CereVA
Visual Analysis of Functional Brain Connectivity

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Abstract: We present CereVA, a web-based interface for the visual analysis of brain activity data. CereVA combines 2D and 3D visualizations and allows the user to interactively explore and compare brain activity data sets. The web-based interface combines several linked graphical representations of the network data, allowing for tight integration of different visualizations. The data is presented in the anatomical context within a 3D volume rendering, by node-link visualizations of connectivity networks, and by a matrix view of the data. In addition, our approach provides graph-theoretical analysis of the connectivity networks. Our solution supports several analysis tasks, including the comparison of connectivity networks, the analysis of correlation patterns, and the aggregation of networks, e.g. over a population.

1 INTRODUCTION

Unraveling the mysteries of the brain's inner workings is one of the great challenges in biomedical research today. Recent efforts including the Human Connectome Project, the Human Brain Project (Van Essen et al., 2013; HBP, 2014) and the BRAIN initiative underline the importance of this task. A core component of these initiatives is to study the patterns that are evident in the brain activity correlation data, known as functional connectivity networks. Differences in the networks between individuals over time, and between individual networks and aggregated networks among the healthy population or groups of patients can be examined to detect and understand the alterations related to disorders, e.g. in the context of Alzheimer's disease (Greicius et al., 2004). The analysis of such functional connectivity networks can foster the detection and understanding of brain activity patterns (Smith et al., 2013).

Brain activity is commonly measured using neuroimaging scanners of functional magnetic resonance imaging (fMRI). fMRI data is used to first derive time-course data, from which correlation matrices are calculated, e.g. (van den Heuvel and Pol, 2010; Smith et al., 2013). These matrices contain activity correlation values between regions of the brain that are either defined by a brain parcellation, based on the anatomy, or by the resolution of the imaging scan, e.g. the voxels of an fMRI session (Destrieux et al., 2010). Functional networks are not directly given by this raw data, but need to be modelled from the correlation matrices. However, a large part of the correlation data is regarded as noise as they are either redundant or does not contain meaningful correlation. It is not obvious how to select the relevant entries from the matrices where each individuals have unique correlations; a constant 'threshold value' might not be sufficient to cover all biologically significant correlations (Lee et al., 2012). The need for interactive selection of the threshold raises opportunities for the application of visual analysis concepts, where modelling a weighted graph that captures the main connectivity patterns in the functional networks then permits graph theoretical and statistics methods to be employed for analysis (Onoda and Yamaguchi, 2013; Wang et al., 2010).

While resting state neural networks, which occur when no conscious activity is being performed, exhibit several specific properties that can be calculated based on the network topology, e.g. (Bullmore and Sporns, 2009; Wang et al., 2010; Chang et al., 2013), visualization of such networks and the underlying data is an important step in facilitating analysis. Visualization allows the researcher to create insight by exploiting the humans expertise and ability to spot patterns, and can also help to cope with the imprecision of the network model and the influence of noise and uncertainty in the data. Research into the analysis of neural activity data often includes visualization of anatomical and functional information, such as brain and brain region depiction, e.g. (Nowke et al., 2013), or neural network visualization, e.g. (Sorger

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et al., 2013). An investigation into these visualizations by Margulies et al. (Margulies et al., 2013) argues that the best views intuitively combine network and anatomical data without cluttering the anatomical context, which could potentially present misleading information. This holds, in particular, when supporting a guided interactive exploration of activity data. The visualization can be accompanied by a network analysis that helps to identify and exploit the structural characteristics of the network (Wang et al., 2010). The overarching goals of these works are comparison across the population and between individuals to derive global patterns and variations, e.g. caused by disease, and to analyze the spatiotemporal dynamics in order to better understand the structure-function relationship underlying the connectivity patterns. Faithful network representations are thus required that convey patterns, as well as strong, clear links to the anatomical context.

We present a Cerebral Visual Analytics tool, CereVA, a preliminary approach that facilitates the analysis of brain activity data by providing a web-based visual interface for interactive exploratory analysis of the data. The interface combines several linked graphical representations of the network data, allowing for tight integration of different visualization views. The data is presented in the anatomical context within a 3D volume rendering, by node-link visualizations of connectivity networks, and by a matrix view of the data. In addition, our approach provides graph-theoretical analysis of the connectivity networks. Our solution supports several analysis tasks, including the comparison of connectivity networks, the analysis of correlation patterns, and the aggregation of networks, e.g. over an aggregated population.

