SPECIFIC AIMS

There is a dire need for biomarkers to identify, diagnose, and predict treatment outcome for mental disorders (Insel and Cuthbert, 2009). Whereas neuroimaging capabilities have grown and computational tools for processing these data have become more sophisticated, comparisons across groups of patients and human subjects resort to overly simplistic representations of brain image data, resulting in simplistic biomarkers. The goal of this proposal is to create network analysis tools for multimodal brain image data to find biomarkers of mental disorders. The specific aims to achieve this goal correspond to three phases over the two-year period:

1. *Create software framework for graph-based encoding of multimodal neuroimaging data.* During this phase we will develop an open-source, well-documented software package for constructing and analyzing graph representations of structural, functional, and diffusion tensor magnetic resonance imaging (MRI, fMRI, and DTI) data.

2. *Quantify and compare graphs using "neural signatures."* In the second phase of this project, we will apply graph metrics and network analysis tools to extract a set of network characteristics for each individual. This set will comprise a neural signature for that individual. We will quantify and compare these neural signatures by computing network analysis metrics on them, and validate this approach by classifying data from publicly available sources. In particular, we will use neuroimaging, demographic and behavioral data from the International Neuroimaging Data-sharing Initiative (INDI), which contains datasets from several neurologically disordered populations. Once developed, we will engage the neuroimaging community to test our software on their own datasets during the remainder of the project period.

3. *Evaluate neurosignatures as biomarkers for diagnosis and prediction of treatment outcome*. In the final phase of this proposal, we will apply pattern classification and regression techniques to identify clinically relevant biomarkers and predict course of illness (e.g., remitter/non-remitter) in the neural signatures in our own datasets, with the long-term goal of personalizing treatment using these biomarkers.

We believe this proposal to be significant because it will provide a means of computing comparisons across rich representations of brain image data and will attempt to diagnose and predict successful treatment options for individuals with mental disorders. This proposal is innovative because it will introduce formidable methods from graph theory and social network analysis to clinical brain research. Furthermore, this project will result in a general, open-source computational framework that anybody will be able to use with their own datasets, thus accelerating the rate at which various neurological disorders are diagnosed and treated.

RESEARCH STRATEGY

1 Background and Significance

Diagnosis of mental disorders and prediction of treatment outcome suffers from a dearth of reliable biomarkers [Insel2009]. The importance of identifying biomarkers is reflected by its inclusion in the National Institute of Mental Health's (NIMH) Strategic Objectives, Strategy 1.3: "Currently, very few biomarkers have been identified for mental disorders due in part to their complexity and an incomplete understanding of the neurobiological basis of mental disorders..." and Strategy 2.1: "Broaden the study of biomarkers and biosignatures of disorders to ... indicate illness onset, progression, relapse, remission, and recovery." We attribute the elusiveness of biomarkers to the fact that traditional methods used to analyze brain image data do not adequately reflect their complexity. In keeping with these NIMH strategic objectives, the most significant contributions we intend to make with the proposed research are to develop alternative methods to overcome this complexity and identify biomarkers of mental disorders, determine the range of variation of these biomarkers, and to use them to try and diagnose individuals and predict treatment outcome. In the following sections we: 1) motivate the need for biomarkers of mental illness; 2) expose the need for better image analysis tools for deriving biomarkers; and 3) introduce graph theoretical methods that provide a mathematically rigorous approach to analyze and mine complex networks for biomarkers.

1.1 Biomarkers and mental disorders

The psychiatry literature contends that fundamental variation exists within current psychiatric disease categories at all levels (genetic, neurobiological, phenotypic, response to treatment). A proper understanding of this variation is essential for characterizing etiologies and enhancing treatments for these diseases. This idea is captured in the concept of **personalized medicine**, which has often focused on genetic variation as a potential predictor of treatment outcome. Neuroimaging measures may also provide important indices of patient variation because psychiatric diseases are understood as brain disorders, and brain structure and function reflect both genetic and environmental influences on current behavior.

