SPECIFIC AIMS

The largest clinical trial of major depressive disorder (MDD) ever conducted, STAR*D, indicates that two-thirds of patients treated with a first-step antidepressant do not achieve remission of symptoms [33]. Depression is a heterogeneous condition whose biological endophenotypes are difficult to categorize and therefore difficult to tailor treatment for. More robust and specific biomarkers of depression that can distinguish these endophenotypes would allow for more effective psychiatric treatment and prediction of treatment outcome. Researchers have recently reported prediction of major depressive disorder (MDD) severity measures from brain grey matter volumes of individual magnetic resonance imaging (MRI) scans [23]. Other anatomical measures derived from neuroimaging such as cortical thickness and gyrification index have been used to characterize depression [24, 22]. To our knowledge, however, no one has attempted to clinically diagnose or predict any mental disorder, including depression, based on the folding pattern of the brain, which is thought to be implicated in the pattern of brain wiring and in heritable and developmental constraints.

Our hypothesis is that differences in the folding pattern of a brain can provide biomarkers for depression. The difficulty in testing this hypothesis is that there is no established way to rigorously identify or compare the folding patterns across brains in a detailed way, let alone to transition one pattern into another to elucidate differences across brains or across time. And any anatomical differences that could be attributable to depression are masked by the great natural variation that exists across brains. Therefore, to find biomarkers that distinguish endophenotypes of depression, we need to first catalog this natural variation and variation within categories of depressed patients. Then we need to establish a means by which we can compare folding patterns across brains.

To this end we propose to introduce automated and robust algorithms for extracting, formally depicting, and quantifying the shapes of folding patterns of the brain in order to target differences related to inter-individual variability, pathology, development, or degeneration. We will show that the automated brain feature extraction and anatomical labeling open source software infrastructure that we have built, called Mindboggle (www.mindboggle.info), is uniquely suited to the development of such algorithms. Cataloging variations in the folding pattern of the human brain will permit researchers to situate an individual's brain pattern within the distribution of possible patterns that characterize healthy conditions and depression. To identify folding pattern biomarkers of depression we will pursue the following goals:

Aim 1: To catalog the most prominent variants of brain folding patterns in healthy and depressed individuals, we will use the Mindboggle software and anatomical database under development by the P.I. to automate extraction and identification of anatomical features such as sulcal fundi from hundreds of MRIs and depict each folding pattern as a graph.

Aim 2: To generate a visual representation of a single or multiple brain graphs (Aim 1) that can be interpreted by a non-neuroscientist or clinician, we will automatically construct an intuitive tree diagram that will enable one to visually pinpoint differences in anatomy across individuals or groups of individuals.

Aim 3: To determine which features of a folding pattern act as diagnostic and predictive biomarkers of MDD, we will visually and quantitatively assess differences (Aim 2) across healthy, remitter, and nonremitter MDD populations.

By enabling researchers to explore and analyze individual and group brain folding patterns, the proposed coherent and comprehensive software interface will aid researchers in their search for biomarkers of depression and other mental disorders.

RESEARCH STRATEGY

1 Significance

Depression is a heterogeneous condition whose biological endophenotypes are difficult to categorize and therefore difficult to tailor treatment for. More robust and specific biomarkers of depression that can distinguish these endophenotypes would allow for more effective psychiatric treatment and prediction of treatment outcome. Researchers have recently reported prediction of major depressive disorder (MDD) severity measures from brain grey matter volumes of individual magnetic resonance imaging (MRI) scans [23]. Other anatomical measures derived from neuroimaging such as cortical thickness and gyrification index have been used to characterize depression [24, 22].

To our knowledge, however, no one has attempted to clinically diagnose or predict any mental disorder, including depression, based on the folding pattern of the brain, which is thought to be implicated in the pattern of brain wiring and in heritable and developmental constraints. There is recent evidence supporting developmental timing of differential cortical growth [35] and heritable aspects to cortical folding [6, 5, 27, 2]. Given this and heritable changes in cortical folding associated with disorders [31, 8], including for example schizophrenia [29, 9, 32], Williams syndrome [34], epilepsy [7], and bipolar disorder [24], we expect that such a tool will be applied much more broadly than the research we are proposing here.

