

Visual analysis of integrated resting state functional brain connectivity and anatomy

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Abstract

Resting state functional magnetic resonance imaging (rs-fMRI) is an important modality in the study of the functional architecture of the human brain. The correlation between the resting state fMRI activity traces of different brain regions indicates to what extent they are functionally connected. rs-fMRI data typically consists of a matrix of correlations, also denoted as functional correlations, between regions in the brain. Visualization is required for a good understanding of the data. Several well-known representations have been used to visualize this type of data, including multi-dimensional scaling, spring embedding, scatter plots and network visualization. None of these methods provide the ability to show the functional correlation in relation to the anatomical distance and position of the regions, while preserving the ability to quickly identify outliers in the data. In this paper, a visual analysis application is presented that overcomes this limitation by combining the strengths of the two-dimensional representations with three dimensional network and iso-surfacing visualizations. We show how the application facilitates rs-fMRI connectivity research by means of a case study evaluation.

Categories and Subject Descriptors (according to ACM CCS): Information Visualization [I.3.3]: brain mapping, interactive, scatter plot, network visualization, functional brain connectivity—

1. Introduction

Recent developments in medical imaging techniques have accelerated research in brain mapping and brain functional connectivity. A number of studies have investigated the relationship between brain activity and functional connectivity. Methods used include resting state functional magnetic resonance imaging (rs-fMRI) connectivity of healthy persons in resting state [SSC*05] as well as diffusion spectrum or tensor imaging (DSI/DTI) to identify structural connections in the human brain.

Resting state fMRI is based on the observation that low-frequency ($0.01\text{Hz} - 0.1\text{Hz}$) signal fluctuations in grey matter regions are perceivable in a resting brain. These signals seem to relate to spontaneous neuronal activity. Correlations between resting state signals from different parts of the brain indicate the functional connectivity between those regions [BYHH95]. Research by Hagmann et al. revealed a strong relationship between structural and functional connectivity [HCG*08]. More recently, Salvador et

al. [SSC*05] studied the organization of the human brain in a resting state by investigating pairwise functional connections between ninety anatomical regions of interest (ROIs). Salvador and his group revealed that the amount of connectivity between regions can be predicted by the anatomical distance between the respective regions, generally satisfying an inverse square law. Pairs of anatomical regions that significantly deviate from this relation were identified as being regions that are anatomically symmetric (interhemispheric) or local (intra-hemispheric, neighboring). Comparing the functional brain architecture of healthy persons with that of a patient affected by brain injury revealed a significant difference in the interhemispheric connectivity [SSC*05]. The output of this type of study usually are the individual matrices containing the correlation between each pair of anatomical regions for each subject. In our case this set of matrices is supplemented with an average connectivity matrix representing the connectivity characteristics of the whole subject group.

The existing analysis pipeline is primarily hypothesis-driven, and consists of compute-intensive offline analysis of the correlation data. Up to now, our collaborators have not been making use of visual analysis capabilities, only seldom using non-interactive visual representations of the correlation matrix.

In this paper we present a system which uses coupled views in order to facilitate scientists' understanding of functional connectivity data. The contributions of this work can be summarized as follows:

- We present a visual analysis approach for studying connectivity in resting-state functional MRI data that couples information and scientific visualization views.
- Our method improves on current work by coupling views providing 3-D structural context with views that focus on representing connectivity without spatial context.
- Our method also gives visual feedback on the *degree* of connectivity between functional regions. Most existing techniques cater only for binary connectivity.
- By means of a case study evaluation, we demonstrate how our technique improves on the existing pipeline for rs-fMRI connectivity analysis.

The rest of this paper is structured as follows; in section 2 related work is examined, followed by our proposed solution presented in section 3. Section 4 briefly summarizes the used software packages. The evaluation of the software can be found in section 5, it includes expert user feedback, case study propositions and general examples. Finally, the conclusion and future work are addressed in section 6.

2. Related work

In this section we discuss visualization techniques that are used specifically for functional connectivity, broadly divided into techniques that either do or do not explicitly represent the spatial layout of the data. We also briefly discuss relevant techniques that are used for network visualization in general.

This type of connectivity data is typically defined, for a network with N nodes, as an $N \times N$ matrix, where each cell (i, j) in the matrix contains the correlation between the regions denoted by i and j . In essence, the correlation matrix defines a network where the nodes represent the regions and links represent functional connectivity. The regions are mostly defined by anatomical templates, such as the Talairach atlas [TT88] and the standard brain templates from the Montreal Neurological Institute [ECM92] (also known as the AAL template).