A range of studies have shown that biomarkers predict prognoses among patients with behavioral disorders, and often more accurately than current behavioral instruments, such as widely used scales and structured interviews. Neuroimaging findings have predicted recovery from depression 8 months later [3], relapse in methamphetamine dependence [23], onset of psychosis in at-risk individuals [12, 30], response to drug treatment for depression [4, 8] and anxiety [21] and for cognitive behavioral therapy (CBT) in schizophrenia [13]. Evoked-response potentials measured in newborns [20] and pre-reading children with familial risk of dyslexia [19] predicted language and reading scores years later. Whereas multiple behavioral tests of reading and language were at chance in predicting reading gains among dyslexic children over the next 2.5 years, fMRI patterns of activation were 92% accurate [10]. We hypothesize that biomarkers and biomarker-based prognosis could be a practical near-term translation of neuroimaging to clinical application.

To demonstrate the potential of biomarkers for prediction of treatment response, Dr. Ghosh analyzed pre-treatment MRI and fMRI data from 30 patients with SAD who later underwent CBT (data collected by Dr. John Gabrieli - MIT, Dr. Mark Pollack - MGH and Dr. Steven Hoffman - BU). SAD is one of the most common psychiatric conditions in the United States. The two gold-standard treatments for SAD are CBT and pharmacotherapy, and are only moderately effective compared to placebo. A large proportion of patients remain symptomatic after an initial intervention, and no reliable predictor of treatment response has been identified. During fMRI, subjects viewed pictures of faces (angry or neutral) or scenes (emotional or neutral) that were matched for valence and arousal to the faces. Preliminary analyses indicated positive correlation between changes on the Liebovitz Social Anxiety Scale (LSAS) and the response to angry faces in regions of the higher-order visual cortex located on the fusiform and the parahippocampal gyri. A cross-validated prediction model yielded a strong correlation (r=0.8) between actual and predicted treatment response using data from these functional activations together with SPM-based VBM analysis of gray matter density in frontal and parietal regions and the pre-treatment LSAS score. Comparatively, the pre-treatment LSAS score alone is a much weaker predictor (r=0.14). These results demonstrate the potential for multimodal neuroimaging to guide clinical decisions that maximize the expected outcome from treatment interventions.

1.2 The need for better analysis tools

Advances in neuroimaging have opened up tremendous stores of rich, multimodal data from which biomarkers may be drawn. Multimodal data include structural, functional, and behavioral data from individual subjects, such as: magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and task-based and resting-state functional MRI (fMRI). These data sets and associated tools for efficient representation, manipulation and analysis will help provide clarification on observed inconsistences across current studies. "... for example, clustering is reportedly increased in the structural networks but decreased in the functional networks of patients with AD... Some of these differences may perhaps be resolved by studies combining network measurements on structural and functional neuroimaging data acquired on the same patients."[2]

Traditional neuroimaging data analysis approaches typically rely on correlational paradigms and group activation maps. More recent work has attempted to characterize connectivity between regions either through structural equation modeling or functional connectivity networks. However, neither of these approaches handle multimodal data effectively. This has led to in-house software packages that aggregate information from structural and functional data in order to perform data maining or prediction. In order to break away from this mold and have comparable results across studies, it is important to have tools that allow users to efficiently integrate and analyze multimodal information. Dr. Ghosh has developed a framework (see http://nipy.org/nipype) that allows optimal analysis workflows using existing software, but there is still a need for a richer framework for data mining and prediction.

1.3 Graph theoretical methods and network analysis metrics

The difficulty with integrating data from multiple modalities is that it is computationally very demanding to analyze, and it is extremely difficult to conceptualize and visualize the relationships between objects in the data. Graph theory, a major area of mathematics concerned with graphs, is *the* field of mathematics to model relations between objects. Graphs are also a natural way to represent a connected network structure such as a brain and to quantify aspects such as similarity, hierarchy and network efficiency.