2 APPLICATION AND VISUALIZATION TASKS AND CHALLENGES

Important analysis tasks for resting state activity data include:

A) identification of relevant differences between individual or aggregated networks

B) identification of significant patterns in a set, e.g. across the whole population

C) identification of network classes, e.g. for healthy individuals, disorders and behavioural patterns

D) investigating changes over time, e.g. during development (BSA, 2014) or due to aging

These tasks lead to challenges including:

i) modelling weighted graphs from the correlation matrix that reflect the main correlation characteristics

ii) modelling aggregated or *aligned* networks that represent a whole set of networks, e.g. the aggregate across the population, covering the overall characteristics well without a large deviation

iii) supporting tasks A and B by intuitive interactive visualizations for comparison to show dissimilarities and similarities

iv) supporting task C by including automated analysis in the visual interface, e.g. classification and clustering

v) supporting task D by allowing the analysis of time series data.

Therefore an intuitive visualization that combines both functional and anatomical contexts is suitable to facilitate an exploratory analysis of functional connectivity networks. Several methods of combining network visualization with imaging data are have been investigated in recent research (Böttger et al., 2014; Sorger et al., 2013; Hagmann et al., 2008). In addition, there is evidence that matrix-based visualizations can be advantageous for several comparison tasks (Alper et al., 2013). Matrices are also well suited for use in small multiples visualizations, which can be exploited to represent temporal dynamics or for comparison tasks. Thus incorporating a matrix-based view into a visualization approach can facilitate comparison as long as it is smoothly integrated into the interaction concept and does not increase the complexity of the visualization.

3 CereVA

As the underlying mechanisms of brain function and the impact of diseases are not yet fully understood, an interactive visual analysis process is proposed to facilitate knowledge discovery. This approach combines the strengths of the human expert to discover patterns and to exploit existing knowledge with the computational power of automated analysis and guided navigation. CereVA provides the researcher with an interactive visual interface that supports such a process, combining visualizations of the activity data, the anatomy and results from analysis. We aim to provide a system of tools that addresses the tasks described in Section 2, where we focus on tasks A, B, and C. CereVA's design was developed according to requirement analysis that included consultations with, and

feedback from, potential users, including an expert. We provide the implementation of our concept in a web-based application to allow users anywhere, anytime access.

While questions asked in the investigation of disease-related anomalies cannot be answered purely by automated analysis, the results of the analysis can still be used to guide the interactive exploration of the data. The visualizations in our system are therefore enriched with the functional activity data and information derived from it. For the exploratory analysis, we facilitate interactive navigation through the given data sets, in particular selection and comparison of networks of interest. Our interaction concept is thus designed to support the following workflow: a user can either visualize a single network or compare networks with each other, wherein the networks are either individual subject networks or aggregated networks that are derived from a set of networks, e.g. the network created by computing the average connectivity value for each pair of nodes. Results from data and network analysis are shown to the user and also mapped onto the network and anatomical visualizations. By filtering and selecting, the user can investigate the structure and patterns of the activity data.

The visualization components, the underlying data, the view enrichment, and the interaction concept are described in the following sections.

3.1 Data Processing and View Enrichment

Providing the results of an automated data analysis and mapping these results in an intuitive way onto the visualizations is important for supporting an efficient interactive exploration of the activity data.

Network Definitions. To cope with challenges i) and ii), our concept includes both automated network creation, and networks based on thresholds interactively defined by the user. Three different types of networks are used in our approach, data, aggregation, and comparison networks. All networks contain the same nodes, brain regions specified in the input data. A *data network* is simply a network modeled using a single correlation matrix to create the edges. An *aggregation network* provides a population view — we create networks that represent the median and the average pairwise correlation values. A *comparison network* is modeled based on differences and similarities between two individuals, including aggregation matrices.

