Chapter 1: Introduction

In the past two decades, functional magnetic resonance imaging, hereafter fMRI, has been extensively utilized to understand various mysteries related to the brain. This technology has enabled scientists to map physical and cognitive actions to different regions responsible within the brain. It has been used to study the effects of using alcohol, smoking and drug abuse, effects of increasing age, gender, and demographic associations. Also, the development cycle of the brain, from infancy to adulthood has been investigated through longitudinal studies on the same set of individuals. This has facilitated our understanding of the brain and some of the most impacting factors that govern its development. However, the primary area of research that continues to profoundly depend on fMRI has been classification of various neurodegenerative disorders through the use of imaging biomarkers. A considerable fraction of the world population is affected by disorders such as schizophrenia, bipolar personality disorder, autism and so on. Through the combined use of advanced classification methods and fMRI, it is now possible for clinicians to identify brain regions that show significant differences, based on activation patterns to certain audio and visual stimuli, between patients and healthy individuals. In addition, fMRI is being utilized to enable examination of joint information between tasks that probe different functional domains in patients and healthy controls. For example, findings show that interesting relationships exist between brain at rest and brain at task for the same set of subjects [1, 2]. In addition to fMRI, other brain imaging modalities such as diffusion tensor imaging (DTI) and structural MRI (sMRI) are being jointly utilized to investigate similarities and differences in function and structure of the brain.

Since the results from first Functional Magnetic Resonance Imaging (fMRI) human-based studies were reported in 1992 by two different groups [4, 5], a plethora of research has emerged using fMRI, revealing the cornerstones of everything from motor and sensory processes to foundations of social cognition in humans. A variety of signal processing algorithms are sequentially applied to the imaging data in order to extract indirect measurements of neuronal activity within the brain. These algorithms can be broadly classified in to three categories: (1) Reconstruction, (2)

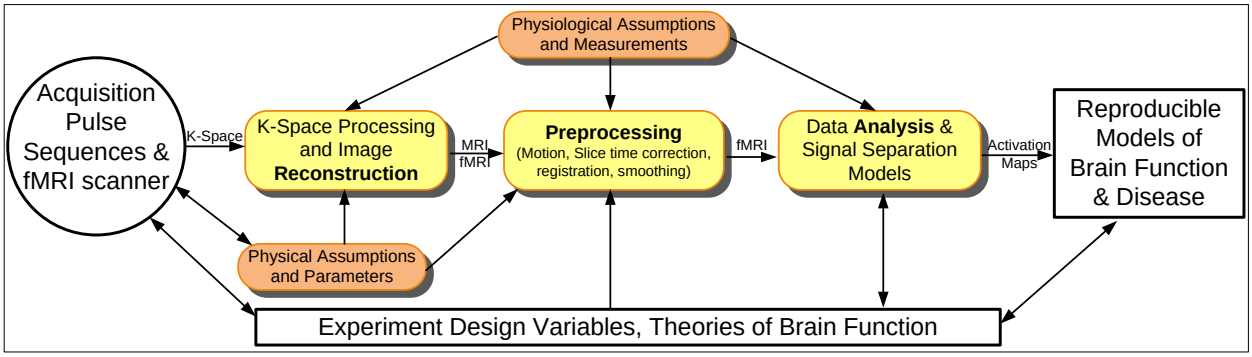

Figure 1.1: A schematic illustration of the data flow through fMRI processing pipeline comprised of following steps after the acquisition of raw k-space data: 1) Computation of magnitude and phase images followed by **Reconstruction** using inverse Fourier transform; 2) **Preprocessing** (motion correction, registration etc.); 3) Data **Analysis** to generate activation maps also defined as statistical parametric images (SPI) in [3].

Preprocessing, and (3) Analysis. The schematic shown in Figure 1.1, first summarized by [3], depicts various relationships between numerous steps involved in fMRI acquisition to processing to forming models for brain function. All three steps are strongly associated with one or more type of assumptions that influence the choice of methods used to perform these operations. These assumptions, independently or collectively, have varying degree of impact on the final results and inference. The purpose of this thesis is - a) to understand, compare and question the applicability of various fMRI image preprocessing pipelines in use today and, b) to present new algorithms that, when used independently or together, can compensate for some of the irregularities introduced in the data and reveal additional information within the data, leading to improvement in detection sensitivity of activation patterns.