Non-spatial visualization techniques that have been used to study rs-fMRI connectivity data include multi-dimensional scaling, spring embedding, matrix bitmaps and scatterplots. These methods are generally used to identify structural clusters in the data, but do not represent its spatial layout. Multi-dimensional scaling results in a spatial configuration that emphasizes functional connectivity: regions that

are similar in terms of function (highly correlated), will be plotted in the same neighborhood in space. MDS has been used by Salvador et al. to visualize the output of a cluster analysis on the partial correlation matrix [SSC*05]. In their study on the maturing of the brain, Fair et al. use 2-D spring embedding to visualize the brain network. This technique seems to be especially useful when investigating change over time [FCP*09], but has also been used by Hagmann et al. to visualize structural patterns in the correlation matrix [HCG*08]. A natural way of visualizing the output of rs-fMRI connectivity research is by representing it as a matrix bitmap (or pixmap). This is a pixel-based representation that results in a matrix of size $N \times N$ for a network of N items, where each cell (i, j) is color coded according to the connection strength between region i and j [FCD*08, BEW95]. Ordering the matrix enhances the ability to detect patterns of relations. A typical ordering that has been used in rs-fMRI connectivity research is based on anatomical hierarchy [HCG*08].

The relation between anatomical distance, as extracted from an anatomical template, and functional distance can be visualized using a scatterplot [SSC*05]. For the dataset used in this paper, this is illustrated in figure 5.

When representation of the spatial layout of the data is required, the most common visualization is a spatially embedded node-link diagram. In this network visualization method, the regions and connections between them are rendered as a network in three dimensions, where each node, representing a ROI, is rendered at the center of mass of the corresponding region. Connections between the ROIs are visualized as lines between the nodes, and the link strength can be encoded by line thickness or color. A two-dimensional pseudo-anatomical variation has been used by Fair et al. [FCP*09], Dosenbach et al. [DFM*07] and Hagmann et al. [HCG*08]. Visualizations in three dimensions in a correct anatomical context have been used by Worsley et al. [WCLE05], and to a lesser degree by Bezgin et al. and Cao and Worsley [BRSK09, CW99].

As can be seen in [WCLE05] combining the contours of the regions with the links in one view quickly starts cluttering the view. Ghoniem et al. argue that when graphs are bigger than twenty vertices, the matrix-based visualization outperforms node-link representations on most tasks [GFC05]. Another way to deal with the cluttering problem is to use the node-link visualization in an interactive fashion, where the user is able to threshold the edges based on their strength. There are tools available for the analysis and visualization of fMRI correlation data, such as the BrainMiner visualization tool [MWZ*00], CoCoMac Paxinos 3-D Viewer [BRSK09], and the commercial software BrainVoyager QX [GEF06], focusing mostly on the basic 3-D representation of connections. Network visualizations are also used in the research domains of communication networks, social networks and biological networks [BEW95, PWS08, HFM07].

