**SCOPE**

***"Biosignatures of Treatment Remission in Major Depression" Admin Supplement for Software Development:***

**Structural MRI-based feature shape analysis to predict treatment response in major depressive disorder**

**Specific aims**

Recently we obtained the first preliminary results that we know of using structural MRI-based features to predict treatment remission for major depressive disorder (MDD). The subject data for our pilot study consisted of T1-weighted MRI data from 18 patients who met criteria for MDD and who had MRIs during a major depressive episode (R01MH074813, PI Ramin Parsey). All subjects were treated prospectively with escitalopram and 8 participants remitted and 10 were non-remitters (remission is defined as post-SSRI treatment Hamilton depression scores <= 7). For this pilot study we *extracted* a ***single feature*** *from a 6-minute structural MRI alone*: sulcal fundi, curves running along the depths of the folds of the cerebral cortex. From these fundi, we derived geometric shape measures such as curvature, depth, and length. We successfully used these shape measures to distinguish between remitters and non-remitters with a sensitivity of 0.75 and specificity of 0.8. We would like to extend our pilot study to the EMBARC data, and to refine our feature-based methods, which overcome the limitations of conventional, co-registered voxel-wise comparisons across brain images. For this supplement, we will accomplish the following:

***Aim 1:*** To enhance the quality and predictive capacity of our newly identified structural MRI-based biomarkers for
predicting response to antidepressant treatment, we will extend our feature extraction, identification, and shape analysis algorithms. Our current biomarkers were based solely on a single feature type extracted from T1-weighted data. We will refine our methods to extract multiple structural features (sulci, medial surfaces, and pits, in addition to fundi), refine our feature identification by segmenting features based on a multi-atlas, multi-registration labeling procedure, and refine our shape analysis methods by incorporating spectral shape analysis.

***Aim 2:*** To test clinical significance, we will develop our feature-based biomarkers using our pilot treatment data and evaluate the prognostic accuracy of our biomarkers using EMBARC data. We will enable queries to identify disorder-relevant features in an existing online shape analysis database.

***Aim 3:*** To enable full morphometric analysis on future EMBARC and other acquisitions, we will make our software fully open source, well documented, and freely available.

***Exploratory Aim 1:*** To extend our structural biomarkers to multiple imaging modalities, we will integrate EMBARC's diffusion tractography (dMRI) and resting state functional (rs-fMRI) data. Specifically, we will build tractography and functional connectivity graphs connecting our structural features, encoding shape information about the features and their relationships.

**Relationship to the parent grant and to supplement topic 4:**
**"Advancing the Development of one or more Biomarkers for Use in Clinical Research"**

The parent grant distinguished between two types of biomarkers for treatment response: (1) biomarkers for selecting optimal treatment for individual patients at the beginning of treatment (moderators) and (2) biomarkers as indicators of eventual response early in treatment (mediators). Aim 1 of the parent grant includes an assessment of the extent to which structural measures of cortical thickness and rs-fMRI measures will differentially moderate treatment outcomes.

While cortical thickness is important in morphometry, there are other, potentially more incisive ways of analyzing the shapes of brains. To give some examples of clinically relevant measures that have been derived from structural MRI-derived features, cortical thickness, curvature, and depth have been used to help characterize disorders such as mild cognitive impairment and Alzheimer's disease[1]. Sulci have been used to compute global and local gyrification indices, which have been used to characterize schizophrenia[2] and early-onset vs. intermediate-onset bipolar disorder as well as bipolar and unipolar depression[3-5]. Pits, points of

maximal depth or curvature in the sulci, are interesting because they may be well conserved structures formed early in development[6-7] and are recently being used to characterize conditions such as polymicrogyria[8]. Fundi, like pits, are thought to characterize early stages of morphological development, and may exhibit abnormalities in developmental and heritable disorders.

Our existing software computes geometric analysis measures and we are developing spectral shape analysis measures that together will enable us to detect far more subtle morphometric variations. And we compute these measures not just for anatomically defined regions, but for features that we extract and identify, enabling much more precise comparisons across individuals. Aims 1 and 2 of this supplement are to refine these feature extraction, identification, and shape analysis capabilities and apply them to EMBARC data, and are therefore a natural extension to the parent grant's standard morphometric approach. The Exploratory Aim 1 of this supplement will integrate EMBARC's dMRI and rs-fMRI data into our definition of biomarkers, and serves as a multimodal extension to the separate MRI, dMRI, and rs-fMRI analyses of the parent grant. Aim 2 of the parent grant includes an assessment of the extent to which changes in the resting state connectivity will differentially mediate treatment outcomes. Since we will compare corresponding multimodal biomarkers across individuals in Exploratory Aim 1, we can also easily compare the 1-week changes in their biomarkers as well.

