SPECIFIC AIMS

Problem: The most important contribution of brain imaging to patient-specific psychiatric medicine is the discovery of "biomarkers" to aid clinicians in diagnosis and prediction of treatment response. Brain morphology measures, for example, have been used as biomarkers to characterize schizophrenia,[1] early- vs. intermediate-onset bipolar disorder, as well as bipolar and unipolar depression.[2-4] However, each of these biomarkers was a coarse descriptor of shape derived from a single imaging technique (modality), anatomical magnetic resonance imaging (aMRI), and was insufficiently discriminative to guide treatments or make predictions of treatment response. Currently, most researchers use each modality independently because there are no established ways of integrating them. Attempts to combine modalities have focused on registering brain images to each other and *assuming* correspondences between aligned voxels or regions defined by a labeled atlas. However, some data are better represented as distributed spatial patterns such as those in functional (fMRI) or diffusion (dMRI) networks. *Features*, whether landmarks, regions, or networks, can help establish correspondences within and across brains, and a biomarker is defined by its ability to use correspondences to distinguish between a clinical and control population. Distinguishing among groups requires that the variation of a suitable measure *within* each group is separable from the variation *between* groups. This can only be accomplished by establishing "normative" data — data that allow accurate characterization of the usual variation within each group. Thus a significant hurdle to discovering better biomarkers for patient-specific psychiatric medicine is the lack of tools to extract, integrate, quantify, and compare biologically and clinically relevant features across modalities, and normative data to compare against.

Current research: To establish what the state-of-the-art is for determining correspondences across brains, we conducted the world's most extensive brain registration evaluation studies.[5,6] This was possible only with the public availability of manually labeled brain image data. These studies guided our research and exposed the limitations of existing labeled data sets and labeling protocols. In response, we created the most consistent anatomical brain labeling protocols and applied them to build the world's largest collection of publicly available manually labeled brain image data sets,[7] which will contain the first set of publicly available test-retest labelings. Our current open source Mindboggle software, which automates anatomical brain labeling and morphometry,[8-11] exploits these labels in many brains rather than relying on an individual atlas. It also emphasizes anatomical feature-based rather than voxel-wise intensity-based correspondences, which we have shown can generate more robust labeling of different anatomies than traditional registration methods.[8] We entered these features into the world's first database that permits queries involving demographics and sophisticated shape analysis measures of anatomical structures.[9,12] This database and the Mindboggle approach enable morphological comparisons between individual brains, but since anatomy alone may not provide sufficient information to identify biomarkers, we propose to extend our current work in anatomy to accomplish three aims: *(1)* automate morphometry in multiple modalities, *(2)* integrate multimodal data so direct comparisons are possible, and *(3)* evaluate the effectiveness of multimodal biomarkers for diagnosing illnesses such as major depressive disorder (MDD).

Aim 1. To facilitate biomarker discovery from brain imaging data, we will extract, quantify and identify biologically and clinically motivated features from different modalities in the same individual, automatically label a brain in a probabilistic manner using these features, and establish a normative data set for each modality.

Example features:

aMRI: surface patches, curves, and points from sulcal folds[11]
fMRI: networks derived from ICA-based and covariance selection procedures[32]
dMRI: tractography bundles, exemplar tracks,[13] and connected brain regions[51-54]

Example labeling methods:

aMRI: semi-supervised label propagation (labeling from partially-labeled data)[67]
fMRI: dictionary learning procedure[50] and network clusters[68] that incorporate spatial constraints[69]
dMRI: tractography-based brain regions (clusters of similarly connected voxels)[54,70]

Aim 2. To enable multimodal analysis, we will integrate modalities via *compartments*, *connections*, and *overlaps*, and enable queries to identify disorder-relevant features in an online shape analysis database.

Compartments: Quantities from one modality are computed within a feature from another modality.
Connections: Multimodal features are related via a connection strength.
Overlaps: Multimodal parcellations are related to each other via overlaps and distances.
Our novel neuroinformatics framework is built on a graph-based database.

Aim 3. To test clinical significance, we will generate and evaluate biomarkers on clinical data.

We will generate multimodal biomarkers from publicly available clinical data, and imaging and treatment data we are collecting from over 400 MDD patients. We will evaluate their effectiveness at diagnostic and prognostic accuracy compared with gold standard psychiatric evaluations.

Our work is a radical departure from the ubiquitous use of atlas-based registration and labeling that has inadequate sensitivity for detecting biomarkers, and is instead aimed at extracting biomarkers specific to an individual. In this renewal we will provide researchers with data and tools to automate multimodal morphometry and labeling as well as use biomarkers derived from these data to diagnose or predict treatment response for individual patients. We show the first results ever using aMRI features to predict treatment response for MDD.

RESEARCH STRATEGY

1 Significance

In this renewal of R01 MH084029-03, we outline plans for building on our current work — shape analysis and labeling of human brain MRI data — with the ultimate goal of creating multimodal biomarkers. This section states the great need for biomarkers of psychiatric disorders, briefly describes how our approach will overcome the problems traditional approaches have had in this search, and the potential impact our approach will have on treatment and diagnosis of psychiatric disorders.

1.1 There is a great need for biomarkers of psychiatric disorders

Great variation exists across brains — in anatomy, physiology, function, connectivity, response to treatment, etc. Unless we account for this variability, we will not be able to characterize etiologies or enhance treatments for mental disorders. This idea is captured in the concept of patient-specific medicine, which has often focused on genetic variation as a potential predictor of treatment response. Neuroimaging-based biomarkers also have the potential to provide important indices of patient variation for use in diagnosis of psychiatric disorders and prediction of treatment response. Some studies have shown that biomarkers can predict prognoses among patients with behavioral disorders, and often more accurately than current behavioral instruments, such as widely used scales and structured interviews. For example, neuroimaging findings have predicted relapse in methamphetamine dependence,[14] onset of psychosis in at-risk individuals,[15,16] recovery from depression eight months later,[17] response to drug treatment for depression[18,19] and anxiety[20] and for cognitive behavioral therapy (CBT) in schizophrenia.[21] Evoked-response potentials measured in newborns[22] and pre-reading children with familial risk of dyslexia[23] 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.[24] We believe that biomarkers and biomarker-based prognosis could be a practical near-term translation of neuroimaging toward clinical application. However, despite the above promising experimental results, there is still a dearth of reliable biomarkers.[25] The importance of identifying biomarkers is reflected by the National Institute of Mental Health's 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..."

1.2 Problems with conventional methods for finding biomarkers

An effective biomarker consists of one or more measures that maximize the separability between groups while minimizing the variance within each group. These measures, however, can only be useful if we are comparing corresponding features across brains. To do this, scientists ubiquitously co-register images to each other, either individually or in groups, commonly with the use of a standard template brain or labeled atlas of the same imaging modality. The goal of such registration is to establish correspondence between brains in order to extract biomarkers. However, registration alone does not guarantee correspondence[26] and templates are often not representative of the group being studied.[27,28] And other factors that affect the quality of registration are often ignored. For example, the P.I. has empirically demonstrated that registration algorithms vary widely in their accuracy [5], that even the best require removal of non-brain matter to perform adequately,[6,29] and conventional registration is less robust to missing regions than feature-based registration methods.[8] These problems limit the accuracy of biomarkers generated from registered data. Moreover, even if an anatomical mapping were achieved between two brains, there is no reason to believe that functional activity, structural connections, or cytoarchitecture would obey the same mapping, so traditional registration alone will not effectively integrate different modalities, and therefore will not lead to effective *multimodal* biomarkers. In summary, current biomarkers generated from co-registered or multimodal data suffer from problems of consistency and accuracy. We propose to overcome the limitations of conventional registration methods to establish feature correspondence across brains by extracting features in an individual (3.1.2), characterizing their shapes (3.1.3), and identifying them based on this characterization (3.1.4). Furthermore, we will do this for each modality and integrate features across modalities (3.2). Establishing correspondence at the level of well-characterized features vs. voxels should be more consistent and accurate, and has a better chance of generating sensitive, consistent, and accurate biomarkers.

1.3 Integrating multimodal imaging data

Extracting corresponding features from different modalities and integrating information across modalities gives us a better chance at overcoming the problems stated above to extracting biomarkers than relying on a single modality. A useful representation for integrating features from multimodal data should make their relationships with one another quantifiable, as well as conceptually and visually accessible. Graph theory is a field of mathematics that models relations among objects, and graphs are a natural way to represent a connected network structure such as a brain, yet only recently has neuroscience begun to use graphs to characterize properties of fMRI data.[30-32] We have given the first completely data-driven probabilistic large-scale description of brain functional signals to learn a detailed model of an individual's full-brain functional connectivity using population data[33] (**Fig.2b**). Some researchers have recently applied graph measures to clinical data, but we are unaware of any work on multimodal graph analysis of psychiatric disorders, perhaps due to the difficulty in establishing correspondences across modalities. We will outline three complementary approaches to doing this (3.2) while employing a rich set of multimodal features (3.1.2).

