Published in final edited form as:
Proc IEEE Int Symp Biomed Imaging. 2014 May ; 2014: 325–328. doi:10.1109/ISBI.2014.6867874.

CONNECTOMICS SIGNATURE FOR CHARACTERIZATON OF MILD COGNITIVE IMPAIRMENT AND SCHIZOPHRENIA

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Abstract

Human connectomes constructed via neuroimaging data offer a comprehensive description of the macro-scale structural connectivity within the brain. Thus quantitative assessment of connectome-scale structural and functional connectivities will not only fundamentally advance our understanding of normal brain organization and function, but also have significant importance to systematically and comprehensively characterize many devastating brain conditions. In recognition of the importance of connectome and connectomics, in this paper, we develop and evaluate a novel computational framework to construct structural connectomes from diffusion tensor imaging (DTI) data and assess connectome-scale functional connectivity alterations in mild cognitive impairment (MCI) and schizophrenia (SZ) from concurrent resting state fMRI (R-fMRI) data, in comparison with their healthy controls. By applying effective feature selection approaches, we discovered informative and robust functional connectomics signatures that can distinctively characterize and successfully differentiate the two brain conditions of MCI and SZ from their healthy controls (classification accuracies are 96% and 100%, respectively). Our results suggest that connectomics signatures could be a general, powerful methodology for characterization and classification of many brain conditions in the future.

Index Terms

Connectome; network-based signature

1. INTRODUCTION

Genomic technologies such as genome-scale gene expression analyses and their derived genomics signatures are transforming medicine in many facets including disease prevention, differential diagnosis, disease staging, disease sub-type identification, personalized treatment, follow-up and prognosis. In parallel, in the neuroscience field, quantitative mapping of human brain connectomes [1] aims to construct a comprehensive description of the macro-scale structural connectivity within the human brain via neuroimaging data. Considering the brain function is realized via large-scale structural and functional connectivities [2], mapping connectomes will fundamentally advance our understanding of brain structure and function. In particular, a variety of neurological or psychiatric conditions such as Alzheimer's disease and Schizophrenia exhibit widespread alterations in brain

connectivities. Essentially, quantitative mapping of brain connectomes in healthy and disease populations and extraction of informative and robust connectomics signatures have significant importance to systematically and comprehensively understand, characterize, diagnose and treat those many devastating brain diseases. Simply, what connectomics is to brain connectivity in neuroscience resembles what genomics is to genetics.

Recently, we created and validated a novel data-driven strategy that discovered 358 consistent and corresponding Regions of Interests (ROIs) in large-scale dataset [3] in which each identified ROI was optimized to possess maximal group-wise consistency of diffusion tensor imaging (DTI)-derived fiber shape patterns. The neuroscience basis is that each brain's cytoarchitectonic area has a unique set of extrinsic inputs and outputs, called the "connectional fingerprint" [2], which largely determine the functions that each brain area performs. This close relationship between structural connection pattern and brain function has been confirmed and replicated in our recent works [3]. Therefore, these 358 ROIs possess intrinsically-established structural and functional correspondences (universal), while their locations and sizes are determined in each individual's space (individualized).

Given DTI data, we can predict and transform the 358 ROIs to a new subject [3] which provide natural structural substrates for the construction of functional connectomes. Based on the R-fMRI BOLD signals extracted from these ROIs, we assessed the large-scale functional connectivities in two brain conditions including mild cognitive impairment (MCI), which is a precursor of Alzheimer's disease, and schizophrenia (SZ), and compared them with those in healthy controls. Fig. 1 shows the main steps of our proposed work in this paper. In particular, after two-stages feature selection including t-test and correlation-based feature selection (CFS) [4], we identified a set of connectomics signatures for characterization of these two brain conditions. Our experiment showed very promising result, which is nearly 100% accuracy of the disease/control classification. We also explored the functional roles of the involved ROIs in the connectomics signatures via meta-analysis, and it turned out that these most descriptive ROIs are very relevant to MCI and SZ based on current neuroscience knowledge.

