

Chapter 2

Background

This chapter reviews the recent neuroimaging studies with a focus on the characterization of neurodegenerative disorders. These studies fall into four categories based on the primary outputs of these analyses, which correspond to the four layers in the neuroimaging computing architecture, as illustrated in Fig. 2.1. These four layers include the data computing layer, the feature representation layer, the pattern analysis layer and the application development layer.¹

This chapter is organized as follows. Section 2.1 introduces the most widely used multimodal neuroimaging databases and software packages for large-scale multimodal neuroimaging studies. Section 2.2 reviews the imaging-based features that are used to encode the brain structural and functional changes caused by neurodegeneration, e.g., atrophy and hypo-metabolism. Section 2.3 discusses the current pattern analysis approaches used for capturing the patterns of neurodegenerative pathologies. Section 2.4 demonstrates supervised and unsupervised models in translational applications. As pointed out in Chap. 1, Sect. 1.1.2, MRI and PET are dominantly used to capture the neurodegenerative changes in brain structure and function. Therefore, this chapter focuses on these two neuroimaging modalities and the findings from them.

2.1 Data Computing Layer

2.1.1 Public Neuroimaging Databases

Alzheimer's Disease Neuroimaging Initiative (ADNI) database is the largest database in neurodegeneration research so far, and its volume is still growing. ADNI was

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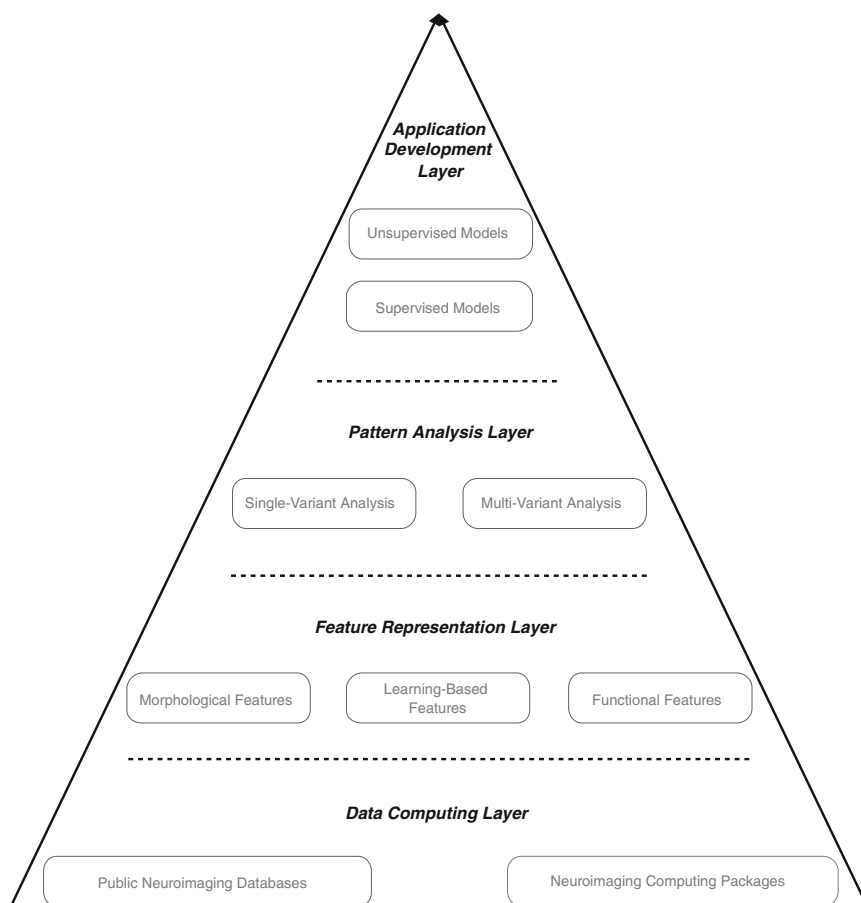


Fig. 2.1 The four layers of neuroimaging analysis architecture, from data acquisition to application development. The higher layers are based on the lower layers

launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California - San Francisco. ADNI is the result of the efforts of many co-investigators from a broad range of academic institutions and private corporations,

and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55–90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years.²