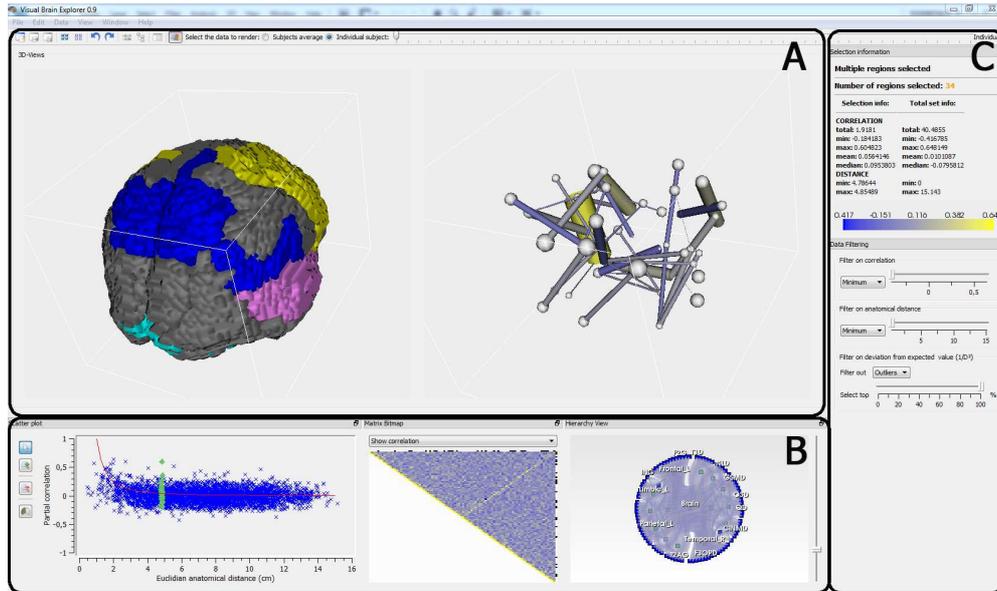


Figure 1: The application’s main window with the three main components. (A) - The Anatomical Views component. Contains the Anatomical Region View (left) and Anatomical Network View (right). (B) - The Abstract Views component. From left to right the Scatterplot View, Matrix Bitmap and Hierarchical Edge Bundling View. (C) - The Filtering and Selection View with the Selection Info View (top) and Filter View (bottom).

We present a visual analysis application that incorporates several of the aforementioned techniques, combining them in various linked views of the same data. The idea of querying in a query friendly view and providing insight in a (3-D) visualization view is proven to be useful in [KPM*08]. Using this approach, disadvantages of one view can be compensated for by using the other views. Our solution improves on the state of the art in the following ways: In contrast to the systems in [MWZ*00, BRSK09, GEF06], our tool interactively couples views for quick outlier and pattern detection with 3-D spatial representations as well as techniques for interactive selection and filtering. In addition, we introduce the application of hierarchical edge bundling [Hol06] to visualize hierarchy and adjacency relations in the brain.

3. Method

The methods that are currently used for studying resting-state functional connectivity MRI data work well in studying basic questions concerning the data, but they do not cope well when both the anatomical information and functional connectivity data are part of the research question. In this section, we present our visual analysis approach that couples the anatomical information and the connectivity data (consisting of data from 53 subjects) by combining existing techniques from information visualization and scientific visualization to improve on the existing pipeline for rs-fMRI connectivity analysis. In the rest of this section we describe

our method, starting by giving a general overview of the system and then following with the details of the system’s components.

3.1. Application Overview

We implemented our method as a software tool that loads the anatomical data (from an AAL template) and functional connectivity data from a file and displays this data in several different linked views. A selection in any of the views is reflected in the other views, where possible. The views are sub-windows in the application’s main window (see figure 1) and can be categorized into three main components: the anatomical (figure 1A), the abstract (figure 1B) and the filtering and selection views (figure 1C).

3.2. Anatomical Views (figure 1A)

The Anatomical Regions and Anatomical Network views use a 3-D window to render their information in anatomical context. The views are linked: Mouse interaction in one view has its effect on both views. The anatomical data is loaded from an AAL brain template with 90 anatomical regions.

Anatomical Regions Using the AAL brain template, iso surfaces are extracted for each of the 90 anatomical regions. A default color map is used to distinguish different regions. The default color map also visualizes brain lobes by encoding the lobe regions in a similar color. The Anatomical

Regions View offers two main modes of interaction: region mode and link mode.

The *region mode* is activated when a single region is selected (as opposed to a selection of links, in which always two or more regions are selected). In this mode, the Anatomical Region View will render this region in its own color, and all other regions according to a colormap that is based on either correlation or deviation from $\frac{1}{D^2}$. Additionally, the opacity of the region surfaces is based on this number, emphasizing highly correlated or highly unexpected linked regions. This mode gives the analyst the ability to quickly see the connection properties for a single region.

The *link mode* is activated when multiple regions are selected (one link or more selected). So, if a selection is made in any of the other views, this mode is automatically enabled. In this case the Anatomical Regions View highlights all anatomical regions that are part of the selection in their default color. Furthermore, this mode has two options. Either the non-selected regions can be completely removed from the view, or they can be rendered in dark gray in order to provide context.

The main role of this view is to visualize regions that are selected (either in the view itself or in other views, see section 3.4) in their anatomical context (spatial location and size).

Anatomical Network In the Anatomical Network view each selected region is represented as a node with its diameter being based upon the total correlation strength of all the links this region participates in. The links are represented as tubes with their diameter being based upon the (absolute) correlation strength of the link it represents.