2. METHODS

2.1. Data acquisition

Twenty-eight participants (10 MCI patients and 18 sociodemographically matched normal controls (NC)) were recruited and scanned in a 3.0 Tesla scanner (GE Signa EXCITE, GE Healthcare). For R-fMRI, echo time (TE) = 32 ms, repetition time (TR) = 2000 ms, FOV = 25.6 cm^2, matrix = 64 × 64 × 34, 3.8 mm^3. For DTI, 25 direction diffusion-weighted whole-brain volumes were acquired axially parallel to the AC-PC line using diffusion weighting values, b = 0 and 1000 s/mm^2, flip angle = 90°, TR = 17 s and TE = 78 ms. The imaging matrix was 256 × 256 with a rectangular FOV of 256 × 256 mm^2 and 72 slices with a slice thickness of 2.0 mm.

DTI and R-fMRI datasets of 10 SZ and 10 controls were downloaded from the publicly available NA-MIC dataset. The DTI used 51 directions with b=900 and 8 baseline scans with b=0. Other scan parameters include: TR 17000 ms, TE 78 ms, FOV 24 cm, 144×144

encoding steps, 1.7 mm slice thickness. The R-fMRI was 10 minutes long, and contained 200 repetitions of a high resolution EPI scan (96×96 in plane, 3mm thickness, TR-3000 ms, TE=30, 39 slices, ASSETT). Two cases of SZ subjects were discarded due to low quality of DTI data, thus 8 SZ cases were used in this paper.

2.2. ROIs initialization and functional connectome construction

In this paper, we constructed functional connectomes based on these structure-derived DICCCOL ROIs which has three advantages: 1) the cortical regions centered on these ROIs provide intrinsically-established correspondences across subjects, avoiding being trapped in seeking unclear cortical boundaries. 2) The nonlinearity of cortical properties is adequately addressed by a global optimization and search procedure, in which group-wise consistency is used as an effective constraint. 3) Individual structural variability is effectively addressed by directly determining the locations and sizes of ROIs in each individual's space, thus avoiding image registration errors.

As illustrated in Fig. 2, in comparison with current methods for brain connectivity mapping that rely on the Brodmann map [1], our functional connectomes based on structure-derived ROIs will offer much finer granularity, much better functional homogeneity, much more accurate functional localization, and automatically-established cross-subjects correspondences [3].

2.3. Feature selection

In the previous steps in Section 2.2, we achieved a 358*358 functional connectivity matrix, or functional connectome, for each subject. Because of the symmetry, we actually have 63903 unique functional connectivity features that is over-complete compared to the number of subjects we have. Our strategy is that through a two-stage supervised feature selection procedure, only the features with the most distinctive and descriptive characteristics for differentiating brain conditions (e.g., MCI or SZ here) will be retained. These preserved features (functional connectivities) will served as connectomics signatures for the subsequent disease/control classification and their neuroscience interpretation.

The goal of feature selection is to recognize and remove the irrelevant and redundant information as much as possible. [4] Since we only have two classes (MCI/SZ patients and their normal controls), we adopted a simple t-test ($p<0.05$) in the first stage to remove the connectivities without significant differences between two disease/control classes. After this step, there are 658 and 757 connectivities passed through the significance test for MCI and SZ, respectively.

Since the t-test evaluates the features separately, the first-stage feature selection did not consider the relevance among the features and thus it cannot capture the redundancy of these preserved features. To tackle this problem, we employed the Correlation-based Feature Selection (CFS) [4] algorithm as the second-stage feature selection. The core idea of CFS is that through a heuristic process it evaluates the merit of a subset of features by considering the goodness of individual features for predicting the class along with the degree of intercorrelation among them. Unlike the first stage t-test, CFS will compute feature-class and feature-feature correlations simultaneously.

Given a feature subset S with k features, the $Merit_s$ is defined as followed:

$$\mathrm{Merit}_s = \frac{k\overline{\mathrm{Corre}(c,f)}}{\sqrt{k+(k-1)\overline{\mathrm{Corre}(f,f)}}} \quad (1)$$

Where $\overline{\mathrm{Corre}(c,f)}$ and $\overline{\mathrm{Corre}(f,f)}$ are the mean feature-class correlation and the average feature-feature intercorrelation respectively. Fig. 3 shows an example of the feature selection processes. It is evident that each stage of the feature selection processes significantly reduced the number of features and only retain the most significant and distinctive features.

3. RESULTS

3.1. Connectomics signature of MCI and SZ

After two-stage feature selection, we finally achieved 43 and 18 dimensional functional connectivities for MCI (Fig. 4a) and SZ (Fig. 4d), respectively. These two sets of features will be treated and used as the connectomics signatures for the following disease/control classifications.