Our hypothesis is that differences in the folding pattern of a brain can provide biomarkers for depression. This section outlines the primary problems with conventional brain imaging methods for finding biomarkers of mental disorders such as MDD and outlines a new and unique software framework developed by the P.I. that we will use to find brain folding feature-based biomarkers of MDD.

Problems with conventional imaging methods for finding biomarkers of mental disorders

Clinical diagnosis or prediction of treatment outcome for a mental disorder demands that consistent differences be found between a group of individuals with and without the disorder. If these differences are to be detected in brain images, they must be located in corresponding regions across the brains. To establish correspondences across brain images, scientists ubiquitously co-register the images with each other, usually via a template image. However, registering makes three primary assumptions that compromise the search for individual or group differences: 1) Where two images are similar, their anatomical location is the same. However, similar looking portions of two images may represent different anatomical regions. Conversely, two very different images with different underlying anatomy can be forced into alignment such that they appear identical. 2) If two points in one brain correspond to two points in another brain, the intervening points also match. However, there isn't a one-to-one, let alone continuous mapping of points across any two brains. 3) The template is representative of the group being studied. Because of the great variation across brains and across imaging centers, off-the-shelf templates are suspect, particularly when they are constructed from subjects with different demographics than those of interest to the researcher. Other factors that affect registration quality are often ignored. For example, the P.I. has demonstrated that registration algorithms vary widely in their accuracy [18] and even the best require removal of non-brain matter [1]. Our approach outlined below analyzes anatomical features independent of registration.

The challenge of treating Major Depressive Disorder (MDD) An example of a mental disorder that is in great need of a reliable biomarker is MDD. The largest clinical trial of MDD ever conducted, STAR*D, indicates that two-thirds of patients treated with a first-step antidepressant do not achieve remission of symptoms [33]. Furthermore, successive treatment steps lead to diminishing remission rates [28] and a large number of patients discontinue treatment prematurely due to side effects [33]. The trial and error method currently used in clinical practice often leads to repeated failures before an effective treatment is identified. Given the relative ineffectiveness of treatments and resulting practice of trial and error multiple treatment steps, there is an urgent need to identify factors to personalize treatment (i.e., markers that

maximize effectiveness and minimize the risk for toxicity). The development of biomarker predictors of antidepressant response languished after multiple candidates, most notably the dexamethasone suppression test (DST), proved to have inadequate prognostic clinical utility [10]. However, the emergence of new technologies in neuroimaging has sparked new interest in developing biomarkers that might predict antidepressant response. Because of limited understanding of the pathophysiology of MDD and the limited range of the mechanism of action of available antidepressants (monoaminergic uptake inhibition or receptor modulators), we are currently unable to match treatments to patients. In addition to having access to expertise, resources, and data related to MDD (details in the Approach section), we wish to focus on MDD because of its overwhelming impact on the health of Americans, as noted by the NIMH:

> Major Depressive Disorder is the leading cause of disability in the U.S. for ages 15-44 (http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_AnnexA.pdf)
>
> Major Depressive Disorder affects approximately 14.8 million American adults, or about 6.7% of the U.S. population age 18 and older (http://www.census.gov/popest/national/asrh/) [16].

Mindboggle features Our neuromarkers will be derived from an analysis of features extracted with the Mindboggle software (www.mindboggle.info), which automates anatomical labeling of human brain MR data. The original version was created by the P.I. and has been downloaded by users in over 20 countries. Publications describing Mindboggle (PMID: 15627570, 16202176) have been cited 37 times and downloaded many times (the latter has been accessed over 10,000 times from Biomed Central's website; they state that "overall statistics indicate that your article will have been accessed on PubMed Central a roughly equivalent number of times...").