3.3. Abstract Views (figure 1B)

This component consists of three 2-D views that focus on the connectivity information outside of its anatomical context.

Scatterplot Having the Euclidean anatomical distance on the x -axis and the correlation strength on the y -axis, the scatterplot shows the relation between distance and correlation. A curve is plotted in the scatterplot showing the rule of thumb ($\frac{1}{D^2}$). The general spread of the points is expected to be around this curve. Points far away from the curve, may be considered outliers. The main purpose of this view is spotting and selecting outliers in the data.

Matrix Bitmap The matrix bitmap is a direct visualization of the correlation matrix, although the rows and columns are re-ordered. The left half of the columns (and top half of the rows) reflect regions of the left hemisphere, the right (and bottom) half reflects the right hemisphere. This way, the horizontal and vertical center lines are mirroring left and right symmetrical regions. The minor (secondary) diagonal defines the line of full symmetry. See figure 2 for a visual explanation.

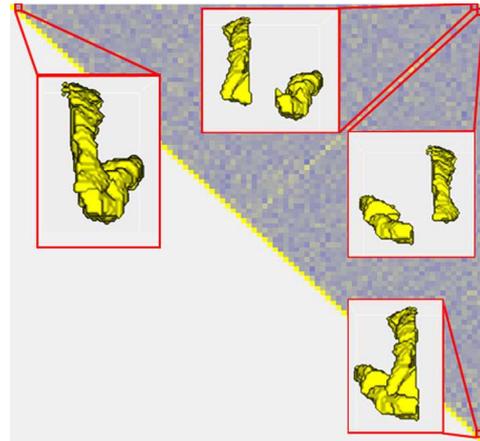


Figure 2: The matrix bitmap with several links highlighted. The highlighted link in the left top is the symmetrical equivalent of the highlighted link in the right bottom. The same holds for the pair of highlighted links in the right top of the bitmap. Additionally, the link in the left top is the half-symmetrical equivalent of the link in the right top (on the same row). The same applies to the two links in the right top and right bottom of the matrix (in the same column).

Each pixel in the bitmap represents a link and the color encodes some statistic for that link. Three statistics are available for each link, resulting in three different matrix bitmaps.

The first matrix bitmap directly visualizes the correlation matrix of the subject, giving each pixel a color value directly based upon the correlation of that link. The second one subtracts the average correlation matrix from the correlation matrix of the current subject, giving each pixel a color based upon the correlation of the link minus the average correlation for that link using a perceptually linear colormap. The third matrix bitmap subtracts the matrix containing the rule of thumb values from the correlation matrix of the current subject, effectively showing for each link the difference with the expected value for that link, thus emphasizing links that deviate significantly from the expected value.

The selected links in the bitmap are currently displayed by placing a black dot in the top and left edge of the bitmap, its place corresponding to the column and row the selected link is in. This way, when all selected links are in one area of the brain the user will quickly notice this as all the black dots are close together.

Hierarchical Edge Bundles This view visualizes hierarchy of the brain, based on the Brodmann regions, in a circular layout. The root of the hierarchy is the whole brain, represented by a node in the center of the circle. The next level in the hierarchy is the distinction between the left and right brain half (with nodes left and right from the root node). The next level are the seven lobes in the human brain for each

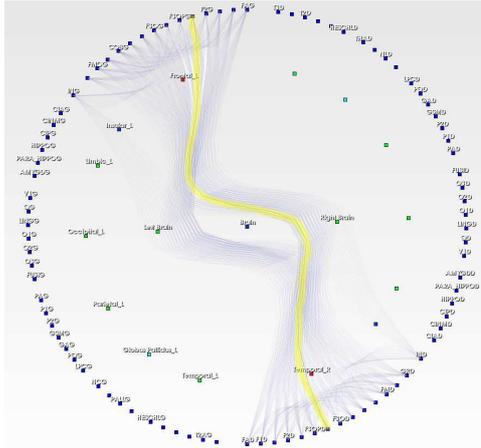


Figure 3: Hierarchical Edge Bundles view with multiple links selected. Edges loosely follow the brain's hierarchy. For printing purposes, the image has been post-processed not to show all links, and to let the selected links stand out more.

brain half and finally, the lowest level in the hierarchy are the 45 regions for each brain half.