1.1 What is fMRI?

Functional brain imaging is widely being used to enhance identification of neurological disorders such as schizophrenia, psychosis, and bipolar personality disorder that are currently diagnosed on the basis of patients' self reported experiences and observed behavior. A type of specialized imaging technique known as functional MRI (fMRI) is used to measure indirect level of brain activity associated with a physical or mental action. Intuitively, brain activity refers to transfer

of electrical and chemical energy between neurons in different parts of the brain. However, fMRI measures changes in deoxy-hemoglobin concentrations in nearby (to neurons) blood vessels, this is known as blood-oxygen-level-dependent or BOLD activity.

The neurovascular linkage between networks of neurons and blood vessels [6] results in exchange of energy that further causes change in oxygenated hemoglobin. BOLD activations are considered an acceptable indicator of *bundled* neural activity by scientists as the spatial resolution of fMRI images is many orders greater than the size of a neuron. However, fMRI can help decipher intensity and boundaries of simultaneous activity across different brain regions, thus making such recordings a viable measure to study and label underlying relationships that link complex external stimuli to corresponding brain functions.

During an fMRI experiment, a subject is asked to perform a task, e.g. pressing a button, while the MRI scanner records the BOLD changes within the brain. Several volumetric images of brain are acquired using a rapid pulse sequence firing technique known as echo-planar imaging (EPI) [6].

1.2 Preprocessing: An Imperative Requirement

The pivotal role of preprocessing steps in the fMRI analysis is evident from its central position seen in Figure 1.1. These algorithms interact with almost every decision made in designing, performing and analyzing results from an fMRI experiment. In addition, the theories of brain function and disease determine the experimental design variables (event-related, block design or both), which in turn guide the choice of scanner pulse sequences. Independent of these attributes, the field strength of the scanner governs the contrast-to-noise ratio (CNR) of the resulting images. Higher field strength (measure in Tesla (1.5T, 3T etc.)) results in higher CNR. However, this advantage is somewhat diminished by higher sensitivity to physiological noise, greater artifacts at air-tissue boundaries, and reduced decay times, thus making choice of preprocessing methods a pivotal decision in fMRI analysis [3]. With the ever-expanding collection of algorithms and software tools for preprocessing, one of the primary challenges facing researchers and clinicians is *How to choose from among this plethora of possible pipelines?*. The most convenient and widely adopted resolution for

this concern is based on a method's availability, familiarity, and ease of use. Usually, this may not be a medically or scientifically robust choice.

The functional properties of the brain stored in the form of fMRI data need to be analyzed by appropriate statistical methods. Due to the inherent system properties of the techniques used for acquiring fMRI, the resulting images are of low spatial resolution and have little anatomical contrast in addition to suffering from geometric (head motion) and intensity distortions (magnetic field homogeneity). These limitations may be tolerable when investigating fMRI data for a single subject. However, in many experiments, researchers want to address two important questions:

- *How does BOLD activity map (spatially) on to the corresponding anatomical brain regions?*
- *How consistent (or different) is this mapping across a sample population (healthy or patients)?*

Both these questions are substantially dependent on the the spatial quality of fMRI images that are tested for activity which in turn depends on the SNR of the data. Thus, it becomes imperative to map the data onto relatively high resolution and high contrast structural images through co-registration of fMRI and sMRI data from the same subject. Nevertheless, there remains a problem of comparing activity across individuals within a study or across different studies. There is a wide variation in size, shape, orientation, and gyral anatomy of the brain across different individuals. Therefore, inter-subject comparisons are performed after warping each subject's data to a common coordinate space using a brain template so that their brains at least have the same size and shape as all of the others. This process is known as spatial normalization, and is the first of the last two preprocessing stages prior to statistical analysis of fMRI.