1.4 Improvements to Mindboggle to find biomarkers

The P.I. is developing the Mindboggle software to automate shape analysis and anatomical labeling of human brain MRI data (3.5). Currently the software is targeted at identifying a single type of brain structure (sulcus; **Fig.1**) extracted from a single imaging modality (T1-weighted MRI), and its output consists of label volumes.

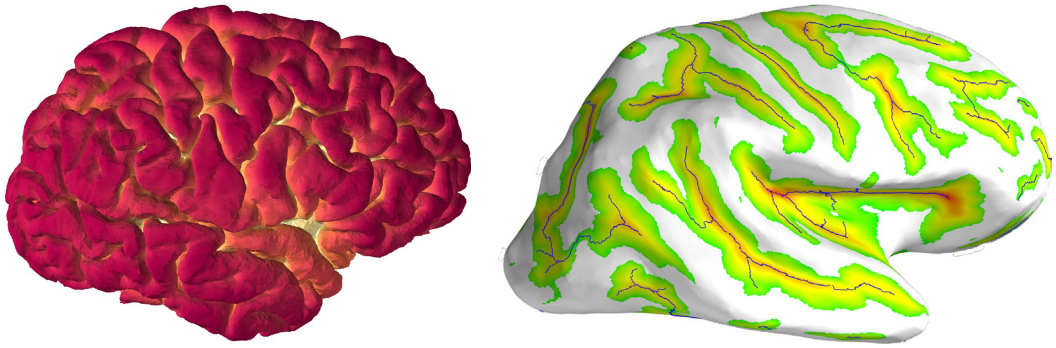

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Fig.1*: Example anatomical features we extract with our current version of Mindboggle. (a) depth map of brain surface, (b) inflated surface with depth-based sulci and fundi (red curves connecting vertices of maximal depth via a minimum spanning tree algorithm)*

As part of the proposed research, we intend to radically enhance Mindboggle's functionality to extract *multiple* features from *multiple* modalities, and perform labeling based solely on these features. The modular architecture will be flexible and extensible enough to accommodate *any* new features in *any* modality and their associated measures. Therefore we believe Mindboggle will provide an excellent infrastructure to integrate and quantify multimodal features and will be an ideal platform to conduct the search for more reliable biomarkers. Other than conventional registration, no method for integrating multimodal information currently exists.

1.5 Example: the challenge of major depressive disorder (MDD)

Although Mindboggle is intended to analyze differences in brain image data between any two populations, and will be applied to data representing several disorders (3.1.1), we will focus development on major depressive disorder (MDD) because of its overwhelming impact on the health of Americans, and because we have access to clinical expertise, resources, and data. Our goal is to generate biomarkers for MDD that exceed the accuracy of current methods without making invalid assumptions about correspondences across brains. This will be used as a test case to establish whether our method for integrating multimodal information is a successful approach for applying to other psychiatric and brain diseases.

MDD is diagnosed by the presence of 5 of 9 symptoms (DSM IV-TR). This means that it is possible to have two subjects who meet criteria for MDD but share only 1 symptom! Additionally, with the ability to have increased or decreased appetite or increased or decreased sleep, etc., there are 1,099 ways to meet criteria for MDD. Yet there is evidence supporting feature-level morphometric characterization of MDD (3.1.2) and we anticipate that biomarkers will help us characterize subpopulations in this heterogeneous disorder. This will aid in targeting physiological and psychotherapeutics. In addition, one of the major impediments to treatment and participation in research studies is the tremendous stigma associated with mental illness in this country and around the world. With a biological signature of the illness, MDD will less likely be seen as a "choice," but rather as a medical condition similar to diabetes or hypertension, thus reducing MDD-associated stigma.

1.6 The potential impact of our work

The accuracy, precision, as well as conceptual simplicity of performing analyses on individuals to extract biomarkers in our approach rather than conventional group-wise analyses that rely on traditional registration methods will take a great step toward patient-specific medicine. The large-scale computations afforded by a graph-based representation and the ease with which one can integrate multimodal data will lead to adoption of these methods well beyond the originally intended applications of Mindboggle. If we are successful in diagnosing and predicting recovery in MDD, as our preliminary results indicate (3.3.2), it will open up the field of patient-specific medicine for this and other disorders.

We have received 24 letters of support (not including from our three consultants) recognizing the significance and innovation of the proposed research and expressing confidence in our strategy from: Drs. Sean Hill (International Neuroinformatics Coordinating Facility), Maryanne Martone (Neuroscience Information Framework), Michael Hawrylycz (Allen Brain Institute), Alan Evans (McGill Univ.), Bruce Fischl (Harvard Medical School), Russell Poldrack (UT Austin), Stephen Smith (Oxford Univ.), Brian Wandell and Michael Greicius (Stanford Univ.), Paul Thompson and David Shattuck (UCLA), James Gee and Brian Avants (Univ. of Pennsylvania), Jean-Francois Mangin and Jean-Baptiste Poline (NeuroSpin, France), Colin Studholme (Univ. of Washington), Joy Hirsch (Columbia Univ.), Matthew Brett (UC Berkeley), Michael Milham (Child Mind Institute), Polina Golland (MIT), Steve Pieper (Isomics, Inc.), Truman Brown (Medical Univ. of South Carolina), Bennett Landman (Vanderbilt Univ.), and Jason Bohland (Boston Univ.).

1.7 Research team

Our team consists of Arno Klein, Satrajit Ghosh, Ramin Parsey, Steven Ellis, Forrest Bao, Yrjö Häme, Eliezer Stavsky, Gael Varoquaux, Eleftherios Garyfallidis, and Neuromorphometrics. **Dr. Klein** (P.I.) is the P.I. on the current R01. He developed the original Mindboggle software (www.mindboggle.info), has conducted the largest evaluations of brain image registration,[5,6] and is spearheading the largest manual brain labeling effort ever undertaken (www.braincolor.org). He will supervise and take part in all aspects of development of the project. **Dr. Ghosh** (MIT subcontract P.I.) has been a close collaborator with the P.I. for years and has considerable skill and experience at software development, brain imaging, image analysis, and in applying statistical learning methods. His current research focus is on using pattern classification approaches for diagnosis and prediction of treatment outcome of neurological disorders (social anxiety disorder, autism). He is also responsible for developing the NiPype software pipeline framework in Python that we are using as Mindboggle's underlying software infrastructure. **Dr. Parsey** (Co-investigator) is a close collaborator of the P.I. and is a leading expert on depression, brain imaging, and imaging-based biomarkers, and will provide clinical expertise to the project with respect to biomarkers of MDD. **Dr. Ellis** (Co-investigator) is a close collaborator of the P.I. and Director of the Statistics and Computing Core of the MIND Division at the New York State Psychiatric Institute and will provide statistical expertise to the project. **Mr. Bao** (Ph.D. student who will be a Postdoctoral Research Scientist on this project) has developed the Python software for extracting anatomical features in Mindboggle as part of the current grant and will develop algorithms for multimodal feature extraction (3.1.2), graph-based analysis (3.2.2), and informatics (3.2.4). **Mr. Häme** (Biomedical Engineering graduate student) has written the Mindboggle tools to match and identify anatomical features as part of the current grant and will extend this work to multimodal data (3.1.4). **Mr. Stavsky** (Neurobiology and Behavior graduate student) is developing the anatomical label propagation algorithms and will extend this work to multiple modalities (3.1.5). **Dr. Varoquaux** (consultant) brings considerable machine learning expertise to the project; he is the project leader of the Python machine learning library scikit-learn (scikit-learn.sourceforge.net) that we will use for feature selection (3.3.1) and biomarker evaluation (3.3.2). We will also use other software he has been developing for fMRI feature extraction (3.1.2). **Mr. Garyfallidis** (consultant) is the developer of the Diffusion Imaging in Python software (dipy.org)[34] and related algorithms for feature extraction and labeling of dMRI data. He will integrate the algorithms for dMRI feature extraction, quantification, identification, and brain labeling components into Mindboggle (3.1.2-3.1.5). **Neuromorphometrics** (consultant, www.neuromorphometrics.com) is a commercial image analysis company that focuses on quantifying structural brain features. They have been providing the manual labels of brain anatomy as a consultant on the current grant. They will be responsible for manual feature identification and manual region labeling for validating feature identification (3.1.4) and automated labeling (3.1.5) components of the project.

2 Innovation

Innovative aspects to this proposal include new normative data for different modalities, new representations of multimodal neuroimaging data, new analysis methods, and a new emphasis on patient-specific medicine.