**Significance**

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. The goal of such registration is to establish correspondence between brains in order to extract biomarkers. However, registration alone does not guarantee correspondence[9] and other factors affect the quality of registration such as the choice of registration algorithm[10] and template[11], removal of non-brain matter[11,12] and anatomical variation that can include missing regions[13]. These problems limit the accuracy of biomarkers generated from registering data. We propose to overcome the limitations of conventional registration methods by establishing correspondence at the level of well-characterized **features** vs. voxels, which should be more robust to missing regions[13] and generate more consistent and accurate biomarkers. Moreover, establishing connectivity relationships among these features using dMRI and rs-fMRI will enable us to integrate these different sources of complementary information in a natural way, as graphs, and gives us a better chance at extracting even more sensitive biomarkers than relying on a single modality.

The accuracy, precision, as well as conceptual simplicity of extracting biomarkers in individuals rather than conventional group-wise analysis that relies on traditional registration methods will take a great step toward patient-specific medicine. Our approach is intended to analyze differences in brain image data between any two populations, but for this supplement we will focus further development on MDD, using existing pilot data to develop and EMBARC data to evaluate our feature-based biomarkers. This will be used as a test case to establish whether our feature-based approach (and multimodal integration) is successful and should be applied to other psychiatric and brain diseases. The precision afforded by feature-level comparison and the ease with which one can integrate multimodal data in a graph-based representation, will lead to adoption of these methods well beyond the present application. If we are successful in predicting recovery in MDD, as our preliminary results indicate, it will open up the field of personalized or precision medicine for this and other disorders. In addition, these features are derived from T1-weighted MRI images and therefore would enable prediction with a widely available, low cost, non-invasive method.

**Innovation**

***Aim 1:*** We will introduce new methods of structural MRI-based feature extraction, identification, and shape analysis to extend our current software. Creating correspondences across individuals in feature space without resorting to currently used group registration to a template space will move the field beyond group-based studies and focus on patient-specific biomarker detection.

***Aim 2:*** We will apply our software for the first time to clinical data in the world's first large-scale attempt to predict recovery in MDD using feature shape information. If successful, it will allow brain imaging data to be used for patient-specific medicine for MDD.

***Aim 3:*** Not only will all of our software be made open source and freely available, but our neuroinformatics framework will as well, which is the world's first shape analysis, graph-based database.
***Exploratory Aim 1:*** Our tools will integrate multimodal data into graph-based representations, and these graphs with all their node and edge properties will be constitute the world's first multimodal shape analysis database.

## Approach

***Preliminary data*** To demonstrate the potential for feature-based prediction of treatment response, we evaluated shape measures for a single structural MRI-based feature from our remitter, and non-remitter pilot data. We used stratified cross-validation to test the performance of a classifier distinguishing remitter from non-remitter participants. Using a permutation test, we demonstrated that the performance of these classifiers is significantly better than chance (**Fig. 1**). In this preliminary analysis, sulcal fundus length was an important measure contributing to the distinction between remitter and non-remitter data.

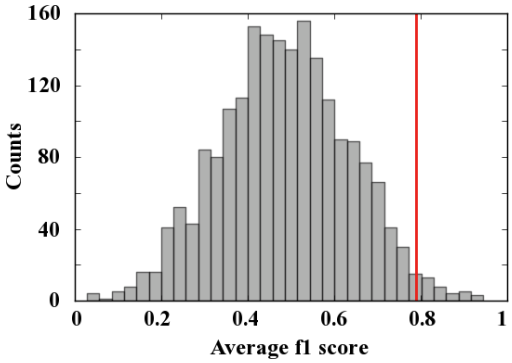
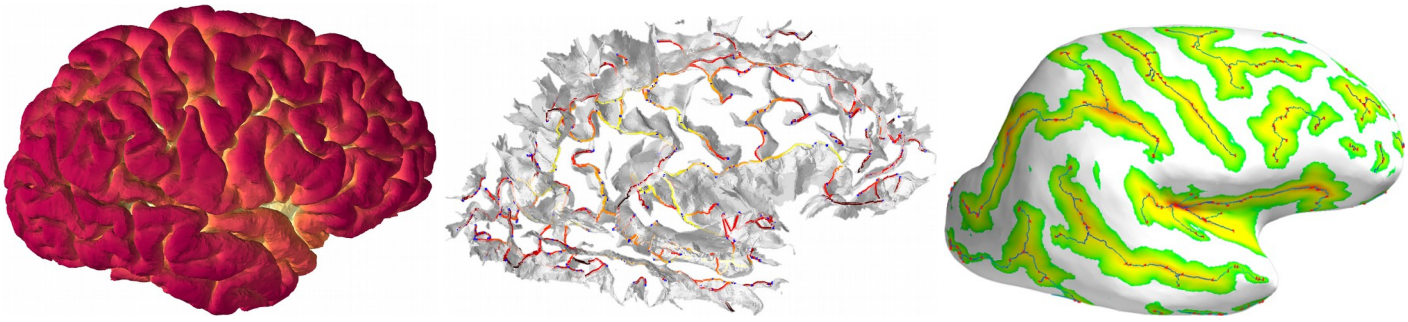