The Australia Imaging, Biomarker and Lifestyle Flagship Study of Aging (AIBL) database is a sister database of ADNI. AIBL aims to discover the biomarker, cognitive characteristics, and health and lifestyle factors that may lead to future development of AD, with a particular focus on early detection, towards lifestyle interventions. It was launched in 2006 as one of largest studies of its kind in Australia. AIBL studies are carried out in four research streams, i.e., the clinical and cognitive research stream, lifestyle research stream, biomarker research stream, and neuroimaging research stream. This database contains the datasets acquired from more than 1,000 participants, including patients diagnosed with AD or MCI and age- and sex-matched healthy volunteers.³

The Open Access Series of Imaging Studies (OASIS) is an older project compared to ADNI and AIBL. OASIS aims at making MRI data sets of the brain freely available to the scientific community. By compiling and freely distributing MRI data sets, we hope to facilitate future discoveries in basic and clinical neuroscience. OASIS is made available by the Washington University Alzheimer's Disease Research Center, Dr. Randy Buckner at the Howard Hughes Medical Institute (HHMI) at Harvard University, the Neuroinformatics Research Group (NRG) at Washington University School of Medicine, and the Biomedical Informatics Research Network (BIRN). Two collections of MRI databases are available in OASIS. The cross-sectional collection contains 416 subjects including young, middle aged, non-demented and demented older adults. The longitudinal collection has 150 subjects including both non-demented and demented older adults. Each subject was scanned on at least two visits.⁴

2.1.2 Neuroimaging Computing Packages

The sMRI computing workflows usually involve artifact correction, skull stripping, segmentation, registration, surface reconstruction [26], and followed by brain morphometry. The most widely used software packages for sMRI computing include FreeSurfer [18], SPM [67], FSL [31] and ANTs [2], BrainVisa [26], and BrainSuite [73].

PET is exquisitely sensitive for detecting the targeted molecules, an attribute conferred upon it by the choice of radiotracers, such as 2-[¹⁸F]fluoro-2-deoxy-D-

²For up-to-date information about ADNI, please see www.adni-info.org.

³For up-to-date information about AIBL, please refer to <http://aibl.csiro.au>.

⁴The detailed description of the OASIS projects can be found at <http://www.oasis-brains.org/app/template/Index.vm>.

glucose (FDG) for the detecting glucose metabolism. PET computing involves serial alignment, spatial normalization and smoothing. SPM and Neurostat⁵ packages are available for PET analysis.

FreeSurfer [18], SPM [67], FSL [31] and ANTs [2] are also the common software packages for multimodal neuroimaging computing. 3D Slicer [22, 32] is the most widely used platform for subject-specific image computing, image editing, visualization and data management. The detailed description of the neuroimaging computing methods and software packages is given in our previous papers [56, 59].

2.2 Feature Representation Layer

2.2.1 Brain Morphological Features

Morphological features, as suggested by the name, aim to model the morphological changes on the brain. They are mainly extracted from sMRI, and can be classified into three groups, the voxel-based features, surface-based features, and ROI-based features.

Voxel-based morphometry (VBM) is a registration-based method used to compute the focal differences between two images, e.g., two scans of the same subjects, two scans of different subjects, or one image and one template. It has been integrated into SPM and FSL packages as a standard method for voxel-wise comparison. It is also referred to as tensor-based morphometry (TBM) when the analysis is carried out in the deformation field. Various voxel-based features can be extracted by VBM and TBM, such as the grey matter density (GMD) derived from the original brain image after registration to a labeled template, or the change rate derived from the registration field based on the comparison of two longitudinal scans [1].

The surface-based features are based on the computing of the brain white matter surface and pial surface reconstructed from the tissue segments. FreeSurfer [18] is a well-established tool for brain tissue segmentation and surface reconstruction. Various measures can be derived from the white matter and pial surfaces, including cortical thickness [23], local gyrification index (LGI) [71], curvedness and shape index [3, 14]. These surface-based features have been extensively reviewed by Mangin et al. [60].

The brain volume can be parcellated into different regions of interest (ROIs) based on a brain template. Popular brain templates include the International Consortium for Brain Mapping (ICBM) template [61] and the Automated Anatomical Labeling (AAL) template [81] in the Montreal Neurological Institute (MNI) coordinates [25]. Grey matter volume (GMV) [28] is the most widely used ROI-feature in neuroimaging analysis. Many other features are also proposed to capture the shape [49, 53] or texture [10, 42, 45, 48, 52, 58, 89] of the ROIs.