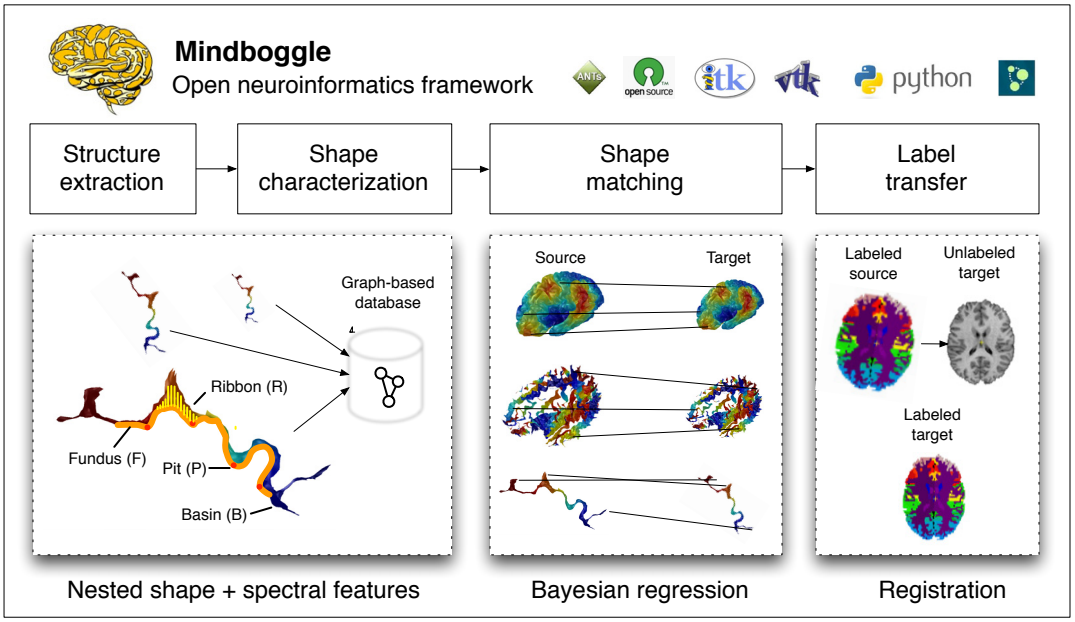


Fig. 1: Mindboggle schematic

The "Mindboggling Shape Analysis and Identification" grant (MH084029-03) which concludes in June of 2012 is currently addressing three needs of the neuroscience community: (a) manually labeled, gold standard brain image data from many individuals, (b) morphometric data to better understand variation of brain structures, and (c) accurate, consistent, and efficient software for automated anatomical labeling of neuroimaging data, in the form of new open source Mindboggle software. A Bayesian framework incorporates the shape information from (b) applied to the labeled brain images from (a) as priors, so that each application of Mindboggle to a new brain image uses these priors in its anatomical feature matching and label assignment.

We are currently extracting the following anatomical features from MRI data using our own algorithms: sulcal pits [13, 12, 21], sulcal fundi [15, 19], sulcal basins [25, 20], and spectral decompositions of the cortical surface based on the Laplace-Beltrami operator [26]. We will compute shape analysis measures (curvature, depth, area/volume, etc.) from each of the anatomical features, and each of the features is expected to have clinical relevance. For example, sulcal pits, which are referred to by different names such as sulcal roots, buried or annectant gyrii, and plis de passage, are particularly interesting because they may be well conserved structures formed early in development [4, 21], and are recently being used to characterize conditions such as polymicrogyria [11]. Fundi run along the depths of the folds, and like pits are thought to characterize early stages of morphological development [21], and therefore may exhibit abnormalities in neurodevelopmental and heritable disorders. Sulcal basins can be used to compute global and local gyrification indices, which have been used to characterize schizophrenia [3], and early-onset vs. intermediate-onset bipolar disorder as well as bipolar and unipolar depression [24, 22].

Our features are nested as follows: sulcal pits (points) lie along sulcal fundus curves, which lie along the depths of sulcal basins (Fig. 2 and 5a). Mindboggle stores the nested features as graphs in a Neo4j (neo4j.org) database that uses a graph-based data model as opposed to a standard relational database (Fig. 2). The primary advantage of nested, hierarchical features is that we can prioritize (or weight) the influence of the features on comparison, matching, or diagnosis in a level-sensitive manner. For example, if there were measurable differences between two populations at the level of the sulcal pits vs. at the level of the sulcal basins, or at the level of primary vs. secondary sulcal folds, this would inform us about how subtle or pathological the differences are. We could also 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.

Finally, Mindboggle identifies corresponding features across brains by quantifying features and collections of features using shape analysis measures. For each cortical surface mesh vertex within a sulcal basin, fundus or pit, Mindboggle will compute curvature, convexity, cortical thickness, and depth [15]; for basins and fundi, spectral quantities using the Laplace-Beltrami operator [26].