Aim 1. We will develop new methods of multimodal feature extraction, probabilistic matching, and probabilistic brain labeling (3.1.2-3.1.5). We will quantify the shapes and distributions of these multimodal features and labels in a variety of ways and include all of this information in the world's first multimodal shape analysis database based on an entirely novel graph-based, online neuroinformatics framework (3.2.4). By extracting, identifying, quantifying, and analyzing an individual's data and creating correspondences across individuals in feature space without resorting to currently used group registration to a template space, we will be able to move beyond group-based studies and focus on patient-specific biomarker detection.

We also avoid the convention of using a single (individual or maximum probability labeled) brain atlas, a so-called "standard" brain, which can introduce bias and variability into extracted biomarkers. Our approach promises to deliver a convenient and easy-to-use tool that will liberate researchers from their dependence on particular atlases, and will, by contrast, fully label the anatomy of a brain on the basis of identified features within an individual and manually labeled data as priors in a Bayesian framework (3.1.4, 3.1.5) without relying solely on conventional registration methods. Moreover, we will generate whole-brain labels for each imaging modality through label propagation between anatomical features and clustering for fMRI and dMRI tractography data (3.1.5). This will generate complementary label sets that can be integrated in new ways and probed for novel relationships between modalities. We will also provide confidence bounds for every label (3.1.5). No software package currently assigns confidence in its feature matches or label assignments. Our software will also show differences among label boundaries generated from different modalities (3.2.3).

Aim 2. We have developed a novel framework for integrating multimodal data, by relating data from one modality as compartmentalizing (3.2.1), connecting (3.2.2), or overlapping (3.2.3) data from another modality. Our tools will integrate multimodal data into graph-based representations in a novel graph-based database. This online shape analysis database will enable multimodal queries to mine and identify disorder-relevant features (e.g., thickness in a functional region or connectivity among regions).

Aim 3. We will apply Mindboggle for the first time to clinical data in the world's first attempt to diagnose and predict recovery in MDD using multimodal information. If successful, it will allow brain imaging data to be used for patient-specific medicine for MDD. In addition, this will validate Mindboggle's ability to extract biomarkers and lead to applications of Mindboggle to detect biomarkers for other psychiatric disorders.

3 Approach

This renewal focuses on creating an analysis platform that integrates anatomical, functional, and diffusion magnetic resonance imaging (aMRI, fMRI, dMRI) data to derive measures for diagnosing psychiatric disorders or predicting treatment response.

3.1 Aim 1. *Extract, quantify, and identify features from different modalities, automatically label the brain using these features, and establish a normative label set for each modality.*

In this section, we will describe our multimodal imaging data (3.1.1), and for each individual and each modality the features we extract (3.1.2), the shapes we quantify (3.1.3), how we identify these features (3.1.4), how we label a brain based on these features to construct normative data sets (3.1.5).

3.1.1 Multimodal imaging data

We will use multimodal data to create the labeled normative data, multimodal morphometry database, multimodal version of Mindboggle, and biomarkers. These contributions are intended to be applied to any psychiatric illness, such as Alzheimer's disease, bipolar disorder, schizophrenia – indeed to analyze differences in brain image data between any two populations. We will therefore use a variety of publicly available clinical data: Functional Connectomes 1000 (www.nitrc.org/projects/fcon_1000), ADHD-200 Sample and the International Neuroimaging Datasharing Initiative (fcon_1000.projects.nitrc.org/indi), as well as clinical data that we are acquiring as part of two different grants for which our Co-Investigator Ramin Parsey, a leading researcher of depression, is a P.I.: "Biological Predictors of Response to Antidepressants" (MH074813) and "Biosignature Discovery for Personalized Treatment of Depression" (1U01MH092250-01). Arno Klein (P.I.) is a Co-Investigator on the second, which is a large, multi-site project acquiring multimodal imaging data (including aMRI, fMRI, and dMRI acquired on the same scanner) from 400 individuals, specifically designed to make data available to find biomarkers for MDD. We will develop our methods on data from the first grant to determine the range of variation of our biomarkers in each population, and will validate on independent data from the second to try and diagnose individuals with MDD and predict treatment response.

3.1.2 Extract features from each imaging modality

We refer to any landmark, region, or distributed network in the brain as a *feature*. We are currently applying our own algorithms to extract the following *anatomical features* related to folds in the surface of a brain (**Fig.1**): sulci,[35,36] fundi,[37,38] and pits[39-41] (we export a surface in VTK format (www.vtk.org) from third-party software such as FreeSurfer,[42] Caret,[43] or BrainVISA[44] run on T1-weighted aMRI data.) We will also experiment with Laplace-Beltrami[45] spectral decompositions of the surface into patches.

In addition to the above anatomical features, we propose to extract features from other modalities by having Mindboggle accept as optional input fMRI data and dMRI data. In the case of fMRI data, Mindboggle will run a NiPype software pipeline in Python[46] that we have built to process temporally correlated resting-state spontaneous activity ("functional connectivity," rs-fcMRI) data using best practices such as the temporal CompCor method for regressing out nuisance variables,[47] and will extract fMRI network features using recent ICA-based and covariance selection procedures.[33] The clinical relevance of rs-fcMRI data is a new area of inquiry that is expected to reveal abnormalities in fMRI activity analogous to abnormalities in white matter integrity exposed by diffusion-weighted imaging and tractography, such as in the presence of tumors[48] and affective disorders, including MDD.[49]

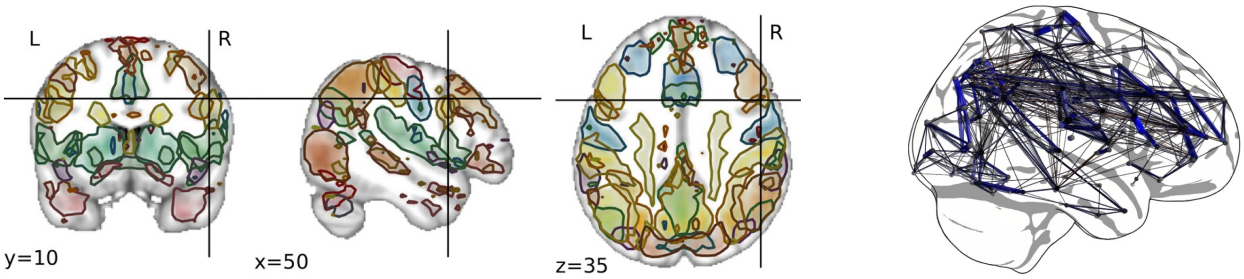

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Fig.2*: Example functional features extracted by our resting state fMRI analysis tools. (a) functional regions,[50] (b) large-scale functional-connectivity graph.[33]*

Given that rs-fcMRI and dMRI tractography data may both be represented as weighted graphs, we can apply many of the same fMRI feature extraction methods to dMRI tractography-based feature extraction. For dMRI features, we will also focus on connected regions of cortex,[51-54] track clusters and exemplar tracks extracted by the DiPy Python package (dipy.org),[34] and will experiment with similarly shaped tracks and clusters of voxels that generate collateral tracks,[52] as well as network hubs.[55,56] Recently our consultant E. Garyfallidis invented a highly efficient segmentation algorithm named QuickBundles[13] which can be used to create robust features and simplifications of complex tractographic data and is currently 500 to 1,000 times faster than other such algorithms (**Fig.3**). For dMRI data, Mindboggle will accept as input deterministic or probabilistic tractography output from programs such as Camino (web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php) and FSL (www.fmrib.ox.ac.uk/fsl).