⁵<http://128.208.140.75/Download>.

2.2.2 Brain Functional Features

The PET features can reflect particular biochemical processes pertaining to the radioactive tracers. For instance, FDG is able to label the glucose metabolism, and has been a standard tracer in brain tumor studies. The percentage of FDG-PET in brain studies has decreased in recent years due to the introduction of new tracers, such as ^{18}F -BAY94-9172, ^{11}C -SB-13, ^{11}C -BF-227, ^{18}F -AV-45 and ^{11}C -Pittsburgh compound B (^{11}C -PiB), which have been reported as tracers for imaging the amyloid plaques in Alzheimer's brains [13, 65, 68, 80].

Cerebral metabolic rate of glucose consumption (CMRGlc) [10, 77] is the most widely used FDG feature at the voxel-level. Recently, Chen proposed the hypo-metabolic convergence index (HCI) to evaluate the hypo-metabolism of the whole-brain, and based on the same principle, he further proposed the amyloid convergence index (ACI) to estimate the amyloid burden on brain [16]. There are also many PET features generic to different tracers, such as the standard uptake value (SUV) [17, 34], mean index [4], z-scores [62], and difference-of-Gaussian (DoG) parametric maps [11, 50].

2.2.3 Learning-Based Feature

Recently, machine learning techniques have been increasingly used in feature extraction from the neuroimaging data. There are many benefits of the learning-based features compared to the hand-engineered features, e.g., they are purely based on the training datasets, but not relying on domain knowledge of the disorders or imaging modalities. Deep learning, in particular, uses a end-to-end learning strategy, which is suitable for learning the high-level and multimodal features. In addition, as the datasets are growing rapidly in volume, machine learning models can further benefit from such increasingly large-scale datasets [5].

Recently, Brosch and Tam reported that deep learning is effective in capturing the shape variations of brain MRI that highly correlated with disease pathologies, such as the enlarged ventricles [6]. In another study, Suk et al. [79] proposed a deep learning approach for extracting high-level features from low-level multimodal neuroimaging features. They trained a stacked auto-encoder (SAE) for each imaging modality, then then combined the learnt high-level features using a multi-kernel support vector machine (MK-SVM). Recently, Suk et al. proposed another deep learning model based on the the deep Boltzmann machine (DBM), which was trained using the 3D patches, instead of the low-level features, from the multimodal neuroimaging data [78].

2.3 Pattern Analysis Layer

Neurodegenerative disorders may progress in certain patterns. In the case of AD, for example, its pathology commonly starts in the hippocampus and entorhinal cortex, then spreads to the temporal lobe and the posterior cingulate, and then to the parietal, prefrontal and orbitofrontal regions, and finally throughout the entire brain [20, 21, 70]. The patterns of pathologies also vary between different neurological disorders. For example, FTD selectively affects the frontal lobe and may extend backward to the temporal lobe, thus its pattern markedly different from that of AD.

2.3.1 *Single-Variant Analysis*

The simplest approach for pattern analysis is single-variant methods, e.g., t-test for two-class comparison and ANOVA for multiple-class comparison. When these methods are applied to voxel-wise analysis, such as VBM, we may able to derive the t-maps [10] or z-score maps [62]. Figure 2.2 illustrates the CMRGlc maps, functional normalized CMRGlc maps, t-maps and thresholded t-maps of an AD patient and a FTD patient. In this example, the t-maps are generated by comparison of the patient's image to those of the normal controls. Same methods can also be applied to ROI-based analysis, as demonstrated in many previous studies [28, 35, 43, 50, 51, 54].

2.3.2 *Multi-Variant Analysis*

Since single-variant analysis methods ignore correlation between individual variants in the analysis, multivariate methods, such as lasso and elastic net (EN), are therefore increasingly used in pattern analysis due to their capability of identifying the most important features/regions as well as reducing the redundant features/regions with high correlation. For example, an elastic net logistic regression model was proposed by Shen et al. [75] to select disease-relevant biomarkers and classify AD and MCI. Recently, Zhu et al. proposed a joint regression and classification framework for AD/MCI diagnosis based on lasso [93].

Multi-variate analysis methods are also inherently suitable for multimodal pattern analysis and not restricted to imaging data only. In the two examples given above, Zhu et al. used MRI, PET and Cerebrospinal Fluid (CSF) biomarkers in their study, whereas Shen et al. jointly analyzed of MRI data and proteomic data.