Threshold Guidance. In general a constant threshold value will not be sufficient for the decision of which correlations are significant, as this might vary across different experiments, individuals, or even time points for one individual. Useful generic models that best support a specific task or question at hand are however not known, and thus our system guides the user in the decision for a correlation value interval of interest. In order to support the user in selecting a threshold, the distribution of correlation values is shown as a heat map. The user can select a correlation value interval of interest using a slider element on which the above information is displayed. Standard characteristics such as connectivity, number of edges and density are calculated for a number of user-selectable threshold values and can be used guide selection of which correlation threshold might be suitable to model the network.

Network Comparison. For correlation values within the interval an edge is then modelled in the network, see Figure 1 top right. In a basic implementation for the comparison of two individual networks, we create a difference network with an edge modelled if the difference of correlations between two nodes is between user-defined threshold values. By using this simple model, the dissimilarities between networks are emphasized. As an alternative, when using the circular layout, we include information on both similar and dissimilar correlation values. A high value in either network with a small correlation difference to the other network leads to the creation of an edge in the comparison network, whereby the visual representation is altered to show the different characteristics, as shown in Fig. 3. With this model, both common patterns and outlier correlations in both networks are shown, however, the resulting network is also more dense and thus can be more difficult to interpret.

Graph Analysis. Analysis methods can be classified into three major categories, the analysis might be based on the raw data, taking into account all correlation values, might use the weighted graph modeled from the data, for example after some user-defined correlation value threshold is taken into account, or at the most abstract level, only the graph's topology might be used. In particular for the graph-based variants a large number of measures exist for analyzing the characteristics. These can be global values, for example the characteristic path length, or local values, such as the node strength. As we have a labeled network with annotations for the different nodes and their brain regions, we assume that purely topological

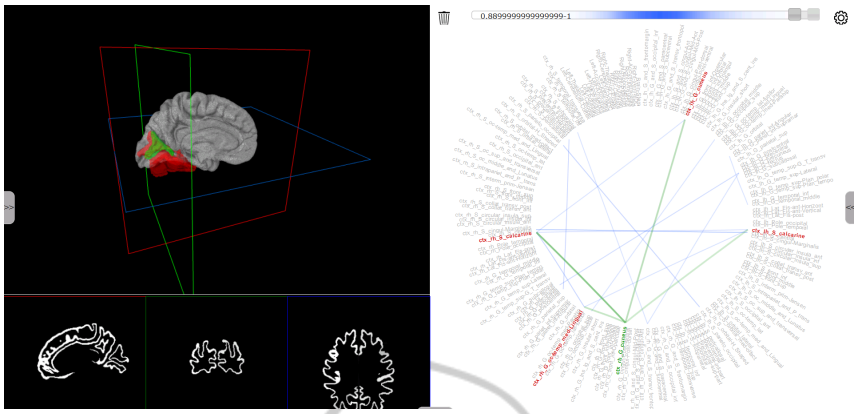

Figure 1: Overview of the visualization interface: Two representations are shown simultaneously, a 3D volume rendering and a 2D visualization of the activity correlation, here a network visualization derived from a single correlation matrix. Sliders can be used to define the range of correlation values that is modeled into the network. The subnetwork consisting of a selected node (green) and its neighbors (red) is highlighted in the same color as the corresponding region in the 3D rendering, and the axes in 3D view are positioned on the selected region.

measures, in particular when they express some value that is aggregated over the whole graph, will not always adequately reflect the brain network characteristics. However, even though networks with similar topological properties may not be similar in terms of neural activity, we still calculate these values as an indicator to separate largely different networks.

Network properties that are calculated and considered useful for the analysis include the clustering coefficient, the characteristic path length, the node degree (weighted, unweighted, and distribution), the number of isolated nodes, and centrality measures.

In addition, we take into account the anatomical and functional annotations to calculate several values for comparison of networks. We calculate an *outlier fingerprint*, based on the partition of the brain into nine brain lobes derived from (Destrieux et al., 2010). For each network we emphasize the amount to which correlations per lobe differ significantly from the whole network set. To this end, we first identify the connections with a correlation that differs more than the standard deviation from the median. For each node, we sum up the number of such connections, and identify the nodes for which that value again differs more than the standard deviation from the respective median number. As the nodes can be mapped to brain lobes, we can aggregate the node values for each lobe and thus create a fingerprint of length 9 that represents the distribution of outlier nodes. The level of opacity of a block in the fingerprint indicates the outlier level, i.e. the stronger the color, the stronger the outlier characteristics regarding our measure. This fingerprint then can be used to identify similar networks, see Figure 4 right.