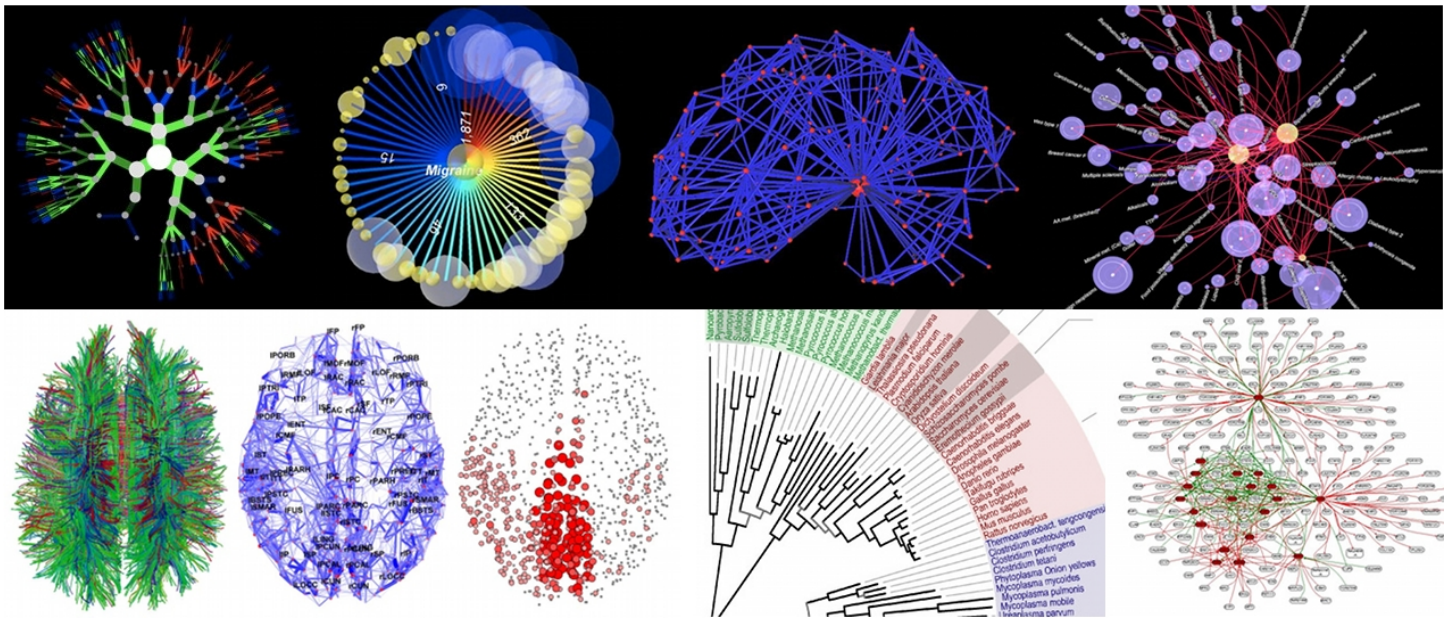


Fig. 1: Examples of graph-based representations of scientific data among hundreds on the www.visualcomplexity.com website (categories on the site include biology, food webs and semantic, social, and knowledge networks). Lower left images of DTI, connectome, and network hubs are from Olaf Sporns (2010, Scholarpedia, 5(2):5584).

Only recently has neuroscience broached the subject of using graphs to characterize properties of functional imaging data [27, 2]. In a recent review paper, Bullmore and Sporns [2] state that "methodological advances allow us to quantify other topological properties of complex systems — such as modularity, hierarchy, centrality and

the distribution of network hubs." While analysis of efficient connectivity of networks (e.g., "small-worldness") have become popular, Bullmore and Sporns point out that "Most graph theoretical network studies to date have used symmetrical measures of statistical association or functional connectivity — such as correlations, coherence and mutual information — to construct undirected graphs. This approach could be generalized to consider asymmetrical measures of causal association or effective connectivity — such as Granger causal or dynamic causal model coefficients — to construct directed graphs. It is also possible to avoid the thresholding step ... by analysing weighted graphs that contain more information than the simpler unweighted and undirected graphs that have been the focus of attention to date." However, no current toolbox, including the one provided by the authors, captures these concepts.

Graphs provide an intuitive representation for each of the multimodal data types (MRI, fMRI, DTI) considered in this proposal. Furthermore, graphs can easily be transformed into adjacency matrices lending themselves to a whole assortment of linear algebra methods. In a recent book, Grady and Polimeni [9] describe discrete calculus on graphs. The combination of discrete calculus, matrix algebra and faster hardware provides extremely powerful computational tools for the analysis of brain structure and function. The ability to perform relatively efficient computations on graphs was not available even a few years back.