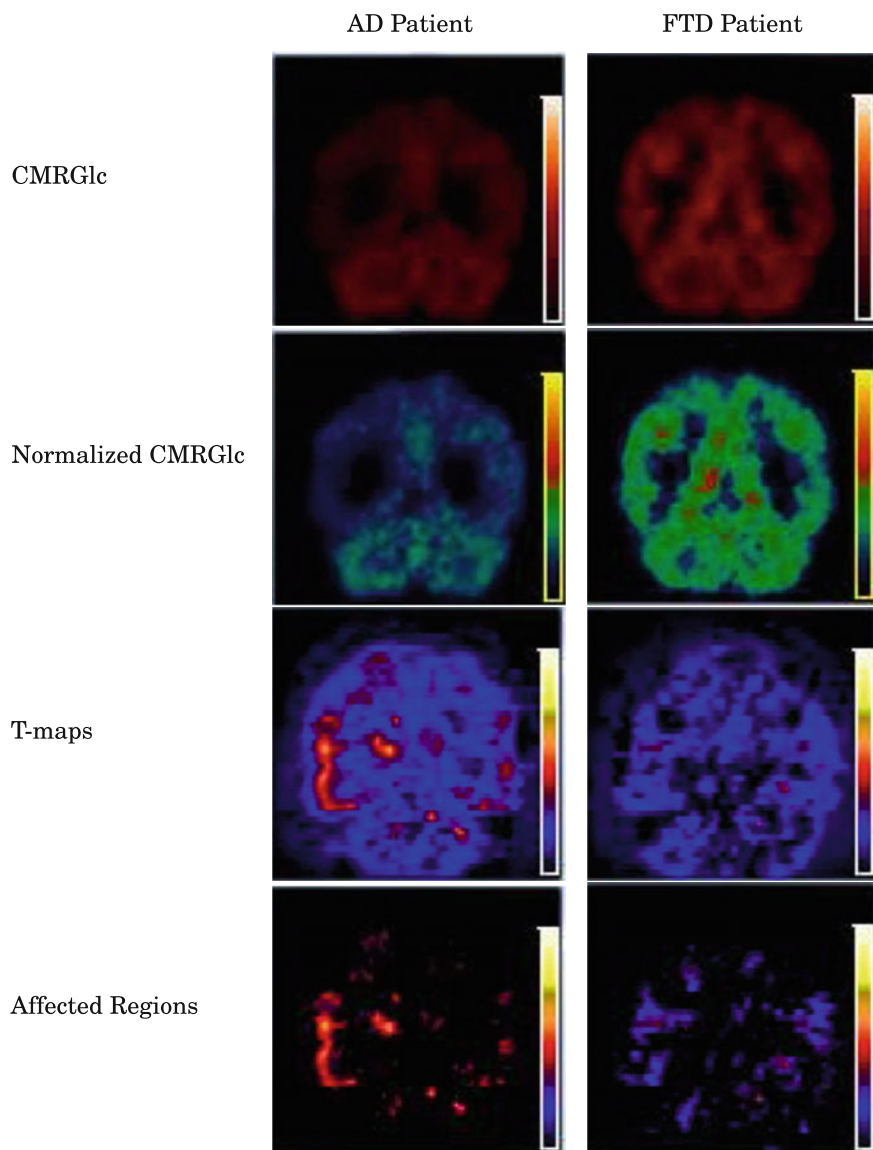


Fig. 2.2 Examples of CMRGlc maps, functional normalized CMRGlc maps, t-maps and thresholded t-maps of an AD patient and a FTD patient. These maps were registered to the MNI coordinates using SPM. Figure reproduced with permission from [10]

2.4 Application Development Layer

2.4.1 Supervised Models

There are a variety of applications developed for neurodegenerative disorder characterization. A substantial proportion of them focus on classification/prediction of the cognitive status. These applications are all based on the supervised models, which require training datasets with ground truth, i.e., the diagnosis confirmed by the doctors.