Each link is represented as an (elastic) edge between two region nodes. The edge is attracted by the nodes from higher hierarchy levels by the bundling strength which can be varied by the user. Increasing the bundling strength results in all edges going through their anatomical parents in the hierarchy, bundling similar links together as long as they take the same route through the brain hierarchy. Decreasing this value results in smooth edges which pass loosely by their anatomical parents. The main purpose of the hierarchical edge bundles view is to show the course of a link from one region through the hierarchy of the brain to the other region. See also figure 3.

3.4. Filtering and Selection (figure 1C)

The last component consists of two views. The info view shows textual, statistical information of the current selection, the filter view enables the user to occlude data from the other views.

Info view The info view (top view in the component) shows information on the current selection. It shows general and statistical information such as the name and ID of a single link, or number of selected links otherwise, distance, correlation, mean, and median for the selected link(s) as well as the total set.

The main purpose of this view is to enable the user to quickly gain insight in the current selection values, and how those relate to the total dataset.

Filter view The filter view enables the user to filter on a min, max or range of correlation or distance. Another option is to filter on a confidence interval around the curve $\frac{1}{D^2}$. In case of the range and confidence interval filters outliers as well as inliers can be filtered. Filtered links and regions will no longer appear in the views.

The main purpose of this view is to occlude values which are not interesting for the data analyst, this way also preventing occlusion of the important values.

4. Implementation

The cross-platform application is implemented in C++, using Qt4, Qt Designer, Qwt, VTK and finally Matlab for loading the connectivity matrices.

All time consuming tasks are performed once, on startup of the tool. This includes generating iso-surfaces of all regions in the brain template image and building the iso-surfaces (nodes and links) for the network representation. Once loaded the complete application is real-time, without any optimization as is.

Creating the fully connected network involves generating 90 spheres and 4005 tubes, which requires under ten seconds on a system having an Intel 2 Core Duo T7300 (2Ghz), NVIDIA GeForce 8600M GT, and running on Windows 7 64-bit Professional. To prevent blocking the user interface, this task is performed in a separate thread and the user is updated on the progress. The total amount of memory used ranges from 170 to about 250 Megabytes.

5. Evaluation

We evaluated the proposed system following the guidelines and terminology set forth for case study research [Yin09]. The main study question was defined as: *How can the proposed visualization tool assist neuroscientists in their research on resting state fMRI connectivity?* We defined the case in this question as being the use of our software by the third and fourth authors of this paper, respectively LF and JM, both published neuroscientists and experts in rs-fMRI connectivity.

For the purpose of this evaluation, two meetings were held with the users. We first conducted an informal interview during which users could give general feedback on the system prototype. Two weeks later we conducted a focused review, during which we used the tool to analyse a real-world multi-subject dataset together with the domain scientists, collecting and structuring their feedback according to the case study propositions that we had formulated before the session. Together the propositions and the accompanying structured feedback function to answer the main study question.

In the following subsections, we first illustrate the general

use of the visualization tool with four examples, after which we discuss user feedback structured according to the case study propositions.

5.1. General examples

The dataset used in the following examples consists of the 90×90 correlation matrices of 53 subjects, as well as the average correlation matrix over all subjects.

Symmetric interhemispheric connections show an unusually high correlation Several long distance connections are correlated unusually strongly and deviate significantly from the expected relation ($\frac{1}{D^2}$). Using the presented tool, just one action is required to see which connections these outliers represent. The user makes a selection in the scatter plot using the mouse (see figure 4 (a)) and the Network View immediately updates the network representation, now only showing those regions that correspond to the selected points in the scatter plot (see figure 4 (b)). At the same time, the Regions View is updated and renders a three dimensional, anatomically correct representation of the selected regions (see figure 4(c)).

Another way to easily spot these outliers is to look at the correlation bitmap matrix. These connections are visible as pixels at the second diagonal (from the right top to the center of the triangular matrix, see section 3.3) and indeed pop out by their bright color. Clicking on any of these pixels will render the corresponding connections in the Network and Regions View. Taking a look at the 'deviation from expected' bitmap confirms that the most prominent outliers indeed are the symmetric interhemispheric connections.

Finally, the same observation could have been made by using the Filter View. By adjusting the sliders, the user is able create a filter that accepts only the connections that deviate significantly from the expected relation ($\frac{1}{D^2}$).