The last stage in fMRI preprocessing is spatial smoothing and is typically the most common data preparation step in a variety of fMRI analysis pipelines used worldwide. Clinical decisions based on BOLD activation patterns are highly influenced by the spatial quality and signal-to-noise-ratio (SNR) of fMRI images. If the image is extremely noisy, some of most intricate details associated with the BOLD signal may get obscured or even misrepresented to a great extent during the statistical analysis. As a solution, spatial filtering is done to improve the functional SNR, reduce apparent noise, and increase the validity of comparisons across subjects. Prior to spatial

smoothing, some studies also apply temporal filtering to reduce scanner drift and physiological noise.

Apart from registration and smoothing, a number of other steps are common amongst preprocessing pipelines for fMRI. These include removing individual slice artifacts due to timing errors and radio frequency spikes; slice timing correction due to a variety of reasons explained in later chapters.

1.3 Motivation for Change

An ever-expanding collection of techniques and software tools is available to the functional neuroimaging community to assemble and apply different preprocessing pipelines to fMRI data sets [3]. Neuroimaging studies often comprise $10 - 20$ or more subjects who undergo an experimental paradigm. The initial few preprocessing steps operate on temporal information stored in a single dimension whereas later stages such as registration, spatial normalization and smoothing utilize complex 3-D brain structures. Thus, the validation of this class of spatial algorithms is not a trivial task due to a number of questions that consequently reveal commonly ignored limitations in context to reliability and reproducibility.

1.3.1 Template-to-Structure Correspondence

Brain templates are normally used as references for mapping different brains in a group analysis study. Normally, a brain template is constructed by averaging images that are premapped to a standard coordinate space. There are two main reasons to use brain templates: 1) to obtain a standard basis for functional activation labeling; 2) to compensate for anatomical variations across subjects. The role of brain atlases and templates has been thoroughly reviewed by some of the most prominent studies in this field such as [7, 8]. However, *there is substantial doubt as to whether there exists a perfect correspondence between a subject's anatomical image and a template.* Numerous studies of anatomical variability in normal [9, 10] and lesioned brains [11, 12] have suggested that alternate methods be considered. Techniques for construction and application of

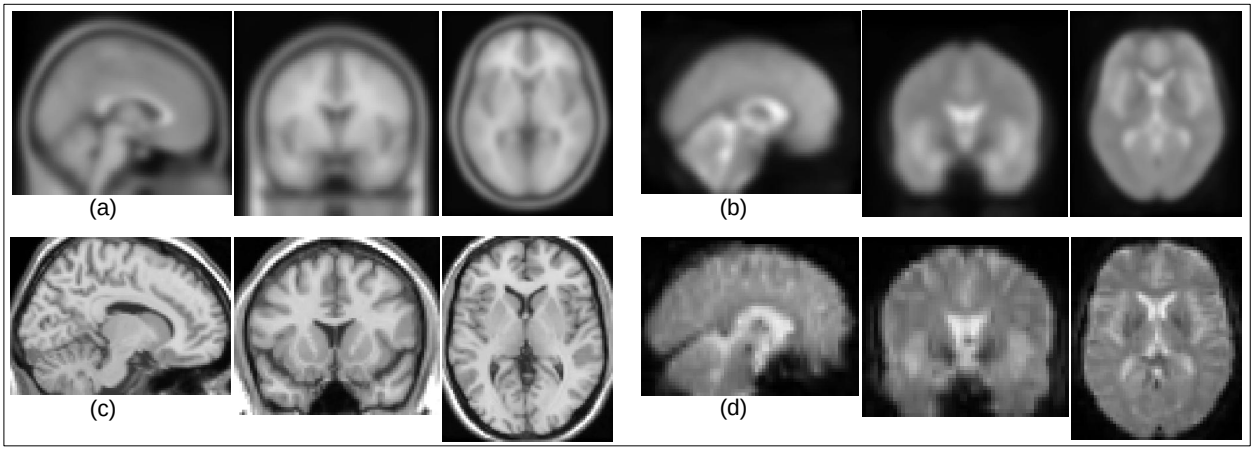

Figure 1.2: **Contrast and CNR Comparison:** MNI-305 standard average templates as obtained from the SPM5 library are compared side-by-side with single subject T1 and EPI images: (a) $T1$ contrast template; (b) EPI template; (c) single subject T1 image; (d) single subject EPI image. These images are all mapped to the Talairach coordinates and correspond to the same physical location in the brain. The contrast difference around the ventricle regions is most notable across all four images. The templates ((a)-(b)) are more blurred than their single-subject counterparts ((c)-(d)) due to the averaging effect. Each image is arranged as Sagittal (Left), Coronal (Center) and Axial (Right) geometries.