2 Innovation

The overall aim of the proposed research is to provide graph-based network analysis tools that help diagnose and predict treatment outcome of mental disorders. This is unique on several fronts.

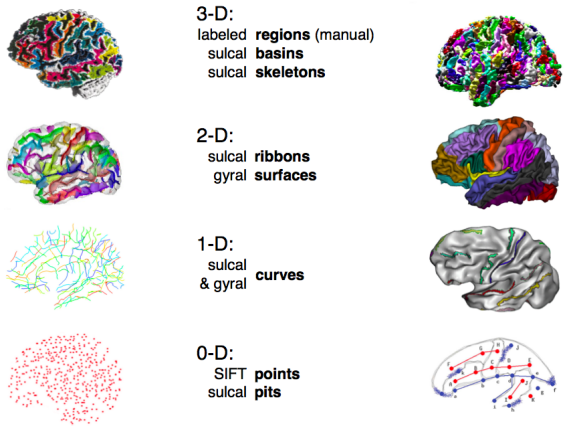
1. **Represent multimodal data in a computationally addressable structure** (i.e., a graph).
2. **Develop new tools in network analysis**. This work will provide the first graph-based brain network analysis software package that combines graph-theoretical representation of multimodal imaging data, discrete calculus and pattern classification approaches.
3. **Move away from group-based studies and focus on individual variability**. Current approaches to comparing brain images across subjects and across modalities rely almost ubiquitously on image registration to establish anatomical correspondence. Although functional ROI-based methods are emerging as an alternative to such registration, these capture very limited task-specific notions of correspondence. Our proposed software will move from macro-anatomy and functional blob-based comparisons towards network-based correspondences across individuals.
4. **Predict treatment outcome and diagnosis** (e.g. graph similarity). This will be the first attempt to diagnose and predict recovery in major depressive disorder (MDD) using DTI, MPRAGE *and* fMRI information. If successful, it will open up the field of personalized medicine for MDD.

3 Approach

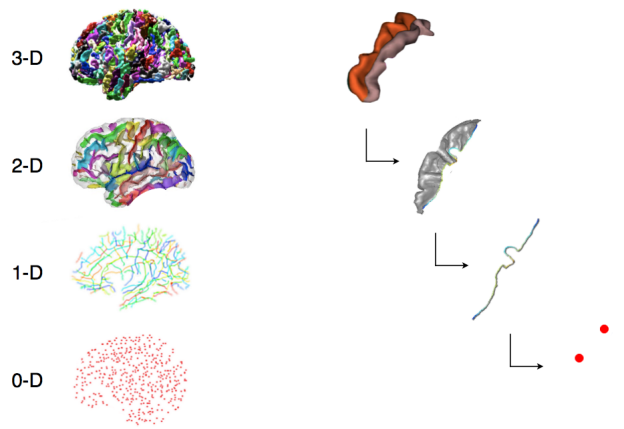
In the field of neuroimaging, most of the focus on graph-based computation has emerged in response to resting-state and other functional connectivity studies [2]. Graph-based representation has the potential to capture important characteristics from other modalities such as diffusion data. However, as stated earlier, a comprehensive toolsuite for graph-based representation and analysis of multimodal imaging data is lacking. The primary aim of this project is to create such a framework in order to capture distinguishing neural characteristics or "signatures" of individuals from their structural and functional data.

3.1 Create software framework for graph-based encoding of multimodal neuroimaging data

The brain, by its nature, lends itself to a graph-based representation. However, the key to a useful graph representation is a prudent choice of features embedded in vertices [31] and the information encoded in the edges. During this first phase we will code several feature extraction algorithms. The goal is to be exhaustive without being redundant, as different combinations of features may encode differential characteristics of neurological disorders.