Based on visual examination of MCI's connectomics signatures, we can clearly observe two distinctive patterns that are highlighted by blue and yellow circles in Fig. 4a. The MCI patients exhibited significantly higher and lower functional connectivity than normal controls in the first and second patterns, respectively (Fig. 4b and Fig. 4c). Specifically, these two patterns were extracted via the K-means clustering (k=2), and 28 and 15 functional connectivities were assigned to these two signature classes accordingly. This result suggests that MCI exhibit a complex pattern of both increased and decreased functional connectivities, in comparison to healthy controls. Also, the result demonstrates that there are widespread connectivity alterations in the whole brain of MCI subjects, which is consistent with current neuroscience studies in the literature. For SZ, all 18 functional connectivities show higher correlations than normal controls, suggesting that the SZ brains are significantly more active than their controls in resting state. A detailed analysis of above connectomics signatures will be given in Section 3.3.

3.2. Disease/control classification using connectomics signature

To verify whether the above selected features, or functional connectomics signatures, have the capability to differentiating MCI/SZ patients from their normal controls, we put them into the widely used SVM classifier [5] to conduct a disease/control classification. Because the numbers of subjects of both MCI and SZ patients are not very large, in this paper, we adopted the widely used leave-one-out strategy and the average accuracies of classification are 96% and 100% for MCI and SZ, respectively. That is, most of the subjects can be correctly classified. It is evident that these two sets of functional connectivities have captured the intrinsic difference between MCI/SZ patients and their normal controls and hence we named them as "Functional Connectomics Signatures".

3.3. Neuroscience interpretation

To interpret the brain science meanings of the connectomics signatures of MCI, Fig. 5a and 5b visualize the hyper- and hypo- connectivities in MCI on a cerebral cortical surface which are corresponding to that in Fig. 4b and 4c, respectively. It is evident that both increased and decreased functional connectivities in MCI are widespread across the whole cortex, suggesting that MCI is a brain condition with large-scale functional connection alteration. Quantitatively, the percentages of increased/decreased connectivities connected to the left frontal, left parietal, left temporal, left occipital, right frontal, right parietal, right temporal, and right occipital lobes are 19%/18%, 11%/18%, 6%/7%, 2%/3%, 34%/36%, 4%/7%, 19%/4%, and 4%/7%, respectively. It can be clearly seen that the frontal lobes exhibit substantially more functional connectivity alterations than other lobes, e.g., the occipital lobes.

Furthermore, we annotated the 358 ROIs into 46 functional networks via meta-analysis in the BrainMap (http://brainmap.org/) database. We visualized the top 22 functional networks that are most frequently involved in the connectomics signatures of the two brain conditions studied in this paper in Figs. 5d and 5e. The names and colors of these 22 networks are shown in the bottom of Fig. 5. Quantitatively, the top five functional networks that exhibit increased functional connectivity are attention, execution, working memory, audition and explicit memory networks, and their percentages among all altered connections are 15%, 9%, 9%, 6%, 6%, respectively. At the same time, the top five networks that exhibit decreased connectivities are emotion, attention, fear, speech language, and working memory networks, and their percentages among all decreased connections are 21%, 18%, 11%, 11%, 11%, respectively. Apparently, the attention network is the most affected one in terms of altered connectivities. In addition, it is interesting that the working memory networks are among the top five networks with both decreased and increased connectivities. Our results are in the line of literature reports [6], but systematically and comprehensively elucidated the widespread functional connectivity alterations via functional connectomics signatures.

It is interesting that all the functional connectivites belonging to the signature of SZ are increased activities for the patients which suggests that SZ is a brain disorder of hyper-connectivity. Fig. 5c visualizes the increased connectomics signatures in the context of 22 annotated functional networks. Quantitatively, the percentages of increased connectivities connected to the left frontal, left parietal, left temporal, left occipital, right frontal, right parietal, right temporal, and right occipital lobes are 15%, 9%, 9%, 6%, 15%, 6%, 27%, and 12%, respectively. It is apparent that the frontal and temporal lobes exhibit substantially more functional connection alterations in SZ, while the occipital and parietal lobes have much less functional connection alterations. In addition, we obtained the top five brain networks of increased connectivities including attention, speech language, emotion, execution, cognition, and their altered connection percentages among all decreased connections are 12%, 9%, 9%, 6%, 6%, respectively. Again, the attention network is the most affected one in terms of increased connectivities. Similar to that in MCI subject, the attention network exhibits the most altered functional connectivities in SZ.