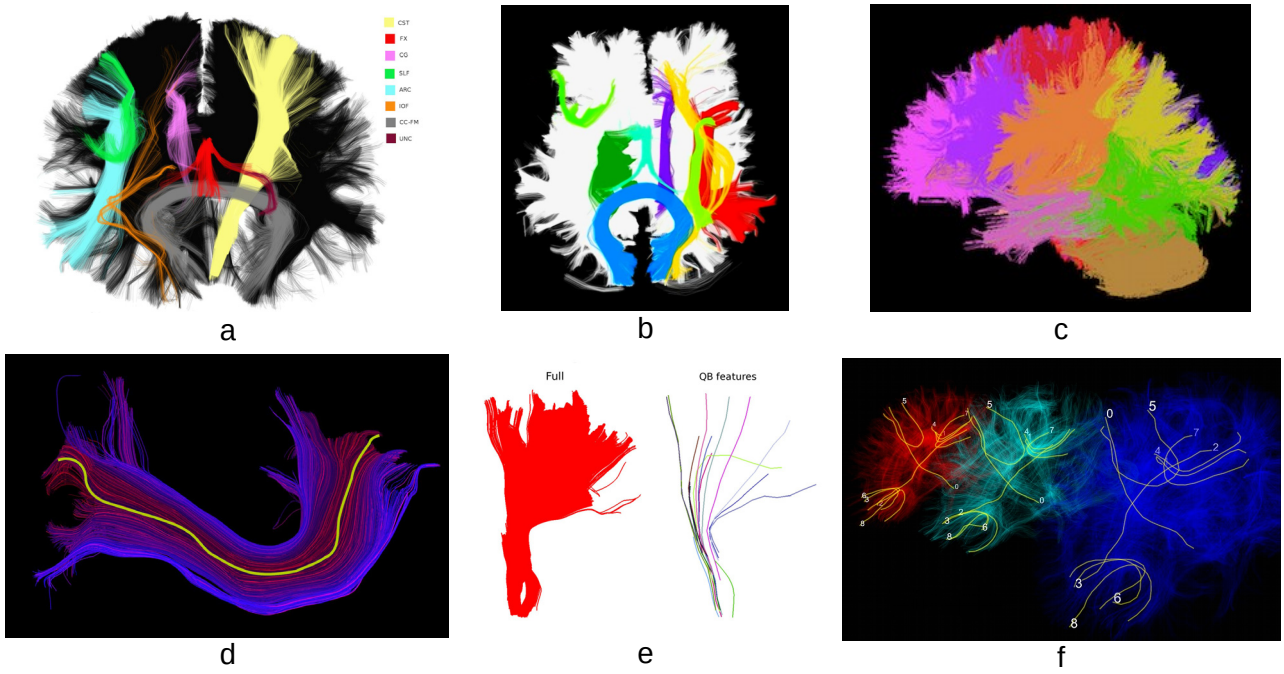

Fig.3*: Example diffusion features extracted by the DiPy package.*[34]
(a-c) supervised and unsupervised bundle segmentation, representation of different features of (d) arcuate fasciculus, and (e) corticospinal tract, which contained ~11,000 tracks and took QuickBundles[13] *0.14s to segment, simplify, and create features that represent different subareas, (f) whole-brain unsupervised track correspondence in three brains*

By integrating clinically relevant features from multiple modalities, we aim to create more effective biomarkers. In summary, our multimodal features will include:

- aMRI: sulcal surfaces, fundus curves, and pits (points of maximal depth or curvature along a fundus)
- fMRI: functional "connectivity" networks
- dMRI: tractography bundles, exemplar tracks, and connected brain regions

Hypothesis: Features from multiple modalities complement each other, and their combined use will improve the efficacy of our biomarkers over those derived from unimodal data.

3.1.3 Quantify the shapes and distributions of features as feature vectors

In order to compare features across individuals and identify them we need to characterize them in a quantifiable manner. For this we compute shape analysis measures for each of the above features and aggregate the measures for each feature in a *feature vector*. To give some examples of clinically relevant measures that have been applied to the aMRI features, cortical thickness, curvature, and depth have been used to help characterize disorders such as mild cognitive impairment and Alzheimer's disease.[57] Sulci have been used to compute global and local gyrification indices, which have been used to characterize schizophrenia,[1] and early-onset vs. intermediate-onset bipolar disorder as well as bipolar and unipolar depression.[2-4] Pits, points of maximal depth or curvature in the sulci, are interesting because they may be well conserved structures formed early in development,[41,58] and are recently being used to characterize conditions such as polymicrogyria.[59] Fundi run along the depths of the folds, and like pits are thought to characterize early stages of morphological development, and therefore may exhibit abnormalities in neurodevelopmental and heritable disorders.

For each point on a sulcus, including points of the fundi or pits, we compute curvature, convexity, cortical thickness, and depth;[9,60] for sulci and fundi we also compute geometric quantities such as area/length, moment invariants, and spectral quantities using the Laplace-Beltrami operator.[45] We will compute analogous measures for fMRI and dMRI features and for regions defined by any of the features (3.1.5), and define new measures where appropriate. For example, we will use a novel method developed by our consultant E. Garyfallidis[13] that can measure many features of a tractographic bundle such as centroid track, thickness, and the bundle's boundary surface (**Fig.3e**).

Hypothesis: Anatomical features with higher shape analysis measures such as deeper fundi and stronger fMRI/dMRI connectivity among features of any modality are indicators of features and relations that develop earlier and will therefore be more consistent across subjects, easier to match, and increase the robustness of our biomarkers.

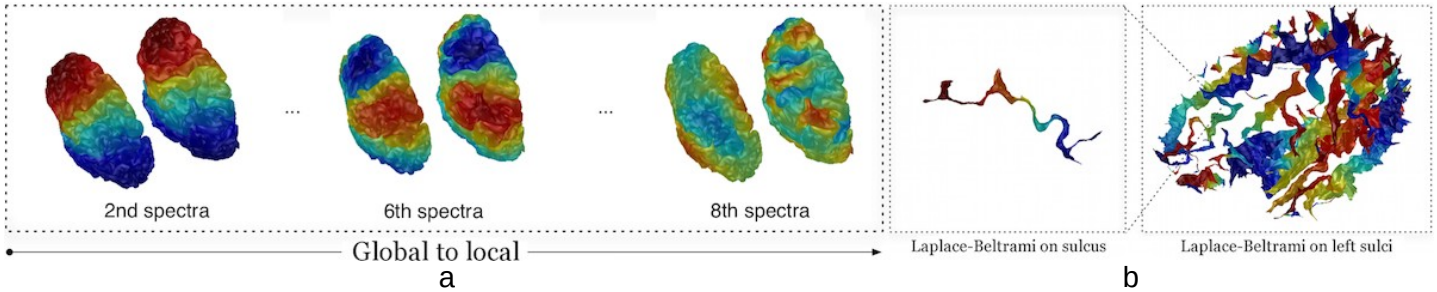

Fig.4*: Example shape analysis measure on our aMRI data: Laplace-Beltrami spectra*

3.1.4 Identify features

We will identify corresponding features across brains by matching them probabilistically using a Bayesian approach, by maximizing the *a posteriori* probability (MAP) of the resulting classifications (feature identities). We will consider the global probability of feature classes across a brain rather than identify features one-by-one. This will provide a more robust result since each class can be restricted to appear only once and classes with high variance can be constrained by surrounding features with more certain classifications. Computing the MAP estimate requires defining a likelihood estimate for each query object. With the amount of manually labeled data we will have available, we should be able to reliably estimate the distribution of feature vectors in the feature space using kernel density estimation.[61] This estimate then provides a likelihood function for each new feature vector.

One important feature is obtained by using our fundi as 3-D trajectories with branches. This will enable pairwise trajectory matching, providing a distance measure directly from the data without the challenging task of constructing a suitable feature vector. This distance measure could be used alone for classification. However, our past experiments show that while trajectory matching gives an effective measure of similarity, additional features are required to obtain an accurate classification. Within a fundus curve, each point has a spatial location defining the trajectory. Additional information can be used such as local curvature and depth at each point. This way, the distance between each pair of fundus curves can be quantified using multidimensional (constrained) dynamic time warping (DTW)[62,63] with linear scaling,[64] which has been effective in time-series analysis.

The individual fundus curves are actually branching tree-like structures, so we will model a fundus as a simple graph where each edge of the graph represents a fundus branch. To identify a fundus, we will compute the distance between its graph and the manually identified graph of another brain by computing the DTW distance between their component edges. Since these are very simple graphs (trees with very few branches) and since we can constrain edge-to-edge matches across a pair of graphs using simple properties such as relative position, orientation, and size, we can test every reasonable edge-to-edge mapping between a pair of graphs to determine maximal correspondence. With a manually labeled training set to establish a prior distribution, we can estimate the variation of feature measures within and across classes, providing the likelihood function for a new object as has been done in face recognition.[65] A new object can then be labeled using pairwise Bayesian classification. Neuromorphometrics (consultant) will conduct independent evaluation of our feature extraction and probabilistic identification by visual inspection and correlation with manually identified features. If a feature is missing in a given brain, Mindboggle will assign a low confidence estimate to a match and to label boundaries that are normally defined by the missing feature. We will also experiment with multimodal graphs to help identify features (3.2.2).

For fMRI, a multi-subject estimation framework[50] directly extracts features at the subject level with a correspondence at the group level. Assigning labels to new subjects is then a MAP estimation in the model corresponding to the group. For dMRI tractography, we will establish corresponding tracks and dMRI-defined cortical regions with the DiPy package[66] (**Fig.3f**) and according to dMRI feature-specific quantities (3.1.3). Our consultant E. Garyfallidis recently introduced a new visualization/interaction tool named fos (free on shades, fos.me) which can be used to label tractographies of unlimited size very rapidly. We are planning to use and extend this tool for identifying dMRI features and labeling our dMRI data sets.