***Fig.1****: Classification results to distinguish remitters from non-remitters. The gray histogram denotes the distribution of chance performance (null distribution) from a permutation test. The red line depicts the performance of the classifier as calculated by average f1 score (the geometric average of precision and recall, or sensitivity). Greater f1 scores indicate better performance and the classifier is performing significantly better than chance:*

*average f1 score =* ***0.79****,* $p =$ ***0.02***

***Aim 1: Extract and identify more structural MRI-based features and shape analysis measures***
We propose to refine algorithms we are currently developing to extract more structural MRI-based features related to folds in the surface of a brain (**Figs. 2 and 3**): sulci, medial surfaces, and pits, in addition to fundi (input consists of a surface mesh in VTK format (www.vtk.org) from third-party software such as FreeSurfer[14] or BrainVISA[15]).



***a*** ***b*** ***c***

***Fig.2****: Feature extraction: (a) depth map of a brain surface (right hemisphere); (b) sulci with fundi (curves colored by their depth values) and pits (blue dots indicating local depressions); medial surfaces are constructed within these folds starting from the fundi; (c) inflated surface with sulci and fundi (red curves connecting vertices of maximal depth via a minimum spanning tree algorithm).*

To compare features across brains, they must correspond to each other. Currently we compare whole features, which can lead to poor matches when features are connected to each other in one brain and not in another. We propose to identify *feature segments* instead. First we will assign labels to all of the vertices in the cortical surface (see below), then assign each vertex of each feature the nearest label boundary. We will then segment features into clusters of vertices with the same nearest label boundary. These feature segments will serve as our features.

To label a subject brain image for segmenting the features, we will register multiple atlases to the subject[16] via an optimal average template[17], then combine the labels in the subject. Each of our 101 atlases is a manually labeled T1-weighted brain image from a publicly available data set, and we have constructed optimal

average templates by iteratively coregistering the brain images to each other. For assigning subcortical labels to EMBARC data, we will use volume affine and nonlinear registration (ANTS[18,10,11]) via a volume template. For assigning cortical labels to EMBARC data, we will use surface nonlinear registration (FreeSurfer[19,11]) via a surface template. Each subject would only need to undergo a single registration to its template, and with the inverse of the resulting transform, all atlas label sets would be transformed to the subject. Finally, to combine all of the label sets in the subject, a majority vote rule[13] will decide on a single label per voxel/vertex in the subject, accompanied by a probability value for that label.

For each point on a sulcus, including points of the fundi or pits, we currently compute curvature, convexity, cortical thickness, and depth[20]. For features such as sulci, medial surfaces, and fundus segments, we also compute geometric quantities such as area or length, moment invariants, and propose to compute spectral quantities using the Laplace-Beltrami operator[21] (**Fig. 4**).