3.2 Visualization Components and Interaction

Visualization Components. The main visualization components for our approach are the 3D brain rendering view and an abstract correlation data view, which can be either a graph-based network view or a matrix view, see Figures 1 and 2. Adding a network visualization directly into the volume rendering can make it difficult for the user to clearly perceive the network structures. We conjecture that a side-by-side visualization of network or matrix view and brain anatomy will give the user a good overview and at the same time allows for an intuitive interactive exploration of activity data. The assumption is based on the idea that the 3D brain rendering allows intuitive orientation regarding the anatomical position and functional annotation of the network nodes, while the network can clearly depict the connection topology and will thus help to detect patterns better than with the 3D view alone. Hence our concept is based on such a combination of a 3D brain rendering and a 2D graph or matrix visualization, and we link the views to enable the user to switch between views during interactive exploration without a large cognitive effort.

In addition, our application features several interactive elements. These include pop-out panels for the selection of networks and view details. Three small subviews for the 3D rendering allow slice-based browsing through the images, see Figure 1, bottom left.

As part of our concept the precalculated network properties for the currently selected network, or the differences of these properties in comparison mode, can be shown in a pop-out dashboard at the bottom of

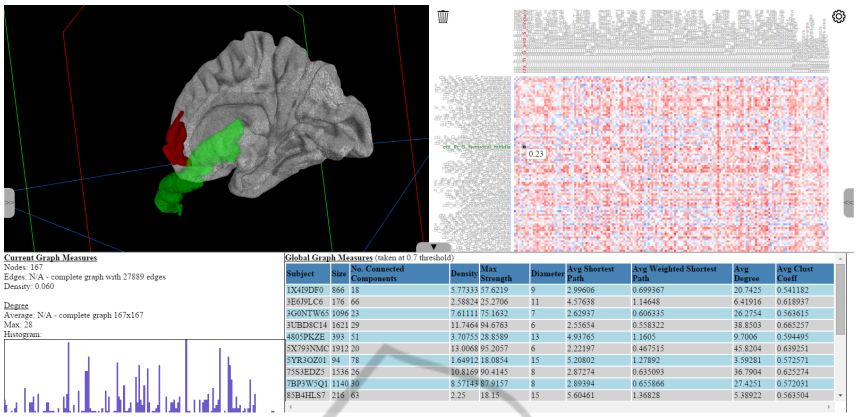

Figure 2: Matrix view of the correlation data. The user can select correlations which then are highlighted both in the matrix and the volume visualization. Red and blue color represent stronger correlation in one of the matrices under comparison. Network statistics for a selected correlation threshold values are shown.

the screen. These values help to characterize a single network, and can also be used for network comparison and classification.

We show a graphical representation of the outlier fingerprint next to each network's name in the network list to enable the user to efficiently select most relevant networks for analysis and comparison, see Figure 4 right. Each brain lobe that contains outlier nodes is depicted by a character that is colored according to the number of outlier nodes. Blue color represents nodes with a significant number of outlier nodes higher than the median, yellow represents smaller numbers, and the intensity is varied depending on the number.

Interaction and Navigation. In the exploratory workflow, a user can freely select networks for visualization and comparison. A correlation value interval can be chosen by using the slider element located on top of the network view, allowing the user to define the range of the values used to model the current network. Whenever the user adjusts the slider setting, the corresponding network is displayed in the network view. To support the user in choosing a useful threshold, the distribution of correlation values is mapped onto the slider by means of a color shading. In comparison mode, two shadings show the different distributions in the networks on the slider, see Fig. 3.

All views are coordinated and linked by a global selection mechanism. In the 2D and 3D views, users can select regions, either represented as a node in the 2D view, or as a rendered region in the 3D view. Selecting elements in the visualization facilitates focus on substructures of the network, e.g. the neighborhood of a node in the network, or the subnetwork corresponding to a brain region. Selection triggers a highlighting by a change in colors for the selected region and its neighbors in the current correlation network in the 2D and 3D views.