3.1.5 Label brains based on features

Brain labeling based on atlas registration assumes that the intensities or features that drive two brains into alignment will also correctly transform label boundaries. However, current atlas labels are not fully determined by identifiable features, but instead are constructed by reference to a labeling protocol. To reduce the subjectivity and inconsistency in labeling, we propose to fully label a brain based on the features we identify within an individual and manually labeled data as priors in a Bayesian framework.

For aMRI data, if we identify a fundus in an unlabeled brain and we know that the fundus usually separates two labeled regions, then we can consider this as the problem of labeling a new brain from a partially-labeled data set. This problem can be more generally formulated as a semi-supervised problem in machine learning, which can make use of the structure of the data including nonlabeled instances. We plan to use a label propagation semi-supervised learning algorithm,[67] as it works naturally on graphs. One of the valuable features of the algorithm we are developing, which is based on a Gaussian random field model, is its

probabilistic assignment of labels. By providing a measure of confidence, the probabilities can guide our use of other sources of label information, such as class priors or external classifiers. The algorithm, with its flexibility in terms of the graph's connectivity and the weighting of the graph's edges, enables us to incorporate our degree of confidence in the features we've extracted into the model. And finally, its use of soft labels in cases where classes may be overlapping or ill-defined provides robustness to the label propagation.

Labeling based on aMRI features not only allows us to derive a labeling specific to each brain, but the labeling protocol itself would be rigorously defined by the feature extraction definitions and label propagation constraints alone. We visually assessed the spatial relationship between our automatically extracted fundi and the manual labels of aMRI regions and determined that our fundi run roughly along the label boundaries (**Fig.5**), suggesting that label propagation between our fundi has great potential for labeling of the entire brain without recourse to standard registration methods or templates. If label propagation fails in parts of the brain we can always fall back on feature-driven registration-based labeling for these parts, as in the current grant. We expect that our implementation of this alternative will be a great improvement over current registration methods, based on preliminary results and because we will prioritize our features in an anatomically reasonable manner (by shape variability or probability of occurrence). Neuromorphometrics (consultant), which has extensive experience in manual labeling of brain regions and is a consultant on the present grant, will manually label anatomical regions to evaluate our automated labels.

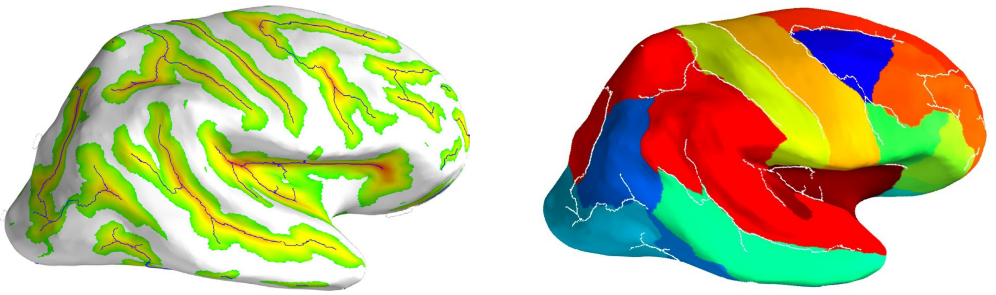

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Fig.5*: (a) fundi in red, (b) fundi in white overlaid atop manual labels*

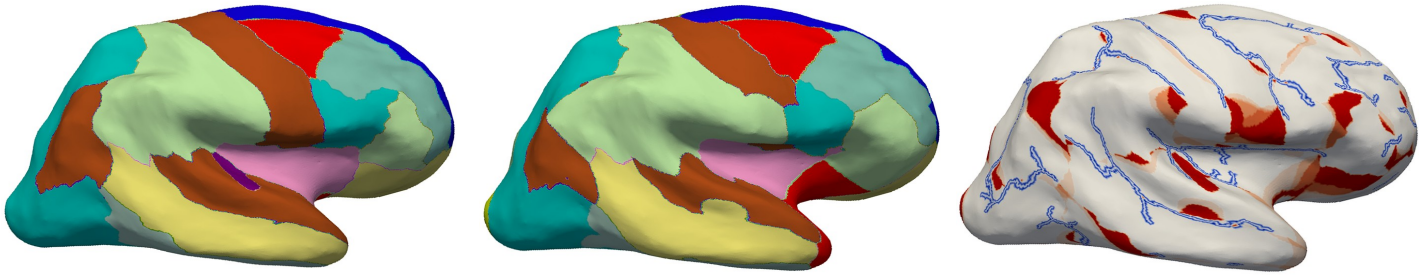

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Fig.6: (a) manual labels, (b) initial test of weighted averaging label propagation from manually labeled fundi, (c) label errors by rank: white indicates correct first guess (78% of vertices were correctly labeled), pink-to-red indicates correct subsequent (i.e., lower probability) guesses, with fundi in blue

For labeling a brain based on fMRI data, we could also apply label propagation initialized by our fMRI network features (3.1.2), but fMRI networks are distributed and do not delimit cohesive anatomical regions. So instead, we will focus on soft-assignment labeling based on a dictionary learning procedure,[50] and will experiment with complete parcellation based on network clusters[68] and incorporate spatial constraints.[69] As mentioned in 3.1.2, rs-fcMRI and dMRI tractography data can both be represented as weighted graphs, so we can apply our fMRI-based labeling method to label a brain using dMRI tractography data as well. For dMRI-based labeling, we can also simply extend the dMRI tractography-based cortical regions — clusters of similarly connected voxels that generate collateral tracks (3.1.2) — to cover the entire brain[54,70] (**Fig.3c**).

Any labeling method will have errors, and yet no software tool currently includes a straightforward quantification or visualization of uncertainty of brain labeling, although first steps have recently been taken to superimpose interquartile ranges on brain images.[71] We will quantify uncertainty in assigned labels as confidence intervals, output label volumes that include this information, and allow removal of labels above a given measure of uncertainty. To estimate posterior labeling error in a statistical learning framework, we will leverage one of two strategies. If our labeling method can be formulated as a generative probabilistic model, we will use this model to derive the posterior probability or simply the covariance of the error. If it is instead closer to a discriminative approach, we will rely on resampling methods that not only give an estimate of the error but have been shown in many cases to yield tighter bounds on the identification of parameters of the model.[72]

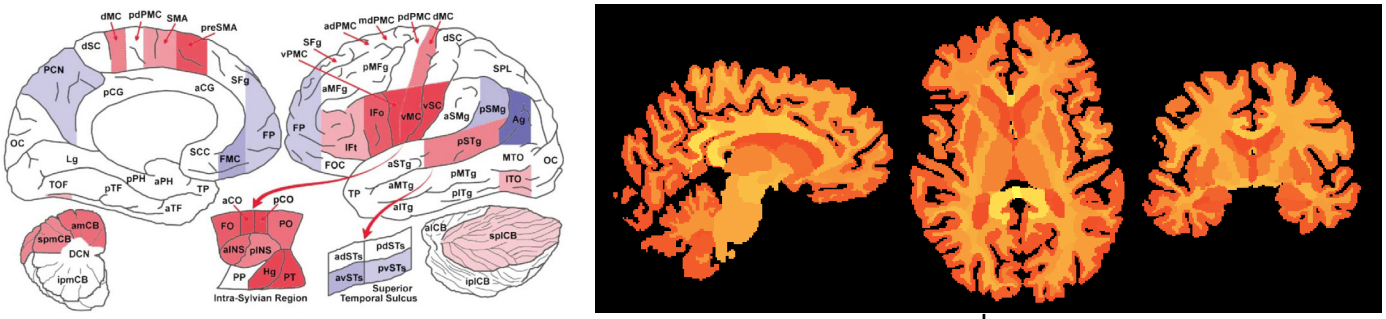
Hypothesis: Feature-based labeling will give more consistent and accurate anatomical labels than will registration-based labeling, and will improve region-based morphometric diagnostic precision, using manual labels as gold standards.[5,6]

3.2 Aim 2. *Integrate modalities via compartments, connections, and overlaps.*

Integrating multimodal data that reflect different aspects of brain anatomy, function, and connectivity provides a multivariate description that can capture inter-individual variation and therefore has potential as a biomarker. We will use three complementary means of integrating multimodal data: compartments (3.2.1), connections (3.2.2), and overlaps (3.2.3), and will store the results in a graph-based database (3.2.4). We will store information related to aMRI, fMRI, and dMRI data acquired on the same scanner. However, if a user does not have all three modalities available, the user will still be able to use Mindboggle to perform automated morphometry and labeling with available modalities since the multimodal Mindboggle is simply an extension to running Mindboggle with a single modality. In the same manner that the original Mindboggle's anatomical feature-based labeling responds better to missing features than conventional registration-based labeling,[8] we can expect Mindboggle to continue to function with missing features from other modalities. We will ensure that the confidence estimates for the label boundaries reflect the missing information.

