Advanced Magnetic Resonance Data Acquisition and Analysis for Neuroimaging

Susumu Mori, PhD,¹ Kenichi Oishi, MD, PhD,¹
Andreia Faria, MD, PhD,¹ Shoko Yoshida, MD,¹
Manisha Aggarwal, PhD,¹ Jiangyang Zhang, PhD,¹
and Michael I. Miller, PhD²

¹Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins University School of Medicine
Baltimore, Maryland

²Department of Biomedical Engineering
Johns Hopkins University School of Medicine
Baltimore, Maryland
**Introduction**

The two most influential factors in magnetic resonance imaging (MRI) are image resolution and contrast. Image resolution defines the ability of MRI to identify precise locations of magnetic resonance (MR) signals, which originate from protons of water molecules. Contrast relies on physical and chemical properties of water molecules. If we image water in a tube, all water molecules have similar properties and, therefore, the image would have no contrast; pixel intensities are homogeneous across the object. Usually, “advanced MRI” signifies a new way to enhance the resolution or to create a new contrast that can visualize locations of specific structures that otherwise could not be well defined. Such new techniques could be achieved by newer hardware, such as a stronger magnetic field or innovative pulse programming.

Since the end of 1980s, two types of new image contrasts were introduced and stimulated a considerable amount of research interests in neuroscience: These are functional MRI (fMRI) and diffusion tensor imaging (DTI). What is common to these two techniques is that they are generated from the “fourth dimension,” the first three dimensions being 3D anatomy. In fMRI, the fourth dimension is time; the same MRI is repeated for a period of time and signal intensity fluctuation is observed. Any brain regions where the signal fluctuation coincides with the time course of a task are considered task-activated sites. In DTI, the fourth dimension consists of multiple measurement orientations of molecular translational motions, from which areas with highly ordered structures (diffusion anisotropy) are delineated.

While various types of data acquisition techniques are being developed, equally important are image analysis techniques, which can harness the new biological information they provide. The analysis approach varies depending on the effect size. When the effect size is large (as in many clinical cases or mouse models with significant anatomical phenotypes), visual inspection can describe the pathology. As the effect size shrinks, however, quantitative measurements and statistical analysis become the key components of the study.

The advancements of data acquisition and analysis are often mutually dependent. In recent years, the importance of a “fifth dimension” has become widely recognized. That is, the fifth dimension integrates multiple MR contrasts (e.g., anatomical image, DTI, fMRI) or multiple modalities (e.g., spectroscopy, PET, CT, histology) and calls for yet newer image analysis approaches. This chapter introduces advanced MRI in the so-called fourth and fifth dimensions and demonstrates their application studies.

**Brain Development Studies**

For the new MRI technologies to be useful, they need to provide new anatomical or functional information that would otherwise not be accessible by conventional MRI. It has been well described that DTI can provide detailed white-matter anatomy information that is not appreciable by conventional MRI (Pierpaoli and Basser, 1996). In addition, DTI is known to provide richer anatomical information of premyelinated developing brains compared with conventional anatomical MRI, which relies on myelin content for the contrast generation (McKinstry et al., 2002; Neil et al., 2002, Hermoye et al., 2006).

![Figure 1. Comparison of various MR contrasts of a neonate brain. The bottom row shows a superimposed brain parcellation map. DWI, diffusion-weighted image; FA, fractional anisotropy map.](image-url)
In Figure 1, six different MR contrasts are compared of a human neonate brain. It can be seen that the internal capsule (one of the largest white matter bundles, indicated by yellow arrows) is most clearly appreciable in the DTI-derived fractional anisotropy (FA) and color-coded orientation maps. By combining the new and useful contrasts obtained by DTI with a microimaging technique, brain development can be studied in detail using various animal models.

Figure 2 shows a series of DTI-based color maps of fixed mouse embryo brains scanned at 24 h intervals (Mori et al., 2001). This type of high-resolution DTI has become possible owing to recent progress in microimaging technology, together with the availability of high-field magnets (Jiang and Johnson, 2011). Currently, image resolution of 50 μm or even higher is possible. In the embryonic stages, the white matter has not fully developed; nonetheless, many early neural structures have high diffusion anisotropy, and many structures are clearly appreciable.

**Brain Atlases**

If MR images have higher resolution and new powers of contrast to define a structure of interest, we can thus measure size or the region-specific MR contrast values, such as T1, T2, Trace, or FA, as shown in Figure 1. To perform such quantitative measurements, the first crucial step is to define the structural boundary, or a group of voxels, that belongs to the structure. For example, if we are interested in the size and FA of the internal capsule, we need to define it as a region of interest (ROI). (This can be also considered as one of the cross-subject image registration steps because the ROI defines corresponding voxels across subjects.)

Defining the ROI is not a straightforward task because there are multiple ways to define a structure in the brain. If the purpose of the study is to detect abnormal regions, we need prior knowledge in order to target the ROIs to such areas; unfortunately, very often the goal of MRI-based analysis is to identify abnormal areas and, therefore, we don’t have a priori knowledge. The defined ROI may miss the target, or the abnormal area could turn out to be only a portion of the ROI. If we define one ROI that includes the entire brain, however, we are sure that it contains putative abnormal areas, though it does not give us a location, and the sensitivity could be low.

At the other extreme, the smallest ROI we can define is a single voxel. In this case, we would need to identify the corresponding voxel of interest across all subjects: the basic concept of voxel-based analysis (Ashburner and Friston, 2000). In it, voxels of an entire brain have to be mapped to all voxels in the other brain. While this approach provides the maximum localization information (the highest granularity), the inaccuracy of voxel-to-voxel mapping and noisy information from each voxel often lead to low sensitivity. Therefore, we usually need to apply a spatial filter to average information from multiple voxels (granularity reduction).