4. CONLUSION

Our novel computational framework identified informative functional connectomics signatures that can distinctively characterize and successfully classify MCI and SZ from their healthy controls. In comparison with other methods for brain connectivity mapping that rely on the Brodmann map [1], our functional connectomes offered much finer granularity, much better functional homogeneity, much more accurate functional localization, and automatically-established cross-subjects correspondence. These large-scale functional connectivities provided novel insights into the organization of human brain function. In comparison with current understanding of brain connectivity within small sub-networks in the literature, the proposed method for representing human brain connectomes can systematically and comprehensively characterize large-scale connectivities over the whole brain. In particular, it is able to reveal how connectome-scale connectivities are altered with different patterns in brain conditions such as MCI and SZ. We envision that the novel methodologies presented in this paper can be potentially applied to other brain disorders with altered functional connectivities, and can be possibly used to derive informative biomarkers for disease diagnosis, staging, follow-up, and prognosis in the future.

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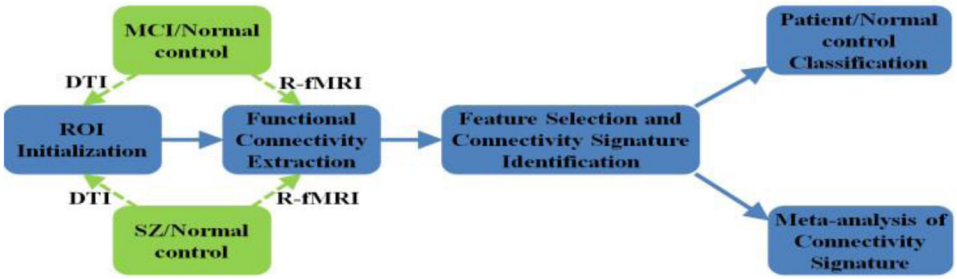

Fig. 1.
The flowchart of our proposed framework.

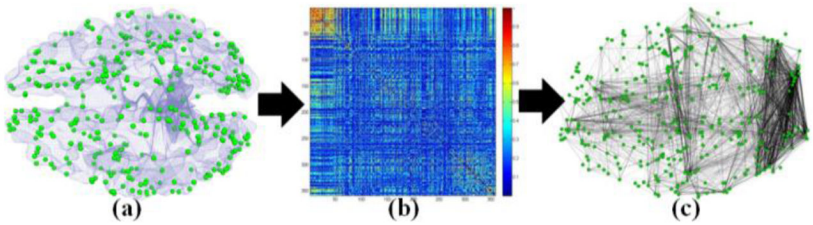

Fig. 2.

The illustration of functional connectome. (a) The initialized 358 structure-derived ROIs (green bubbles). (b) Functional connectivity matrix based on the ROIs in (a). (c) Functional connectome is projected onto a 2D plane.

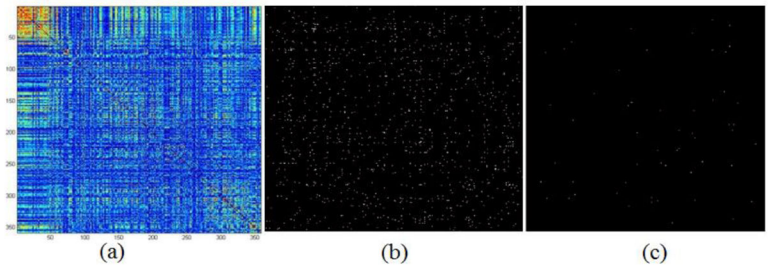

Fig. 3.

The illustration of feature selection. (b), (c) are binary images and the white dots represent the preserved features. (a) The original features. (b) Features after the first-stage selection (t-test). (c) Features after the second-stage selection (CFS).