3.2.1 **Compartments**: *Quantities from one modality are computed within a feature from another modality.*

Compartments are standardly employed in region-based fMRI analysis, where fMRI activity is measured in an aMRI region. Another example is cortical thickness measured within an fMRI cluster.



a b

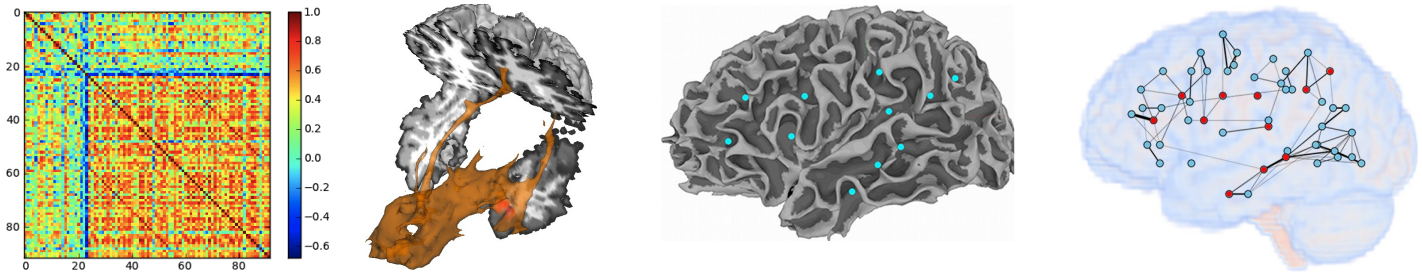
***Fig.7**: Examples of multimodal integration via **compartments**:*
(a) fMRI activity for a speaking task detected within aMRI regions (Ghosh et al, 2008),
(b) dMRI average fractional anisotropy in aMRI white and gray matter (red-to-yellow for higher anisotropy)

3.2.2 **Connections**: *Multimodal features are related via a connection strength.*

Examples include dMRI tracks between an aMRI region and fMRI network, or fMRI connectivity between a dMRI cluster and aMRI region. We will represent these relationships as graphs, where each feature is a node and the relationship between any pair of features is an edge, the properties of the node are contained within the feature vector, and the properties of the edge are edge weights in our graphs. For example, any aMRI feature such as a fundus will have a feature vector with associated measures of surface curvature, depth, gray matter thickness, etc.; the fundus node would inherit the properties in the feature vector. We will use dMRI tractography as edges connecting aMRI or fMRI seeds as nodes, functional connectivity as edges connecting aMRI or dMRI nodes, and anatomical paths as edges connecting fMRI or dMRI nodes. We will use the following edges and weights for the three modalities:

- aMRI: anatomical distance (Hausdorff distance based on geodesic or Euclidean separation)
- fMRI: functional connectivity (temporal correlation of activity)
- dMRI: structural connectivity (assigned by third-party tractography software)

We have experimented with connecting aMRI nodes (regions, pits, and fundi) with fMRI edges (functional connectivity) or dMRI edges (probabilistic tractography using FSL[73] with connection probability greater than 0.01), and have constructed graphs from these connections using the Python library NetworkX (networkx.lanl.gov).



a b c d

***Fig.8**: Examples of multimodal integration we are conducting via **connections**:*
(a) fMRI connectivity matrix among aMRI regions (ADHD subject),
(d) orbitomedial frontal dMRI tractography connections with other aMRI regions (MDD subject),
(e-f) aMRI pits on a white matter surface and connected by dMRI edges (MDD subject)

Within a given modality we also represent our features as (in this case nested, hierarchical) graphs. Our aMRI features are nested as follows: pits (points) lie along fundus curves which lie along the depths of sulci. fMRI data will be nested by increasing the number of network clusters[68] and dMRI tractography data will be nested by graph analysis methods such as clique-set (graph containing nodes that connect to each other) or k-core decomposition (graphs with nodes of degree at least k). Building on the community extraction strategy[33] developed by our consultant Gael Varoquaux, we will strive to formulate the graph analysis of fMRI with appropriate regularization to cope with the challenge of estimating a rich subject-level description from a few minutes of rest. The primary advantage of a hierarchical representation is that we can prioritize (or weight) the influence of the features on matching or diagnosis in a level-sensitive manner. For example, if there were measurable differences between two populations at the level of pits vs. sulcus, or at the level of primary vs. secondary folds, this would tell us a lot about how subtle or pathological the differences are. We might also be able to ascribe a level of confidence about the discriminability between the two populations based on the variability of the features at a given level, and perhaps even make inferences about the stage of morphological development when the deviation took place.

We will experiment with identifying corresponding features across brains by matching graphs and then matching corresponding nodes of the graphs (features), using graph analysis measures computed by the NetworkX. This should improve feature identification over matching individual, disconnected features, since providing the context of a given feature in the form of its relations to all other features will greatly constrain the potential candidate matches in another brain. We will evaluate different similarity measures within NetworkX relevant to brain architectures, such as eccentricity difference (a measure of how close or how far vertices are to each other in a graph), centrality of weighted graphs (extent of a vertex's connections to important vertices), [74] and will investigate all metrics in.[75]

Hypotheses: (1) Grouping structures into nested hierarchies within brains will improve matching across brains and improve biomarker specificity relative to disconnected structures. (2) The position of a structure in its nested hierarchy will predict how variable the structure is across individuals. (3) When differences related to a disorder are detectable between two groups for a given structure, the structure's position in its nested hierarchy can predict how subtle or pathological the condition is. (4) Comparing collections of features as graphs will result in more accurate identification of corresponding features than comparing individual features directly (also applicable to fundus graphs in 3.1.4).

3.2.3 Overlaps: *Multimodal parcellations are related to each other via overlaps and distances.*

Here we are interested in the relationship among independentally derived, modality-specific parcellations. An example is an fMRI network overlapping with an aMRI region. We can measure the similarity between them by their overlap or by the proximity between their boundaries. Or we can treat the overlapping activity and anatomy maps as one would a Venn diagram, and select their union or intersection within which to measure a quantity such as fMRI activity. And if the maps are assigned different confidence estimates (3.1.5), one map could be weighted more heavily or take precedence over another map based on a higher estimate. From the standpoint of biomarkers, overlaps can be also be useful for establishing structure-function relationships and clinical-radiological correlations (AnaCOM[76]).

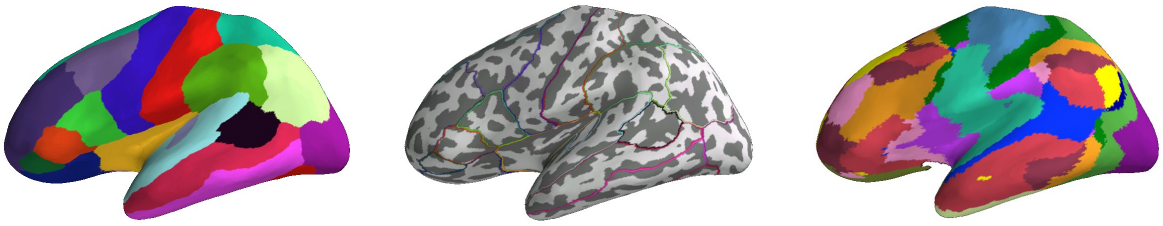


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Fig.9*: Example of multimodal data we are integrating via* ***overlaps****:*
(a) aMRI parcellation, (b) boundaries, (b) network cluster-based parcellation of the same brain

Hypothesis: Multimodal boundaries will coincide more often in primary sensory and motor areas.

3.2.4 Store graphs in a graph-based database

To store our graphs and query them by node and edge properties, we will make use of Neo4j's (neo4j.org) noSQL database using a graph-based data model as opposed to a standard relational database because we want (1) our feature database to be flexible enough to accommodate changing data and knowledge representations, (2) to naturally represent and store connected and semi-structured data, and in the case of Neo4j (3) to support large-scale storage while also exploiting the power of graph inferences to perform feature analyses in populations and efficient queries.