2 Innovation

- *We will introduce a completely new visualization and analysis method* for studying individual and group brain anatomy and their variation.
- *No one has ever used a network visualization approach to transform one individual's brain pattern into the pattern of another individual*, to the best of our knowledge.
- *Our approach focuses on individual variability* by matching, quantifiying, and visualizing an individual's data without resorting to conventional template-based registration methods.

3 Approach

3.1 Specific Aim 1: Catalog variations of nested anatomical features

To catalog the most prominent variants of brain folding patterns in healthy and depressed individuals, we will use the Mindboggle software and anatomical database under development by the P.I. to automate extraction and identification of anatomical features such as sulcal fundi from hundreds of MRIs and depict each folding pattern as a graph.

We will use Mindboggle's entire database of anatomical features (Fig. 2) to catalog the variations in the features across many brains. The database contains brains of healthy individuals, so to study variations in individuals with MDD, we will process MDD data from two different grants for which our Significant

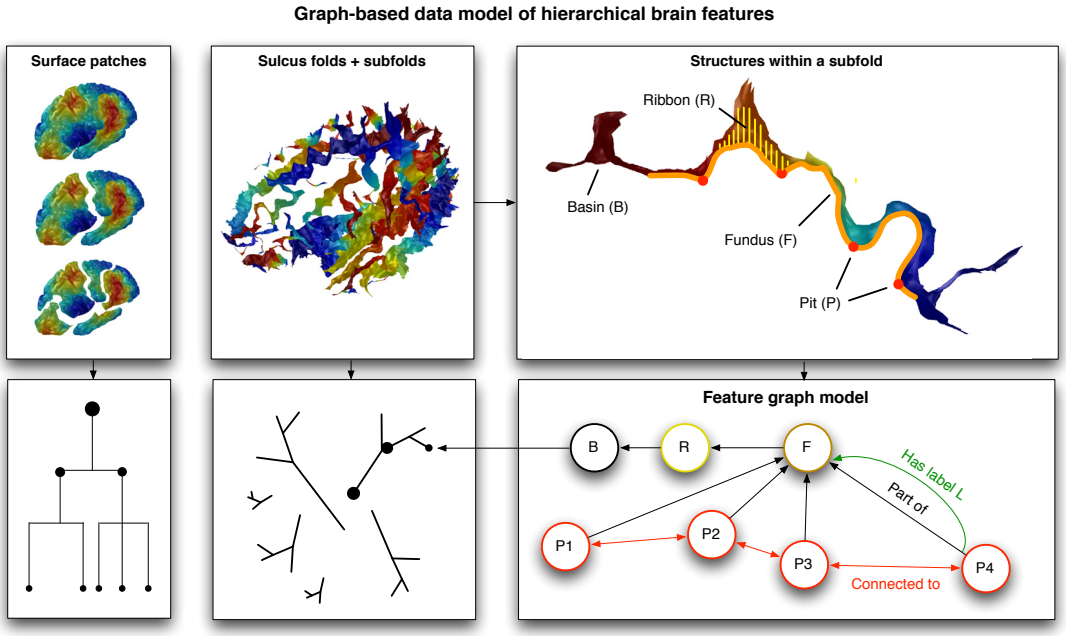


Fig. 2: Schematic of Mindboggle's graph-based database of anatomical features. Top: different structures derived from brain images: surface patches fragmented by application of the Laplace-Beltrami operator, sulcus folds and subfolds, and structures within a subfold. Bottom: schematic graph diagrams representing the relationships among the nested structures. Bottom right: examples of features as properties of edges (relationships such as Part of, Connected to, Has label) and nodes (geometric, shape, and spectral measures).

Contributor Ramin Parsey, a leading researcher of depression, is a P.I. (Arno Klein (P.I.) is also a Co-Investigator on the second). We will develop our methods on data from the first grant to determine the range of variation of our features, and will validate on data from the second (U01) grant to try and diagnose individuals with MDD and predict treatment outcome based on remitter/non-remitter data. The U01 is a large, multi-site project acquiring multimodal brain imaging data from 400 individuals, specifically designed to make data available to establish MDD biomarkers.
— "Biological Predictors of Response to Antidepressants" (MH074813)
— "Biosignature Discovery for Personalized Treatment of Depression" (1U01MH092250-01)

3.2 Specific Aim 2: Tree diagram representation of brain patterns

To generate a visual representation of a single or multiple brain graphs (Aim 1) that can be interpreted by a non-neuroscientist or clinician, we will automatically construct an intuitive tree diagram that will enable one to visually pinpoint differences in anatomy across individuals or groups of individuals.