(a) Example structural features (left lateral views of volumes, surfaces, curves, and points)



(b) Schematic feature hierarchy: 3-D gyrii surround a 2-D sulcal ribbon with 1-D fundus containing 0-D pits

Fig. 2: Examples of automatically extracted features (MRI)

Vertices

We will automatically extract features from brain image data and represent them as vertices. Each vertex can have multiple quantities associated with it. For example, any MRI feature could have an associated average measure of cortical surface curvature, gray matter thickness, etc. We will experiment with the following features to determine how consistently they can be extracted and how robust their correspondence is across brains:

- MRI: Scale Invariant Feature Transform (SIFT) points [18, 17, 28], sulcal pits [11, 16], sulcal fundi [25, 14], sulcal ribbons [5], sulcal folds [7, 6, 5], sulcal basins [24, 15], and manually labeled regions
- fMRI: "blobs" of activity and functional connectivity clusters
- DTI: whole-brain network hubs [26, 29] and clusters of voxels within gray matter that generate collateral tracts

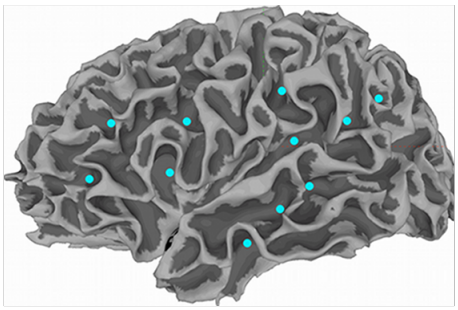
Edges

We will automatically compute relationships among the vertices and represent these relationships as edges in our brain graphs. The vertices and edges will be computed from within the same type of image as well as from different types of images. For example, we will connect MRI sulcal pits with DTI tracts (Figure 3b), connect DTI-based network hubs using functional connectivity, etc. Example relationships that we will compute include:

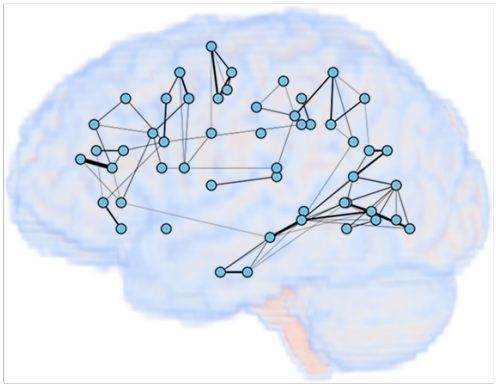
- MRI: physical path connecting two vertices
- fMRI: functional connectivity between vertices
- DTI: structural connections based on tractography

Network architecture based on sulcal features

We have automatically extracted SIFT points, sulcal pits, and sulcal fundi from patients with MDD and from controls, computed structural connections between these features using DTI probabilistic tractography (using FSL's probtractx tool [1]), and have demonstrated that we are able to construct network representations from these connected features using NetworkX. For example, in Figure 3b, the vertices represent sulcal pits [11] and each edge indicates a DTI connection probability greater than 0.01 between two vertices. We are currently evaluating standard social network analysis measures such as those listed in (3.2) to compare graphs from individuals with and without MDD and from remitter vs. non-remitter subjects within the MDD subject pool.



(a) A gray/white matter surface (left lateral view) with (visible) sulcal pits highlighted. These features go by different names (sulcal roots, buried gyrii, annectant gyrii, plis de passage) and may be well conserved structures formed early in development.



(b) DTI connectivity graph computed on the same patient with depression as on the left panel. Vertices represent automatically extracted sulcal pits and each edge indicates a connection probability greater than 0.01 between two vertices.

Fig. 3: Example of a graph-based representation of MRI and DTI features

3.2 Quantify and compare graphs using "neural signatures"

We will use the Python library NetworkX (http://networkx.lanl.gov/) to construct our graphs from the vertices and edges computed above and compute network analysis metrics on these structures. NetworkX provides a set of functions to quantify graphs for comparison and prediction. Among the metrics that we will evaluate which are relevant to brain architectures are the following:

1. *Eccentricity difference:* The minimum (radius) and maximum (diameter) eccentricity is a measure of how close or how far vertices are to each other in a graph. For example, if vertices and edges represent functional regions and their connectivity, then low differences between minimum and maximum eccentricity would mean that the graph is strongly connected.

2. *Clique-set*: A clique is a subgraph containing vertices that connect to each other. For example, if a graph contains edges that represent functional connectivity, then cliques from this graph would represent brain regions that behave like each other. The set of 3-vertex or higher cliques from such graphs can thus represent functionally similar networks.