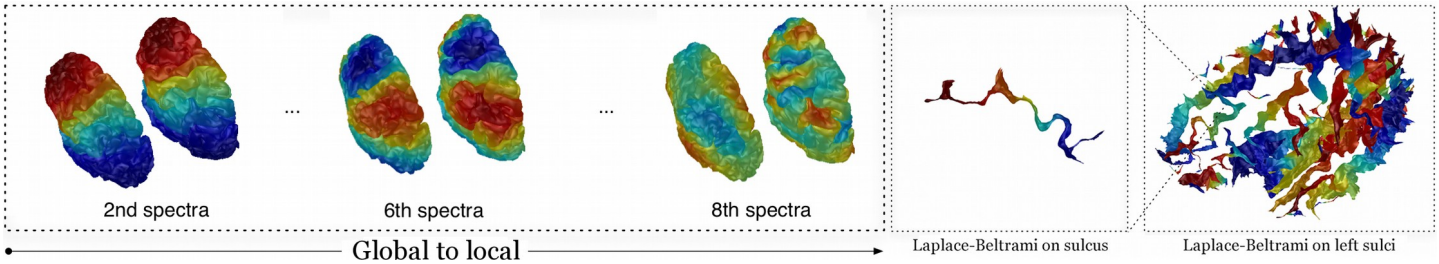



***Fig.4****: Laplace-Beltrami spectral shape analysis on whole hemispheres and on sulcal folds*

***Aim 2: Evaluate shape measures as possible biomarkers***

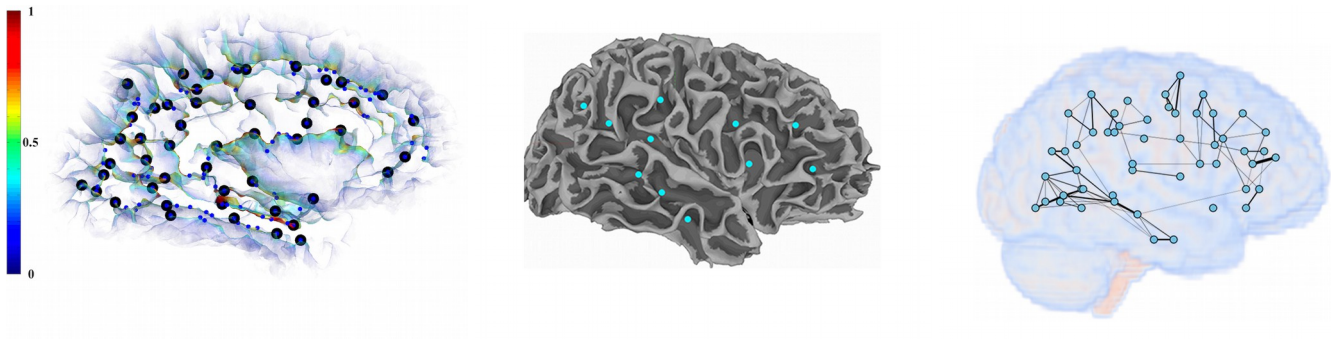
Based on the results of our pilot study, we will investigate the use our shape analysis and graph analysis measures (queried from our online shape analysis database, see below) as "learning features" for pattern classification (remission/treatment response prediction). We will use the extra Trees machine learning algorithm[24], an improvement on the widely used Random Forests algorithm[25]. The main benefits of using such decision tree-based algorithms over approaches such as support vector machines are their robustness to noise and their explicit determination of feature importance. Determining feature importance is crucial to understanding any classification results in terms of biological characteristics (e.g. brain regions, sulcal landmarks, etc.). Thus, this approach provides a mechanism to both evaluate and determine possible biomarkers of treatment remission and treatment response prediction and compare with gold standard psychiatric treatment. These methods and others are all available in the Python machine learning library scikit-learn (scikit-learn.org), a software package for which our consultant Dr. Ghosh is a contributor.

***Aim 3: Make our software fully open source, well documented, and freely available***

To ensure that our methods are accessible to anyone to extract and analyze features from EMBARC and other MRI data, our software will be fully open source and freely available with a liberal Apache 2.0 license. This includes not only our feature analysis algorithms, but our entire neuroinformatics framework as well. To store our feature graphs (see below) and query them by node and edge properties, we will make further use of OrientDB's (http://www.orientechnologies.com/orient-db.htm) noSQL database using a graph-based data model as opposed to a standard relational database. This will allow our feature database to be flexible enough to accommodate changing data and knowledge representations, to naturally represent and store connected and semi-structured data, and to support large-scale storage while also exploiting the power of graph inferences to perform feature analyses in populations.

***Exploratory Aim 1: Relate features to one another as multimodal graphs***

Our structural MRI-based features are nested (pits in fundi on medial surfaces within sulci) and therefore may be represented as a graph. The features may also form larger graphs by connections among them according to dMRI and rs-fMRI connectivity. NiPype software pipelines[22] will process rs-fMRI connectivity and dMRI probabilistic tractography (using Camino, http://cmic.cs.ucl.ac.uk/camino/). The shape measures above would serve as node properties in the graphs and graph analysis measures would characterize the graphs as a whole[23].




**a** **b** **c**

***Fig.3****: (a) Sulcal pits on an uninflated cortical surface of a healthy subject. Color indicates likelihood value (high values are red and opaque, low values are blue and less opaque). Blue circles represent pit candidates and black circles represent extracted pits. (b) Gray/white matter surface (flipped left lateral view) of a patient with depression, with visible sulcal pits (derived with [1]) in cyan. (c) dMRI connectivity graph for the same patient. Each edge indicates a connection probability >0.01 between two pits (using FSL).*

## Hypotheses

In addition to our overarching hypothesis that feature-based shape analysis will help to characterize the biology of treatment response for an individual, we have specific hypotheses related to the supplement:

***Aims 1 and 2:*** Structural features with higher shape analysis measures such as deeper fundi and stronger dMRI or

rs-fMRI connectivity among features 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.

***Exploratory Aim 1:*** Multimodal biomarkers integrate complementary information from multiple modalities, and their combined use will improve the efficacy of our biomarkers over those derived from unimodal data.

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