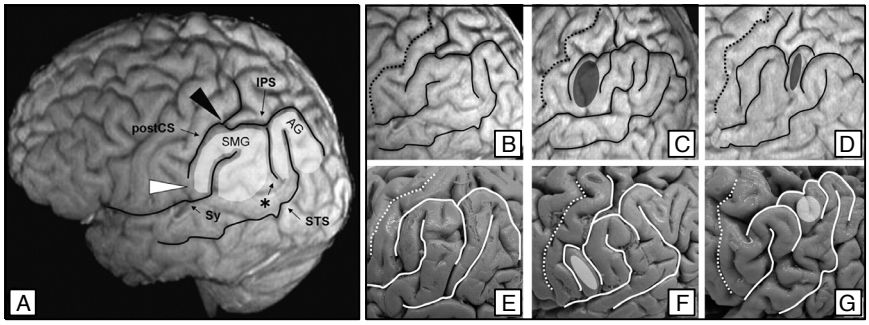


Fig. 3: Example of natural morphological variability: left inferior parietal lobule (IPL; figure from [17]). (A-D) are MRI data and (E-G) are post-mortem specimens. (A) IPL is highlighted and folds are outlined. (B,E) Typical folding pattern. (C,F) PreSMG pattern: an additional gyrus (ellipse) lies between postCS and SMG. (D,G) PreAG pattern: an additional gyrus (ellipse) lies between SMG and AG.
[SMG: supramarginal gyrus; AG: angular gyrus; postCS: postcentral sulcus; IPS: intraparietal sulcus; Sy: Sylvian fissure, STS: superior temporal sulcus; *sulcus intermedius primus]

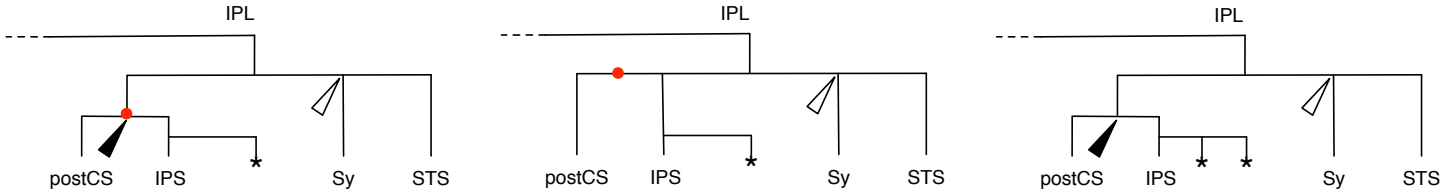


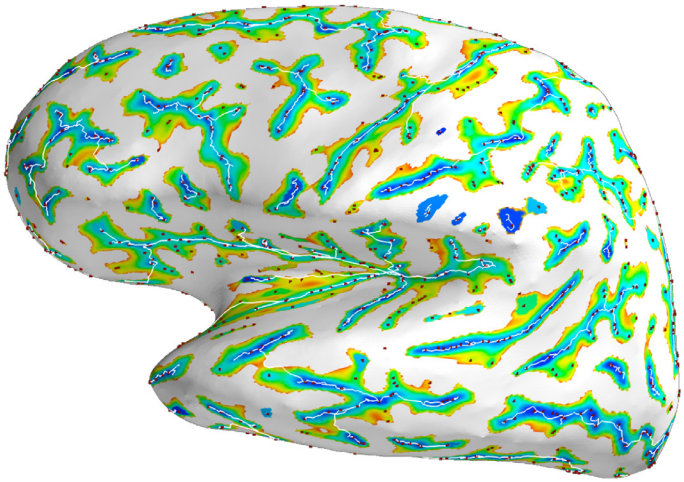
Fig. 4: These three diagrams correspond to the three folding patterns in Figure 3 (left to right): typical, PreSMG, and PreAG. Red dots indicate a critical node that distinguishes the typical and PreSMG folding patterns.