3. *Centrality of weighted graphs*: Centrality quantifies the extent to which a node or vertex is in the center of things (e.g., highly connected to important nodes). However, weighted graphs are more suited for representing brain features where the edges are often weighted by strength of connectivity or correlation. Centrality in weighted graphs has until recently evaded quantification. Opsahl and colleagues [22] have demonstrated how this can be calculated for social networks.

4. *k-core decomposition set:* This operation defines subgraphs where every vertex has degree of at least k. This measure can be used to study the clustering of graphs and therefore break down whole-brain activation or structures into manageable subgraphs for comparison.

These metrics represent some of the network characteristics of an individual's brain. We will test the discriminability of the different metrics on our data using recursive feature elimination. The most discriminable metrics will be collated into a vector of numbers to form the "neural signature" of macroanatomical structure, function and their connections for each individual, which may be quantified and compared against other individuals. We will determine the variation of these neural signatures by analyzing data from publicly available sources, such as the new International Neuroimaging Data-sharing Initiative (INDI), which contains multimodal datasets from several neurologically disordered populations.

3.3 Explore and quantify stable biomarkers for diagnosis and prediction of treatment outcome

The neural signatures above will then be used as input features for pattern classification (to predict diagnosis and remission) and regression (to predict treatment outcome). We will use the Python library PyMVPA (pymvpa.org) for pattern classification. In addition, we expect our data to be noisy, and will therefore invoke methods from discrete calculus [9] to filter our graphs, penalize outliers, and aid in clustering and analysis.

The tools we will develop to identify biomarkers are intended to be applied to any mental illness, such as Alzheimer's disease, bipolar disorder, schizophrenia – indeed to analyze differences in brain activity between any two populations. However, we have targeted MDD and SAD to guide development and conduct validation of our methods. We will be processing SAD data (as described in (1.1)), and MDD data from two different grants for which our Co-Investigator Ramin Parsey, a leading researcher of depression, is a P.I. (Arno Klein (P.I.) is also a Co-Investigator on the second):

- "Biological Predictors of Response to Antidepressants" (MH074813)
- "Biosignature Discovery for Personalized Treatment of Depression" (1U01MH092250-01)

We will develop our methods on data from the first grant to determine the range of variation of our topological biomarkers, and will validate on some of the data from the second (U01) grant to try and diagnose individuals with MDD and predict treatment outcome based on remitter/nonremitter data. The U01 is a large, multi-site project acquiring multimodal brain imaging data from 400 individuals, specifically designed to make such data available to establish biomarkers for MDD. We will make use of the structural, functional and diffusion tensor 3.0T MRI data acquired from at least 40 of the U01 subjects that will be available within the next year:

- Structural 3D axial MPRAGE images (TE: 3.29 ms, TR: 2200 ms, Flip angle 9°, Field of view: 256x192 mm, Slice thickness: 1 mm, Matrix: 256x256, 192 continuous slices, 7:02 min)
- 4 fMRI tasks (emotional conflict, reward processing, PASL, and resting-state connectivity acquisition): 39 axial slices (3.1mm thick, TR/TE=2000/28msec, FOV=205x205cm, matrix=64x64; Flip angle=90°)
- DTI using echo planar imaging (voxel size: 2x2x2mm, 61 and 25 non-colinear directions; b-value=1000s/mm2)

If successful, this graph computational framework could be used to incorporate data from other neuroimaging modalities, such as electroencephalography, magnetoencephalography, positron emission tomography, angiography, and functional near-infrared spectroscopy. And whereas the focus in the present proposal is on macroscopic neuroimaging data, the framework could easily be applied to microscopic (histological) data, and indeed to non-brain medical imaging data as well.

3.4 Conclusion and timeline

In the beginning of this proposal, we described the dire need for effective biomarkers of mental illness. We then presented formidable new computational tools that can find relationships in complex data – tools that could overcome shortcomings of present methods applied to brain image data. After outlining our methodological innovations, we described our research approach to find biomarkers of, for example, major depressive disorder. Our timeline will be as follows:

Year 1: Develop software to extract features within individuals to build graphs.
Create software to compute biomarkers on the graph-based framework.

Year 2: Determine the biomarkers' range of variation.
Test their validity on clinical data.
Refine, test, and completely document the software for public distribution.

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