The visual cues to highlight elements during the interactive exploration process are kept consistent over all views. The selected node together with its local neighborhood are emphasized in the network view by a change in the color, see Figure 1, and the corresponding brain regions are colored in the same way. All colors are user-adjustable.

The volume rendering allows the user to freely navigate within the 3D visualization that shows the brain's anatomy, rotating and zooming to the region of interest (ROI). The volume axes in the 3D view are automatically positioned to indicate the selected focus region, thereby also updating the slice views to show the current selection. By interacting with the slice subviews, the user can move the volume axes and scroll through all individual slices. An ROI atlas can be mapped onto the 3D rendering that allows links back from selected brain regions to the network visualization.

By changing the setting in the pop-out panels, the user can select different networks for visualization and comparison, and also toggle the visibility of the volume rendering of white matter and pial for each hemisphere depending on the user's requirements. Both the network and the matrix view support a comparison mode that allows visualization differences between selected networks. A color coding scheme is used to show differences and similarities, see Fig. 3 for the network view. For the comparison network described in Section 3.1, the edges with a difference value within the threshold are drawn in red and blue, where the color is determined by which network has the higher correlation value. Strong correlations occurring in both networks are drawn in yel-

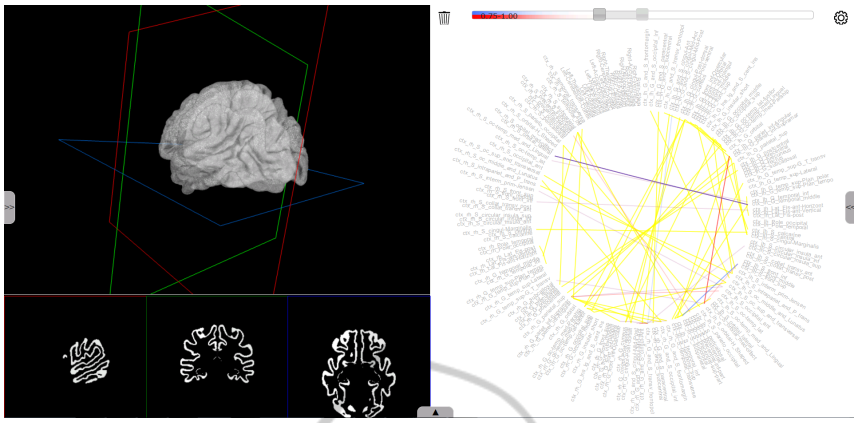

Figure 3: Network comparison combining similarities and dissimilarities for two networks. Differences above the user-defined threshold value are shown in blue and red, common patterns in yellow.

Figure 4: Using the outlier fingerprint to analyze correlation data. The fingerprint shows significant differences and similarity both of a network to aggregated networks and between several pairs of individual networks, e.g. the networks labeled 3E6J9LC6 and SVP271T6 (selected for visual comparison) are quite similar regarding the outliers, whereas SVP271T6 and Q7C341EB differ largely.

low. This helps the user to distinguish between networks that are similar besides a few differences and networks that vary a large amount. The opacity of the graphical edge representation depends on the difference values, such that more prominent patterns are emphasized. This way, differences and their amplitude are highlighted in the 2D view, allowing refined filtering or selection of ROIs.

Network Layout. CereVA uses a circular layout for graph visualization as the default layout, as it is established in biomedical network visualization, including recent iterations of brain network visualization tools (Margulies et al., 2013). The view allows relatively compact visualizations with a static aspect ratio, facilitating the side-by-side presentation. In order to minimize the effort to switch between 2D and 3D view, we use a fixed node order that reflects the anatomical location — clockwise from the top it shows left hemisphere, right hemisphere, then central regions. The membership and vicinity of network nodes with respect to the brain regions are shown in the 3D view. For an improved visualization of the connection patterns, we apply edge bundling, where the tension dynamically adjusts for the number of visible edges, to visually aggregate edges with a similar route. While the single edge representations still exist in the visualization, the bundling allows better identification of global connectivity patterns by joining similar edge sections to bundles, while also reducing visual clutter.

We assume that for an in-depth visual analysis of more complex patterns, different layout methods might prove more valuable, and are therefore investigating the use of other methods for filtered subnetworks. As such layouts might be subject to constraints, constraint-based methods of the WebCoLa (Webcola, 2014) library might be best suited to provide flexible layouts including data-driven constraints, e.g. to emphasize a spatial clustering of the brain regions in the network layout.