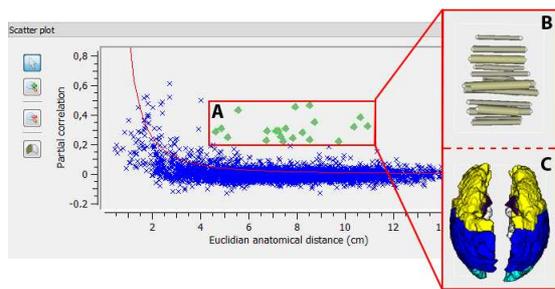


Figure 4: Identifying outliers. Identifying the outliers is just a matter of selecting them in the scatter plot (A) and the corresponding connections (B) and regions (C) are immediately rendered in the 3-D views.

Local intra-hemispheric connections show an unusually high correlation. In a similar way, the user can identify the

links in the low distance region of the scatter plot. Selecting these regions (distance between 1.5cm and 3cm, correlation between 0.2 and 0.6) either in the Scatterplot View or using the sliders in the Filter View identifies the points as connections between regions that are in proximity to each other. If the user has defined a color map for the regions based on the hierarchical structure of the brain (regions in the same lobe get similar color), the regions view will identify the selected regions as being either in the same lobe (correlation between 0.2 and 0.35) or symmetrical (correlation between 0.35 and 0.6).

Other highly correlated regions. Depending on the research, the unusually strong connections between symmetric regions may or may not be interesting. The 'compensate for symmetry' mode enables users to treat symmetric regions as being equal (see section 3). Enabling this option has a significant effect on the scatterplot view. Points that correspond to symmetrical connections are now disabled, see figure 5(b). This puts emphasis on highly correlated regions that are not symmetric and can be used to verify the observation made by Salvador et al., that non-symmetric regions in different hemispheres are infrequent.

Differences in the population. One additional feature that our method offers is the ability to see whether the relations also hold for individual subjects. For instance, using the subject-slider in the top of the application's main window, we were able to observe that the selected connections in figure 5(b) are not consistently highly correlated throughout the set of individual subjects.

5.2. Case study propositions and user feedback

The scatterplot allows the rapid localization of interesting correlations (outliers). This proposition was confirmed, although the possibility of using absolute correlation would make it more useful. This will be implemented in future versions of the software.

The matrix bitmap allows the rapid detection of interesting correlations (high, deviating from expectation or from average, etc.) and visual patterns of correlations. Patterns could point in the direction of whole groups being correlated. This proposition was confirmed, with the users adding that high correlation in fact pops out. It was noted that the ordering of the elements is very important.

The hierarchical edge bundles are better than the dendrogram for showing connectivity through grouping, as they are able to represent connections between parcels in different hemispheres through the hierarchy in-between. Dendrogram can be double-sided, but packing is inefficient. Both users claimed that due to this technique being new in the context of this application, they would need to use it more extensively before being able to comment. They agreed speculatively that it could be useful and commented that the specific hierarchy chosen becomes important and further that the color

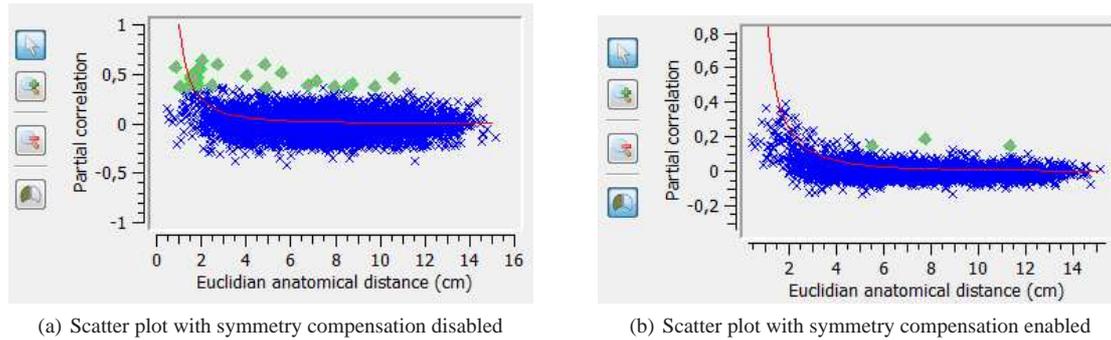


Figure 5: The Scatterplot View with the symmetric intra-hemispheric connections visible (5(a)) and hidden (5(b)). The latter view immediately reveals an unusually strong connection at $D = 4.8$ for this subject. Selecting this region shows the connection in anatomical context (representing the connection between *Frontal_Inf_Oper_R* and *Temporal_Pole_Mid_R*).

map should be adapted so that high correlations should be more visible, especially so due to the visual complexity of this representation.