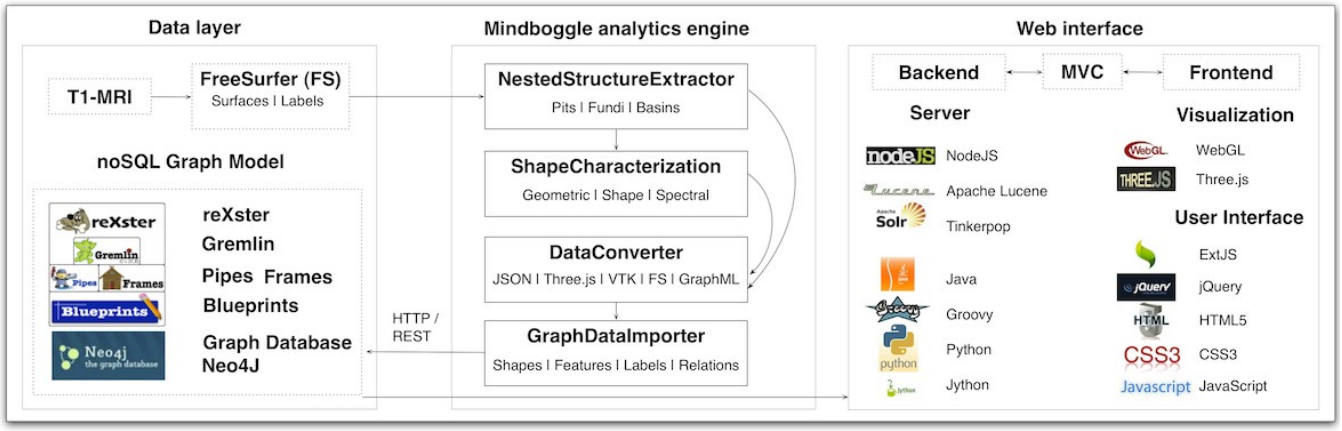

***Fig.10**: Mindboggle infrastructure schematic showing the working components of the data layer, analytics engine, and prototype of the web browser interface.*

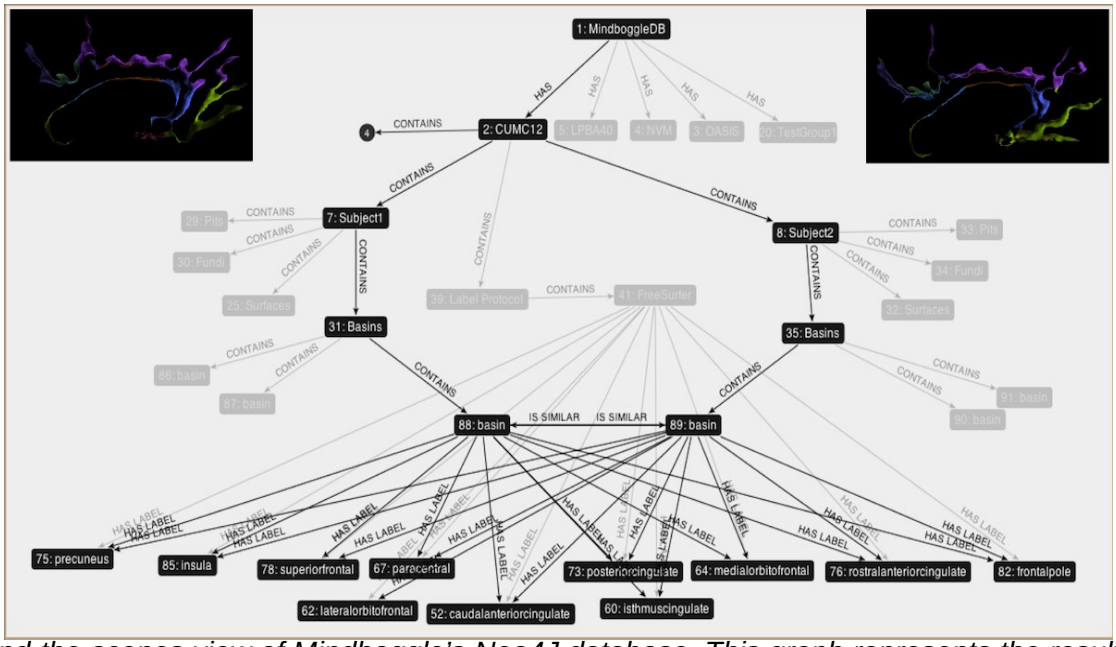

***Fig.11**: Behind-the-scenes view of Mindboggle's Neo4J database. This graph represents the results of a query to find similar structures between two subjects' brains. In this simple example, sulci from subject 1 (top left overlay) are found to have similar shape as sulci from subject 2 (top right).*

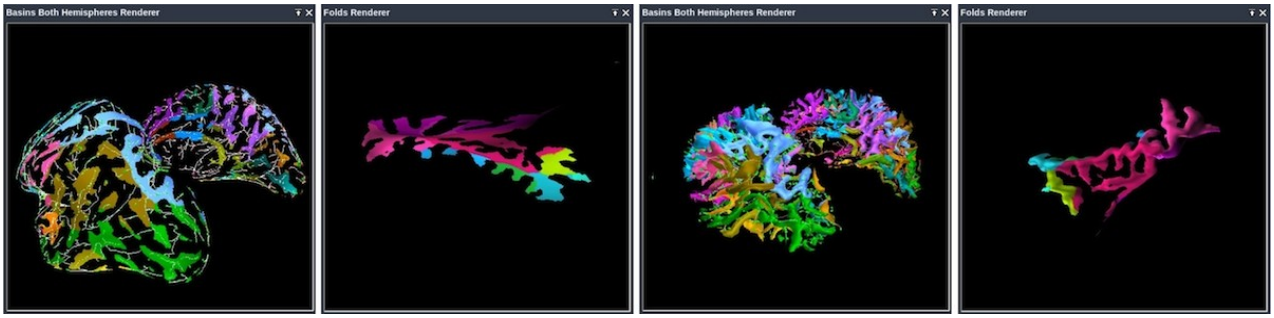

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***Fig.12**: Mindboggle's interactive web browser-based interface provides a flexible way to visualize and explore the database: (a) inflated and (c) white matter surfaces of (b,d) sulcus folds*

3.3 Aim 3. *Generate and evaluate biomarkers on clinical data.*

3.3.1 Use statistical learning methods to select disorder-relevant measures

We will use our feature vectors (3.1.3) and graph analysis measures (3.2.2) as "learning features" for pattern classification (diagnosis, remission, prediction) and regression (treatment response prediction). We will use statistical learning methods to select the learning features that correlate with our classes of clinical populations. For this purpose, we will rely on the expertise in machine learning of our consultant, Gael Varoquaux, project leader of the Python machine learning library scikit-learn (scikit-learn.sourceforge.net).

3.3.2 Evaluate measures as possible biomarkers

We will evaluate the effectiveness of the above learning features as possible biomarkers by diagnostic and prognostic accuracy compared with gold standard psychiatric evaluations. To this end, we will use scikit-learn for pattern classification. One challenge faced in learning a discriminative model between graphs is that graphs do not live in a metric space: the appropriate distance between two graphs representing different subjects may be a factor of the number of branching differences between the graphs. To tackle this problem, we may resort to the spectral regression framework that can learn discriminative comparison kernels from the data[77]. Importantly, it can perform well in semi-supervised settings, i.e. in the learning database of subjects for which the healthy/patient diagnostic is not established. Another challenge that we have to face is the non-smoothness of many graph distance measures. To give a simple example, seeking features that maximize the number of graph recombinations from one population to another gives rise to a non-smooth and non-convex optimization problem that is not only hard to solve, but also gives rise to unstable estimation in noisy settings. To make the problem smooth, we can rely on confidence bounds estimated in 3.1.5 and formulate the distance as an overlap in these bounds, which corresponds to comparing probability densities, possibly with a smoothing kernel. This approach has been successfully used to extract distances between brain fibers[78] or sulci.[79]

Preliminary results: To demonstrate we can use compartmentalized information for prediction, we evaluated aMRI shape metrics (3.1.3) from remitter and non-remitter data of 17 individuals (remitters are depressed subjects who had post-SSRI treatment Hamilton depression scores <= 7). We used a stratified cross-validation with a polynomial kernel support vector machine to classify these data. Using a permutation test (**Fig.13a**), we demonstrate that our average f1-score is highly significant. *These are the first results that we know of using features extracted from anatomical MRI to predict treatment response for MDD* (**Fig.13b**).

To demonstrate that we can use feature-connected graphs (3.2.2) for diagnosis or prediction, we evaluated 27 graph analysis metrics on graphs constructed (as in **Fig.8d**) from dMRI-connected aMRI pits in 17 MDD patients and 14 controls. Using these metrics as inputs, we used the scikit-learn library to perform a leave-one-out k-nearest neighbor classification. To eliminate model parameter-selection bias (e.g. what k to use?), we used a cross-validated grid search to tune the predictive model prior to prediction on an unknown datum. Even with these preliminary features, we achieved an overall accuracy of 71% (precision: 83%, recall: 59%) in distinguishing controls from MDD patients. We expect these numbers to improve as we incorporate more relevant multimodal features and perform better feature selection. In the event that our diagnosis and prediction attempts fail, we will apply our methods to simulated data to evaluate sensitivity and robustness under controlled conditions, and to other suitable clinical data.