brain templates depending on class of subjects under investigation, such as disease-specific atlases, are a viable option to study the differences between diseased and normal populations [13]. The question raised by many researchers is even if such correspondence does exist with minimal errors in certain specific studies, *how do we measure the accuracy of the transformation estimate*? Several studies have shown that residual variability is of the order of several millimeters [14] with an average isotropic voxel's size $\approx$ $27mm^3$.

In a series of studies, the Montreal Neurological Institute (MNI) created a brain template called MNI305 (see Figure 1.2) by averaging a large number of normal MRI brain images [15]. The International Consortium for Brain Mapping (ICBM) adopted the MNI template by registering 152 normal brains to the MNI template and named the new template $ICBM152$ [16]. These are the two most commonly used templates for spatial normalization of fMRI data sets and the have been incorporated in to several computer analysis packages. These standard *templates* are representative of the brain size and shape, whereas the cortical structures are difficult to identify and blurred in these atlases due to the obvious low pass filtering effect caused by averaging. The classical brain

Figure 1.3: **Templates vs Atlas:** INSERT A FIGURE TO SHOW DIFFERENCE BETWEEN TEMPLATES AND ATLAS. ATLAS will be psuedolabeled images WFU-Pick Atlas, Talairach etc.. Templates will have images from various labeled atlases.

atlas (anatomical) of Talairach and Tournoux [17] is universally used as an anatomical reference standard by the neuroimaging community. Note that, the results from analysis done post-mapping (using $ICBM152$ or $MNI305$) are reported in the Talairach coordinate system.

Given the limited power of Talairach transformation in accounting for anatomical variability across different brains, the spatial locations in template (from MNI or ICBM) and atlas space do not exactly overlap, the most extreme case being the temporal lobes in MNI space extending $10mm$ below the temporal lobes in Talairach brain [7]. As a remedy, an affine transformation to improve the registration between the two spaces [18] and is used intensively used by those who follow the aforementioned approach for reporting results. Nevertheless, the inaccuracies introduced due to the differences between the template used and the reference coordinate space, clearly pose substantial re-alignment requirements.

1.3.2 Function-to-Structure Correspondence

Intrinsically, an exact correspondence does exist between functional and anatomical images of a subject, but usually these are not visible when both modalities are compared side-by-side. Factors such as spatial resolution, signal-to-noise ratio (SNR), difference in sources of contrast, cause the brain structures to appear vague in fMRI images as illustrated in Figure 1.2.

Current methods for anatomical alignment rely on anatomical features that are identified through high-resolution structural MRI scans. However, a crucial precursor for developing models of brain organization and activity is to identify functional neuro-anatomical markers that assist in

realignment of boundaries corresponding to BOLD activity across various individuals in a population. A precision of less than $5 - 10mm$ in anatomical correspondence between structural (MRI) and functional images (fMRI) is usually difficult to achieve due to the distortions of echo-planar imaging (EPI) [19]. For current methods, this correspondence problem between structural and functional data is largely overlooked especially in the case of spatial normalization where the data is mapped to a template-based coordinate space. So the question arises, even if we can construct a viable structural template, how accurate will its correspondence be to functional data, that is the domain of interest in context to the present analysis. We discuss the different classes of currently used methods for establishing structure-to-function correspondence and propose a new technique for functional normalization in the upcoming chapters.