The best granularity depends on the nature of the abnormality. Two commonly used filters are the isotropic Gaussian blurring filter and the structure-
Relationship of voxel-based to atlas-based analysis. Both techniques rely on voxel-to-voxel mapping using an image transformation tool such as linear or nonlinear transformation. The transformation renders all subject images as similar shapes, thereby registering the locations of corresponding voxels. Then voxel-by-voxel statistical analysis can be performed. For atlas-based analysis, a structural definition file such as White Matter Parcellation Map (WMPM) is needed, which is back-transferred to individual brains and parcellates them into multiple structures. LDDMM, Large Deformation Diffeomorphic Metric Mapping.

Applications of Quantitative Analysis
Figure 4 shows an application of atlas-based analysis to a mouse model of Huntington's disease. In it, the degree of brain atrophy is monitored longitudinally (Duan et al., 2008, Zhang et al., 2010). In this analysis, the brains were parcellated to more than 10 structures and their longitudinal volume changes monitored. The analysis clearly demonstrates the time courses of atrophy. Once this type of experiment model is established, it will provide an exciting opportunity to investigate the efficacy of various disease interventions.

Although atlas-based analysis can monitor anatomical changes of parcellated structures, reducing granularity could be a problem. For example, in Figure 4, the anatomical information of the entire cortex is reduced to one scalar: the volume. If there is regional heterogeneity of the atrophy pattern within the cortex, such information is degenerated. Also, depending on mutation, the atrophic cortical areas could differ, and this could be important information for understanding the disease's pathophysiology.

One could argue that to correct this lack of granularity, we could subsegment the cortex or perform the voxel-based analysis. However, the MRI might still lack anatomical contrasts within the cortex to provide finer localization information. In such a case, shape analysis is one way to retrieve the granularity from the atlas-based analysis results, as shown in Figure 5.

Multimodal Integration
When dealing with multiple images, such as T1, T2, DTI, and fMRI from each subject, the integrative analysis (fifth dimension) gives more power to detect abnormalities and distinguish abnormal populations from healthy subjects, rather than merely analyzing each image separately. This analysis, in turn, leads
Figure 4. Longitudinal volume measurements of mouse brains. T2-weighted images of wild-type (WT) and R6/2 mutant mice were obtained for 3–12 weeks, and the degree of brain atrophy was monitored. At each time point, the brains were automatically parcellated and the volume of each structure measured. The atrophy of two severely affected structures (striatum and neocortex) is demonstrated.

Figure 5. Shape analysis results of the neocortex from the data shown in Fig. 4. Regions with atrophy are indicated in red.
to better diagnosis or more sensitive methods for evaluating the efficacy of interventions.

One of the most difficult steps toward cross-modal integration is effecting spatial or structural registration across the modalities. For voxel-based analysis, all images need to be accurately registered even though each image has different resolution, contrast, head positions, and distortion. What is even more problematic is the sheer number of variables. If the images are registered to the MNI coordinates with $1 \times 1 \times 1$ mm resolution, each modality would have more than 1 million voxels, and each voxel has multimodal data (e.g., size, T1, T2, trace, FA, fMRI). Then, if one wants to correlate these data with patient functional status, one needs to introduce yet another information dimension.

Among these many dimensions, the reduction of the spatial dimension (granularity reduction) is the most effective approach. This is especially true for brain connectivity analysis, such as DTI-based anatomical connectivity and fMRI-based functional connectivity, in which the anatomical domain has to be squared ($N$ voxels$^2$). If we reduce the location information from 1 million voxels to 100 structures, for example, it would be a $10,000 \times$ reduction for location-based anatomical studies and $10,000^2$ for connectivity analysis. This reduction effectively converts the multimodal image data into a matrix with $100 \times$ [measured parameters] elements, as shown in Figure 6. This image–matrix conversion makes the data compatible with advanced statistical analysis, such as principal component analysis, linear discriminant analysis, and support vector machine analysis.

**Figure 6.** Examples of image–matrix conversion. Multiple MR images from each patient are simultaneously divided into pre-defined structures. (Currently the maximum structural definition in our atlas contains 241 structures.) For each structure, volume and signal intensities are quantified and compared with controls or among patients. For example, by measuring the degree of deviation from normal values (e.g., <3SD means three standard deviations smaller), the set of images is converted to a matrix that captures the anatomical features. T2, FA, and MD represent three types of image intensities. T2, T2-weighted images; FA: fractional anisotropy; GM, gray matter; MD, mean diffusivity; Vol., structural volumes; WM, white matter.
Figure 7 demonstrates an extension of the atlas-based analysis to the anatomical and functional connectivity study (Faria et al., 2012). The same parcellation map as for fMRI and DTI is applied to the resting state fMRI (rs-fMRI) and DTI in order to parcellate the brain into a common set of structures. The rs-fMRI identifies functionally connected parcels. Next, the same set of parcels can be used in DTI to define the tracts that connect these regions. In this way, the connectivity information can be reduced to a 241 × 240 matrix for both rs-fMRI and DTI, which are more manageable if one wants to quantitatively analyze population data.

Conclusion
As neuroimaging methods steadfastly advance, with higher spatial resolutions and new image contrasts, the amount of anatomical and functional information increases drastically. Currently, the bottleneck in neuroimaging studies has largely shifted to image analysis steps, in which it is necessary to extract useful information from huge anatomical dimensions. Thus, the advancement of data acquisition and analysis needs to evolve synergistically. In this chapter, several frontiers of neuroimage applications and importance of image analysis from multiple granularity levels have been demonstrated.

References