The 3-D spatial embedding of functional correlation allows the study of these connections in their anatomical context & Being able to query in the anatomical view (click on region, see all connected regions) aids in the understanding of brain architecture. This was considered useful especially in the comparison of cases to controls, where research is able to focus on specific regions of the brain, based on prior knowledge of the pathology under study. For example in Alzheimer's Disease patients, it is expected that the hippocampus plays a role, so researchers can use spatial querying to rapidly see how other regions are connected. Also, an initial selection in 2-D views, based on obvious high correlations, can be further specified in the spatial view in order to determine the total connectivity of a region and hence localize communication hubs.

Visual filtering and zooming alleviates clutter problems in the 3-D spatial view and scatterplot & Linked interaction leads to the conceptually different views strengthening each other. Users agreed with both these propositions, even claiming that the linked interaction was an essential element of the tool.

The tool is useful during the pre-processing of data, in order to detect interesting aspects (outliers) for further analysis using the traditional pipeline. Although the users thought that the tool might be useful during the exploration phase, they commented that current research focuses on local and global efficiency of the neural architecture, in which none of the connections can be discarded. In this case, the tool is less useful in its role as data filtering method. However, in the future data will be acquired on a much larger number of connections, in which case the tool could be more useful in determining which parts to focus on.

The tool is useful for checking the quality of the data, i.e.

whether it satisfies expectations & The tool could be useful for rapidly finding subjects that deviate from the whole collection. One of the users explained that in a previous study there had been some errors during data acquisition resulting in zero correlation between a specific region and all others, and that it had taken a while before this error was finally discovered. Such an error would have shown up as an obvious black line in the correlation pixmap and hence the error would have been detected at an early stage. Also being able to scroll through all the subjects in the study, visually inspecting a subset of the connections, could be helpful in rapidly locating outlier datasets and other errors in the data acquisition. Users claimed that with this tool they would more readily do visual checks of their data in the future in order to help ensure its quality.

Detecting 'outlier' links with a specific region without actually selecting all the links is easy using the link view. In the link view, comparing the diameter of the node to the diameter of the tube indicates the relation between this link compared to all other links this region participates in. When the diameter of the node (ROI) is small compared to the diameter of the tube (link) the link is an outlier in the set of links the region participates in.

Generally, both users were very enthusiastic about possibilities the tool offered for future research. An important point for future improvement was the addition of visual encodings of group statistics over connections, so that for example mean and standard deviation could be visualized for the whole group.

Based on this case study and its analysis, we conclude that the proposed visual analysis tool can facilitate research on rs-fMRI connectivity by offering new ways of looking at study data that enable the rapid localisation and anatomical contextualization of interesting characteristics, whether they be the result of acquisition errors or genuinely interesting phenomena. However, to fully answer the main case study question, all the propositions need to be taken into account.

As we are planning to release the tool as open source, we expect to analyze a wider range of user feedback in the future.

6. Conclusions and Future Work

In this paper we have presented a tool that strongly couples a number of well-known visualization techniques in order to enable the visual analysis of data acquired in rs-fMRI connectivity research. An analyst is able, using the tool, to quickly identify correlated brain regions, visualize the relation to their corresponding distances in the anatomical space and spot connections that deviate from the general relation.

Currently, the proposed tool uses a rough approximation for the anatomical distance, but even with this approximation it is possible to replicate many observations made in a study typical for rs-fMRI connectivity research, by Salvador et al. [SSC*05]. A distance measure based on the center of mass of the regions, or even a shortest surface-to-surface distance, may improve the reliability.

Several improvements and additions will be reviewed, such as visualizing change over time to visualize differences between different subjects. Another addition that will be evaluated is combining rs-fMRI connectivity data with data that is acquired from research on the structural connectivity of the brain (DSI/DTI studies). This could give insight in the relation between functional connectivity measured by brain activity and structural connectivity.

In addition, we will collect case study data of the users to perform more formal case studies and quantitatively compare this to results found with other visualization methods. When it appears that multiple users perform the same task multiple times, the case studies will be extended with task performance measurements on those specific tasks. Finally, new visual representations for connectivity exploration, (especially to improve on the visualization of *continuous connectivity*) will be studied.

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