stria terminalis) and SFO (superior fronto-occipital fasciculus) (or FX/ST-L, SFO-L, SFO-R, and FX/ST-R.)

To compare these results to the results obtained in the first dataset, Lucy highlights all regions that are significant in one of these two datasets by clicking in both dual-row bar-charts. The visualization of these collected regions is then shown in Figure 3a. Lucy sees that the BCC and SCC regions in the second dataset are not as important as those in the first one.

To learn the locations of these regions in both datasets, Lucy selects all regions in Figure 3a, the corresponding regions in the spatial view are shown (Figure 3b to 3d). She concludes that FA deficits measured in these regions of the brains differ between datasets since the colors (indicate effect size) of these regions are very different.

4.2. Discussion

We have several extensive discussions with two brain scientists who study DTI mega-analysis on a daily basis and who are paper co-authors. The dual-row bar-charts are designed with these two brain scientists and they both felt that those charts worked very well to communicate the analytical results. They also liked the brushing-and-linking among all views and felt that the three-dimensional representation was also intuitive and visually pleasing. Their feelings on the usefulness of the merge-tree were mixed: one brain scientist felt that this method carried potentials but was too abstract to be useful; the other scientist was intrigued by this approach, especially for new ROI construction and thought it might be worth further improvement.
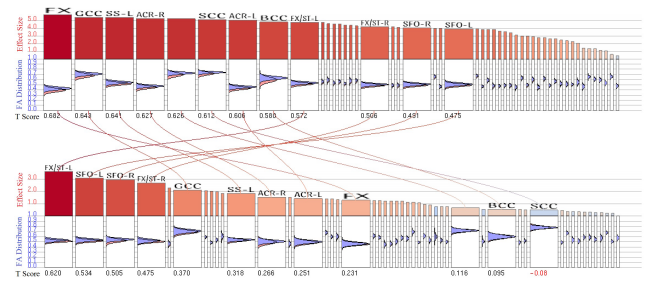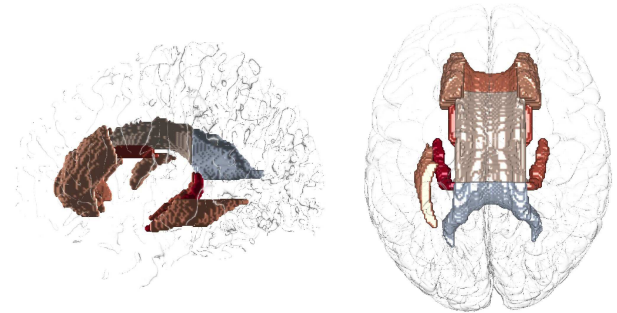

(a) Comparison between data from 1st (top) and 2nd (bottom) dataset

(b) 1st dataset (left view) (c) 1st dataset (superior view)

(d) 2nd dataset (left view) (e) 2nd dataset (superior view)

Figure 3: Meta-analysis on two datasets from two collection sites.

5. Conclusions

We have provided two complementary approaches for visualizing mega-analysis results in brain cohorts using dual-row bar charts and merge trees in a multiple view environment. Our preliminary results on studying the use of the tool for cohort comparisons suggest:

- Bar charts overlaid with statistical results provide effective multiple-view displays for cohort comparison related to ROI analyses.
- Interpreting the occlusion-free merge tree is visually challenging despite it shows a global overview of the FA value distributions.
- Interactive visualization methods to customizing ROIs will be useful to study regions not defined in brain atlas.

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