1.3.3 Inter-Subject Variability

There is enough evidence to support the fact that the size, shape, and position of brain structures are anatomically non-uniform for individuals and show significant differences associated with race, age, gender, or state of healthiness [20, 11, 21, 7, 22, 23, 24, 25, 26, 27]. However, these structural differences do not account for any functional variability across subjects. More work is required to further develop inter-subject registration and spatial normalization techniques for group-based fMRI studies. During the past decade, methods targeting group-analysis such as using study-specific templates [28, 29], and cross-task functional re-alignment [27] are gaining popularity and show substantial promise in reducing post-analysis artifacts due to inter-subject morphometric differences and even reveal new and improved statistical relationships across different regions of the brain. These studies can be seen as compelling evidence that anatomical variations within a group as well as differences in scanners (sequences, other errors) used for acquisition of various templates or subjects' images can cause considerable spatial distortion when mapping data to a common co-ordinate space. Eventually, such distortions cause the statistics to change significantly, and lead to partially incorrect spatial maps showing patterns of cognitive activity.

One of the primary challenges researchers have repeatedly pointed out for future research is the effect of spatial normalization on functional maps in group studies. With the advent of MRI

systems that provide higher fMRI resolution and localization of brain activity, a parallel effort in advancing high resolution template construction and hybrid spatial normalization methods is called for. Identification of functional biomarkers signifying good health or disease at an individual level are being given prominent importance in studies which will eventually help in advancement of personalized drug discovery, patient-specific, and use of disease specific medicine.

1.3.4 Gaussian Smoothing: Brain is not Isotropic

Interestingly, the smoothing and spatial normalization steps rather share a very close relationship, specifically in terms of their sequential application within the preprocessing pipeline. The concerns raised in Sections 1.3.1-1.3.3 earlier have long been known, and have been discussed before by [30, 14] along with illustrative examples. The first and classical solution to address these has been to sacrifice the spatial resolution of fMRI to increase robustness against registration and normalization errors. The most commonly utilized method for this task is to smooth the fMRI image with full-width half-maximum volumetric Gaussian kernels [31]. It is not unusual to apply an 3-D $8-10mm$ smoothing kernel to fMRI datasets (with isotropic voxel size up to 3mm) before performing a group analysis.

Two straightforward implications of such an approach for smoothing can be realized as follows:

- *Isotropic smoothing kernels are not optimal for neuro-scientific observations since they do not necessarily address the underlying variations in shapes and sizes of the anatomical regions or the functional clusters.*

- *This method also overlooks the spatial variations across subjects. These differences may be subtle structurally, but due to the variability in genetic and epigenetic factors across subjects, functional variability plays a major role in group analysis as also depicted in [32].*

The Gaussian smoothing methodology is also widely applied as it suppresses high-frequency noise. Furthermore, it is simple to implement and most importantly increases the overall signal-to-noise ratio (SNR). The drawbacks of Gaussian smoothing in the signal domain include considerable

change in true intensity values (as a function of the size of the smoothing kernel), and the long-standing issue that the noise is averaged along with the signal. These effects make it more difficult to accurately separate signal and noise during the later stages of analysis, particularly when the noise is spatially or temporally varying. In addition to the above, the Gaussian smoothing approach suppresses the edge details and other medium-frequency information present in the original image.

1.4 Research Goals & Broader Impact

Neuroimaging researchers continue to pursue methods that may assist in overcoming the shortcomings discussed above. The goals of this doctoral study are to identify specific properties of existing spatial preprocessing methods and subsequent effects on the data, and develop new techniques that may tie together and help alleviate some of the undesirable effects of the normalization-smoothing pair applied just before analysis of fMRI data. In this thesis, an argument detailing the method and its need for function-specific templates and a novel normalization framework is presented. In addition, an adaptive wavelet-based denoising technique is proposed that proves to be a viable alternative to Gaussian smoothing. The wavelet-based method is exercised for its ability to address issues discussed above, specifically improving the specificity of activation contours and preserving the true shape of activations. This approach weaves in with our proposed functional normalization framework and provides a basis for answering questions raised above that mostly revolve around inter-subject variability and other problems relating group fMRI preprocessing pipelines. The contributions of this doctoral work are briefly listed and discussed as follows:

1. We present a framework for spatial normalization for a group of subjects by utilizing their intrinsic functional boundaries in contrast to other existing methods which use structure as a reference [33, 34]. We enable our framework by a method for constructing a functional template that represents default boundaries of various regions involved in performing various functions of the brain. This template can be modified to comprise one or more networks available from analysis of resting-state fMRI data. The number and class of networks depends on the nature of the cognitive task that the target data set corresponds to in addition to brain

regions activated during the task.