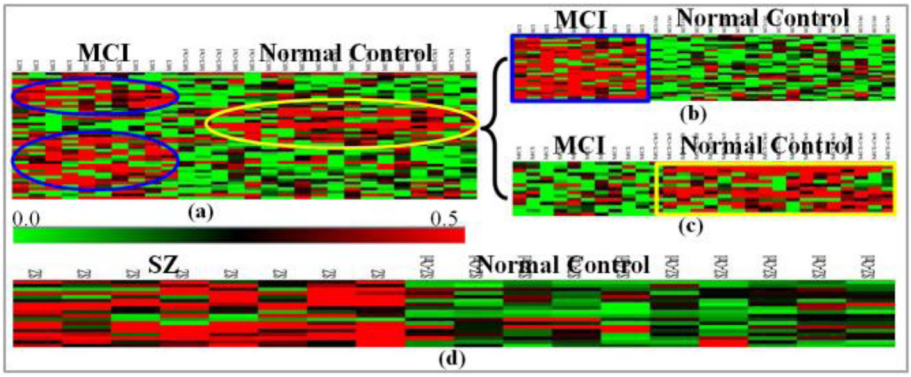

Fig. 4.

The functional connectomics signatures of MCI and SZ. (a) MCI's connectomics signatures after CFS. Two distinctive patterns are highlighted by blue and yellow circles and extracted via K-means clustering (k=2) as shown in (b) and (c). (d) SZ's connectomics signatures after CFS. All the functional connectivities in the signatures show higher correlations for SZ patients than normal controls.

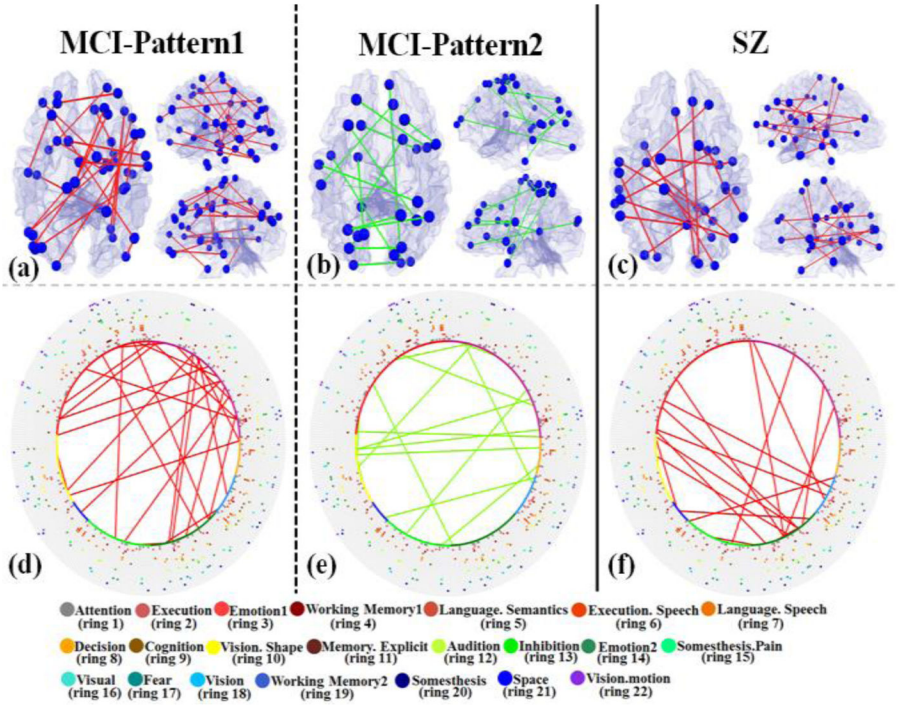

Fig. 5.

The neuroscience interpretation of the functional connectomics signatures. (a) and (b) Visualization of the hyper- and hypo- connectivities in MCI on a cerebral cortical surface which are corresponding to that in Fig. 4b and 4c. (c) Visualization of functional signatures of SZ on a cerebral cortical surface. All the functional connectivities in the signature show higher correlation for SZ patients than normal controls. (d)–(f) Result interpretation of connectomics signatures of MCI (d–e) and SZ (f). 358 structure-derived ROIs are represented by an inner ring of color-coded nodes, connections (corresponding to those in (a–c) and Figs. 4b–d) are represented by colored edges, and 22 functional networks are represented by 22 outer rings of colored nodes. All of the colored nodes in each ring of 358 nodes stand for a functional network. The names and colors for 22 networks and their corresponding rings are shown in the bottom.