3.3 Implementation

Our implementation allows the user to visualize resting state networks in the context of the brain's anatomy, and to compare networks using a node-link representation. In addition, the raw correlation data can be visualized and compared in a matrix view. The comparison can be done visually in both the node-link and the matrix view, while data- and network-based indicators highlight network similarities and differences, facilitating analysis tasks A and B.

We created CereVA as a web-based solution, as

it can be easily made available and updated, without the need to download and install an application. As a web-based solution, we expect it to have advantages when collaborative work on a data set is required, and when interactive analysis of larger data sets can be supported by cloud-based computing.

Our implementation uses several libraries for the different parts of our interface. For the rendering of 3D visualizations in the browser we employed WebGL (WebGL, 2013). WebGL enables the browser direct access the Graphics Processung Unit (GPU), resulting in more seamless interaction and performance compared to non-GPU implementations. The XTK library (XTK, 2014), a wrapper for WebGL, is used as it is specifically designed to support rendering of 3D medical image data. For the graph and matrix visualization and layout we used the implementation provided by D3(D3, 2014), a well-established library for web-based graph drawing.

4 DISCUSSION

To derive meaningful information from network visualizations, the networks need to be modeled in an intuitive way that facilitates knowledge discovery. Our preliminary implementation allows the user to select an interval for the correlation values that is used to filter a subnetwork of the data set. While we think that it is useful to allow the user such a filtering in an interactive fashion to focus on ROIs, the search for a reasonable threshold should be guided by an automated analysis. We use a constant threshold to start with, and give the user visual hints based on network characteristics to support their search.

Network comparison is an active area of research, and there is no obvious optimal visualization of brain activity networks. While our solution presents the difference and similarities in a single cumulative graph-based view, separate views, for example individual graphs representing specific characteristics (small multiple graphs), might be useful to quickly detect patterns and to identify outliers. We aim to investigate further whether calculations such as weighted maximum common subgraphs help to better identify common patterns. The reason for this suggestion is that we could see that for several pairs of threshold-filtered networks, the dominant differences consisted only of one or two additional edges. Our network analysis so far does not make use of the fact that we have labeled graphs, i.e. we have some specific brain location associated with each node of the network. As the combination of this information may prove useful, we will include it in the analysis in future steps.

Aggregation, including of subnetworks, may reduce the complexity and emphasize patterns in the poplation. However we have not seen enough evidence so far of which network characteristics could be subject to aggregation. We aim to answer this question in ongoing discussions with collaborating neuroscientists. This might also help to further support analysis task C, in particular when clustering and classification methods will be included, as this task is so far mainly supported by giving the user information on network and correlation characteristics. Finally larger neighborhoods or subnetwork patterns than the distance one neighborhood might be of interest for highlighting or semi-automated selection.

5 OUTLOOK

In this paper, we presented CereVA, a preliminary concept for the visual analysis of brain activity correlation data. CereVA is implemented as a web service that provides an interactive visual interface for data exploration. Our approach currently supports a basic correlation matrix format as input, and we plan to provide import and export of data and visualizations in standard formats, e.g as provided by the large brain research projects. Further, we aim to integrate additional knowledge that is available for example in such public databases or publications.

In order to extend our solution towards a visual analysis approach, we will embed additional information for analysis and visualization. This will include an analysis of time series data, as we believe that an analysis will provide further insight into the variation of correlations for a single subject, and thus allow experts to derive better characterizations of similarities and differences across the population. Visualizations and interactions based on a decomposition of the network, e.g. using modularity clustering or functional aggregation, will be considered for addition to the system. While the linked complementary 2D and 3D views demonstrated its capabilities to provide a 3D anatomical reference for the visualization of activity networks, adding information from structural MRI and diffusion tensor imaging might greatly improve the analysis of individual brain activity, e.g. after brain damage.

To assess the usefulness of our system beyond the feedback from domain experts during the development, and to make decisions on the further implementation and features, we will perform a formal evalution with domain experts. This paper presented our findings from the use of resting-state MRI networks, however our system is not limited to this data type and

we will explore extension of our system for use with different types of networks.

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