2. We developed a novel 3-D wavelet-based fMRI denoising framework to improve the quality of images while being able to get rid of the spatial noise [35, 36, 37]. This is a flexible smoothing method that is independent of its point of application, that is, it may be applied before or after spatial normalization. Our proposed technique is able to preserve the edges, and other spatial details within the brain images while maintaining the homogeneity of the original BOLD signal values across the brain. The denoising method has been repeatedly verified using simulated as well as real data and compared successfully against the currently used methods for denoising. The algorithm is available for download on the web as a MATLAB ®based software toolbox.

3. The third and final contribution of this work is a validation method to quantify the 3-D spatial shape of BOLD activity within the brain. This technique focuses on comparing two 3-D activation clusters based on shape, size and anatomical location finally resulting in a single number or metric that represents this difference. This metric utilizes slice-wise measurements of 3-D shape in order to create a metric for comparing two shapes. This algorithm has been validated on multiple group fMRI data sets and presented as a validation method in our recent work [35, 36, 37]. Other applications of this metric were also identified during its development such as understanding the spatial dynamics of brain activity during rest. This application is discussed with examples in later chapters. The metric is metric has been incorporated in to a MATLAB-based toolbox for ease of use and application.

1.5 Perspective

I hope this doctoral work will help alert researchers to important concerns regarding current preprocessing approaches in fMRI and help them to select the methods best suited for their research. Some of the pivotal features of this doctoral work that, in my opinion, may leave a lasting impact on the field of neuroimaging, specifically fMRI analysis, are listed below:

- Preprocessing of images substantially governs the outcome of fMRI analysis, with direct implications from the use of fMRI data for diagnosis and discerning brain function. With

better techniques available, diagnosis can be more specific and new unseen imaging biomarkers can be identified. The methods proposed in this thesis may help in reduction of false positives and improve the functional localization of brain activity.

- Methods developed in this work offer increased flexibility in terms of point of application of various preprocessing methods. For example, if smoothing is independent of its association with normalization, it may be applied at the beginning of preprocessing (before motion correction). This added flexibility, if validated with proper methods, can help remove other sources of noise that may have been amplified by other steps such as motion correction and realignment.

- The role of some unexplored regions in the brain that are obscured due to nonadaptive processing can be more clearly understood. Better functional localization of brain activity may reveal additional relationships between spatial dynamics across various sub-regions of an activation region. Undesired effects such as intensity leakage from inactive neighboring voxels may be reduced, thus improving the statistical significance of the active clusters and revealing relatively small regional activity that may have been averaged out before.

- Use of multiple states of the brain (at rest or during a cognitive task) can be used collectively to form a stronger foundation for understanding of a normal brain as well as that of a patient with certain neuro-development disorders.

- Shape Metric may assist in quantification of the spatial structure of activation maps and related variability within a group (subject-to-subject) or across groups (health-to-patient). Clustering subjects based on their similarity in shape of activation can provide powerful priors for data fusion (fMRI,EEG etc.) and subsequent analysis where subjects with largely different activations can be segregated from the fusion study and examined separately.

- Resting state dynamics of the human brain have been under increased investigation within the fMRI brain imaging community but are still not largely understood in terms of spatial modulations over smaller units of time. With the help of adaptive signal separation, spatial

activity corresponding tothe parcellated time axis can be compared based on shape and the amount of change in shape over time. Metrics proposed in this thesis can be used to investigate these dynamics in healthy controls, the patients and help to identify the region-specific relationships separating these two groups.

1.6 Organization

The rest of this document is organized as follows: WILL FOLLOW ONCE I ORGANIZE ALL THE CHAPTERS.

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