We will represent a given brain's folding pattern by a hierarchical graph and visually represent this graph as a tree diagram. As a very simple example focusing on the exterior of one region of the brain, in Figure 4, we show three simple tree diagrams corresponding to the three folding patterns in Figure 3. The left two diagrams are distinguished by the presence or absence of a single branch (red dots), indicating a transition point in the tree diagram corresponding to a critical point in development (whether or not the postCS connects with the anterior end of the IPS). This critical node in the tree diagram can be removed to map the typical folding pattern (left) to the PreSMG pattern (middle). Likewise, the addition of a single node to the leftmost diagram will produce the rightmost diagram. To compare topologically different graphs, we will implement the basic transformations between graphs that have been described in the context of constructing Reeb graphs [14, 30].

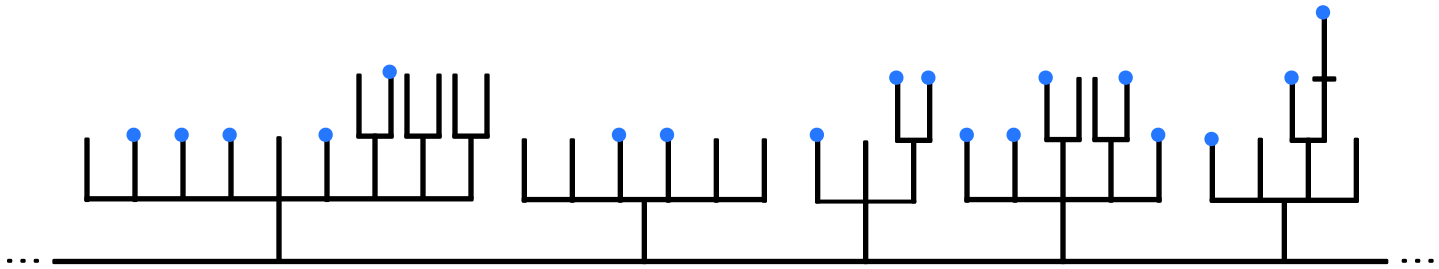
3.3 Specific Aim 3: Application to major depressive disorder data

To determine which features of a folding pattern act as diagnostic and predictive biomarkers of MDD, we will visually and quantitatively assess differences (Aim 2) across healthy, remitter, and nonremitter MDD populations.

For this aim we will combine the different tree diagrams generated from all of the brain data in the Mindboggle anatomical database (Fig. 2) as well as from all of our MDD data (3.1) into a single, multi-brain tree diagram. Similar individuals are expected to have similar trees, and it will be clearly apparent when two anatomies differ by differences in their schematic representation. For example, visually comparing a given sulcus in 100 brains is untenable, even if it has only two subfolds. But if one were to schematically represent that sulcus as a root node in a tree diagram with two branches representing the two subfolds, then any deviations from this folding pattern would appear as extra or missing branches in the tree diagram. If



(a) Mindboggle-extracted sulcal basins (colorful patches), fundi (white curves), and pits (red dots) on an inflated brain surface. The basins are colored by curvature (blue indicates high curvature).



(b) Tree diagram of a few Mindboggle-extracted fundi in the brain above, with blue dots indicating fundus branches with sulcal pits.

Fig. 5: Mindboggle features and schematic diagram

one then arranged the 100 schematics as frames in a movie or in a 3-D slice stack, one could very quickly see any differences among them. If a portion of the frames or slice-stack were generated from healthy controls and the remaining portion from populations with MDD, then this visual comparison could guide one to structures implicated in the different conditions.

We will build on top of Mindboggle's web browser-based webgl interface to include the individual and collective tree diagrams, and interactive selection and highlighting of branches and branch points to reference the corresponding individual brains and populations of brains. By enabling researchers to visually explore and assess brain folding variation across individuals in an elegant and efficient interactive software interface, we will provide a means of finding brain folding biomarkers of depression. We will measure success by diagnostic and prognostic accuracy compared with gold standard psychiatric evaluations. If the diagnosis and prediction attempts fail, our alternatives would include applying our methods to other clinical data and to simulated data (to evaluate sensitivity and robustness under controlled conditions).

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