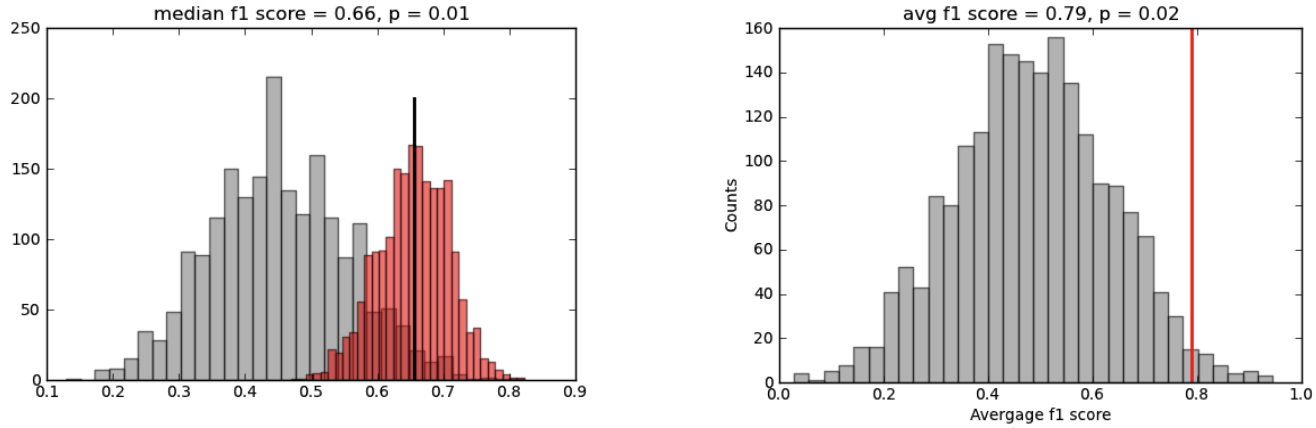


Fig.13*: Preliminary results*: *(a)* Permutation test results classifying remitter and non-remitter data. The histogram shows the null distribution from the permutation testing (gray) and (b) the classifier result (red line). Result: average f1 score =0.79; p=0.02.

3.4 Progress Report (7/2009 to 6/2012)

The original version of the Mindboggle software was created by the P.I. and has been downloaded by users in over 20 countries, and publications describing Mindboggle (PMID: 15627570, 16202176) have been cited 47 times and have been accessed over 10,000 times (Biomed Central's website states "overall statistics indicate that your article will have been accessed on PubMed Central a roughly equivalent number of times...").

The specific aim of the currently funded proposal was to automatically identify/match anatomical brain structures based on an analysis of their shapes by means of a Bayesian framework. The secondary aim was to develop Mindboggle software to automatically label an entire brain based on these probabilistic matches. We are ahead of schedule to meet all of the goals of this proposal. Our software is maintained via git distributed version control as a Github account (www.github.com), and we are using Sphinx documentation (sphinx.pocoo.org). Here we will outline our progress according to the six sections in the original proposal.

1. Optimize the automated extraction of brain structures from brain image data

We have developed software to extract sulci, fundi, and pits based on curvature or depth of the cortical surface and presented an evaluation of these features at the Human Brain Mapping 2011 Conference.[11]

2. Analyze the shapes of brain structures
We have quantified the shapes of cortical regions, sulci, and fundi using an initial set of geometric shape measures: volume/area/length, curvature, and depth, and Laplace-Beltrami spectra.[45] We entered these features into the world's first database that permits queries involving demographics and sophisticated shape analysis measures of anatomical structures, and presented it at the Neuroinformatics 2011 Conference[12] and BioImage Informatics II 2011 Conference at Janelia Farm.[9]

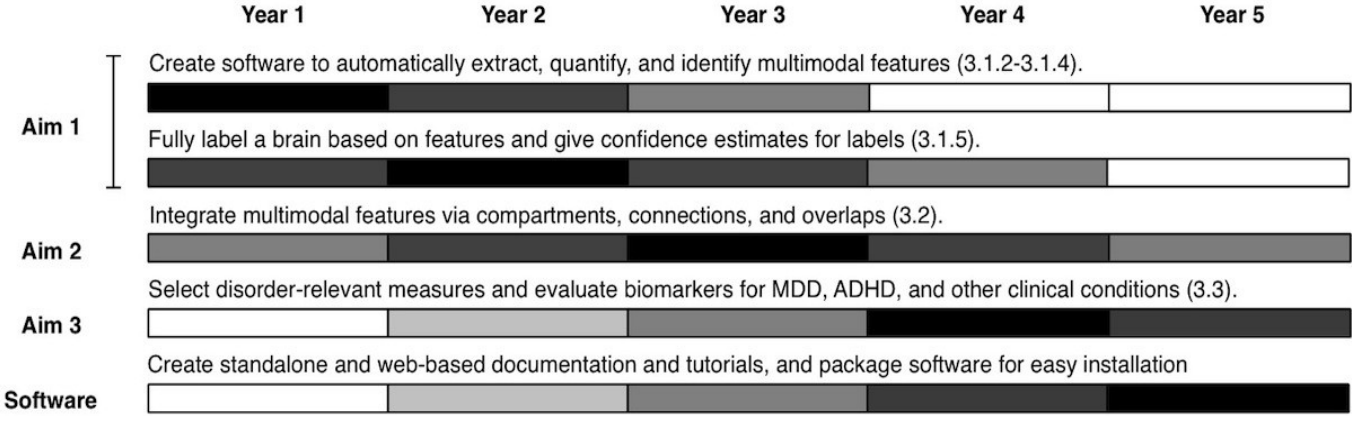
3. Manually label brains for training, testing, and brain atlas construction
Our consultant Neuromorphometrics has created the world's largest collection of manually labeled brain images, with more than half of the 101 brain images completed. They have identified ambiguities and inconsistencies in FreeSurfer's standard Desikan-Killiany protocol, and have created what is perhaps the world's most consistent and accurate anatomical brain labeling protocol. They have applied this protocol to images from publicly available data sets: OASIS, Multi-Modal MRI Reproducibility Resource, PLoS 12-subject,[80] and NKI/Rockland. In addition to meeting these requirements, we also formed a brain labeling advisory group and the www.braincolor.org website, created an online brain image viewer and presented it at the Human Brain Mapping 2010 Conference (www.braincolor.org/roygbiv), and created open source software to automatically create optimal colormaps to make it easier to label and view labeled image data, and demonstrated it at the Society for Neuroscience 2010 Conference (www.braincolor.org/colors).

4. Construct a Bayesian framework to identify brain structures using shape analysis
We proposed to match brain structures to corresponding manually identified structures to determine their probablilstic label identities. We therefore match fundus curves with a Bayesian MAP classification and use the posterior probability as a measure of label certainty. For an initial test, we performed the classification using a simplified version of the DTW-based[62] measure to quantify shape-based similarity between fundi. To test feature matching independent of our feature extraction methods, we used manually identified sulcal ribbons generated by the BrainVISA software[44] in 62 individuals.[79] The bottoms of these ribbons correspond loosely to fundi but were unfortunately available to us as discontiguous voxels in an image volume rather than curves as we are generating. However, even with these data and a simplified initial version of our similarity measure we have already obtained a preliminary accuracy of 55 percent correct fundus identification in unseen brains. We expect a significantly higher accuracy using the higher quality fundus curves that we are now generating, a constrained version of DTW with linear scaling,[64] a spatial prior probability term and the planned graph representation for fundus trees. We will exert much of our effort in the remaining half-year to implement these and other advances to improve matching accuracy. Our Bayesian matching framework is ready to use with the improved fundus similarity measure on our data, and can be easily modified to classify other types of structures with defined feature vectors or similarity measures.

5. Facilitate brain parcellation using these identified structures
We proposed to use the identified structures as landmarks and to perform landmark-driven nonlinear registration to transfer manual labels to the unlabeled brain image data. We evaluated whether landmark-driven registration can generate more accurate results than intensity-based nonlinear registration alone, and determined the upper limit to the improvement we should expect, based on a pair of images that did not register well in one of our published evaluation studies.[5] Without using landmarks, we transformed the manual labels of the source brain to the manual labels of the target brain using ANTs (a top-ranked registration method in the study) and obtained a Dice overlap of 0.7780 (averaged across all labeled regions). When using all of the manually identified landmarks, there was a great improvement in registration and labeling accuracy: 0.8956. We expect to increase this upper limit when we register individually matched landmarks. These results give us confidence that using automatically extracted structures will improve the accuracy of labeling brains.

6. Evaluate the automated identification of structures and ROIs
We have in place an evaluation protocol that we have successfully used in 5 studies (3 published) in the last 2 years,[5,6,81] including the world's most extensive volume and surface brain registration evaluation studies.

3.5 Proposed timeline



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