Most neuroimaging classification/prediction studies are carried out in a similar fashion. The primary features are usually extracted from the MRI data [19, 21, 66, 70, 75, 76, 79, 85] and/or PET data [75, 76, 79, 85], and sometimes combined with other biomarkers, e.g., CSF measures [19, 76, 79, 85], genetic biomarkers [75, 76, 85] and clinical assessments [85]. The features are then fed into the classifiers, which are trained for future classifications. Various classifiers have been used in these studies, predominantly SVM [19, 21, 53, 79, 85], complemented by Bayesian [55], Elastic Net [75], k-nearest-neighbors (kNN) [66], linear discriminant analysis (LDA) [76], and softmax regression [37, 41].

With increasing attention given in the multimodal analysis, a number of multimodal classifiers have been proposed, which create a new feature space for the multimodal features and then train a single model to classify the patients. The most straightforward solution is to concatenate input multi-view features into high-dimensional vectors, and then apply dimension reduction or feature selection approaches, such as t-test [51], ISOMAP [66], Elastic Net [40, 75], or combinations of these methods [35, 54], to reduce the ‘curse of dimensionality’.

These concatenation-based methods are simple and effective, but the inter-subject variations cannot be eliminated, since the inter-subject similarity measured by different features vary in scales and variances. With a focus on the subjects, the multimodal analysis advances rapidly due to the research efforts on the multi-view embedding (ME) methods, such as Multi-View Spectral Embedding (MSE) [84], Multi-View Local Linear Embedding (MLLE) [74], Co-Neighbor MSE [15], Supervised MSE [49], which are based on manifold-learning. These methods extract the geometric structures of local patches across multiple feature spaces, and then align the local patches in a unified feature space with maximum preservation of the geometric relationships. Hinrichs et al. [29, 30] and Zhang et al. [86], on the contrary, extended the kernel tricks in SVM to the multiple feature spaces, and combined the features at the classifier level.

2.4.2 *Unsupervised Models*

The unsupervised models are different from the supervised models in that they do not directly provide a second opinion for the physician, but support clinical decisions in an indirect way. Ground truth is not necessarily needed in these applications.

Medical content-based retrieval (MCBR) is a typical unsupervised application that can provide clinical decision support by retrieving the similar subjects as references for a query. Various content-based neurological image retrieval systems have been reported [7, 9–12, 24, 35, 36, 38, 42–48, 52, 57, 58, 69, 82, 87–92]. These studies mainly focused on single modal data or features, such as High Resolution Computed Tomography (HRCT) [24], Positron Emission Tomography (PET) [9–12, 38, 42, 44, 45, 48, 52, 54, 58, 91], Single Photon Emission Computed Tomography (SPECT) [69], Magnetic Resonance Imaging (MRI) [35, 43, 57, 82], and functional MRI (fMRI) [7]. For example, Cai et al. [9] previously proposed a dynamic brain PET image retrieval system based on pixel-wise tissue time activity curve (TTAC). They further extended their previous work to a volume of interest (VOI)-based retrieval system [33]. Wong et al. [83] established a neuro-informatics database system (NIDS) with co-registered static PET and MR image data, supporting geometric, metabolic and textual features. Batty et al. [4] designed a PET image retrieval system based on a combination of anatomical and functional ROI features for retrieval of demented cases. There is a clear trend of using the bag of visual words (BoVW) model for MCBR. Various visual words and models were proposed [8, 24, 27, 90], mostly based on the low-level features, such as texture, shape, size, intensity or a combination of them. Some studies also tried to add semantic annotations [44, 64, 72, 88, 89, 91] to the medical images.

Recently, the MCBR model has been extended to retrieving longitudinal brain deformations. In one of our recent studies, we developed a MCBR model to simulate the future brain development, based on both the longitudinal and cross-sectional information. It was assumed that brains with similar morphological deformations at both previous and current time points will have similar future development [39, 63]. Figure 2.3a–c illustrates the longitudinal images and the deformation field of registration; (d–f) shows an example of the query (deformation field) and the retrieval results with the most similar longitudinal changes. As the database is growing in volume, we may expect better performance with the increasing large-scale database.

Another extension of the current MCBR framework is multimodal MCBR methods, which take the benefits from the the emerging multimodal medical data with complementary information. For example, a bag of semantic words (BoSW) model based on deep learning was recently proposed for multimodal MCBR. A set of low-level features were extracted from the multimodal medical imaging data and then translated to the symptom severity degrees by clinical symptom quantization. Finally, high-level semantic words were deduced by learning the patterns of the symptoms [47].

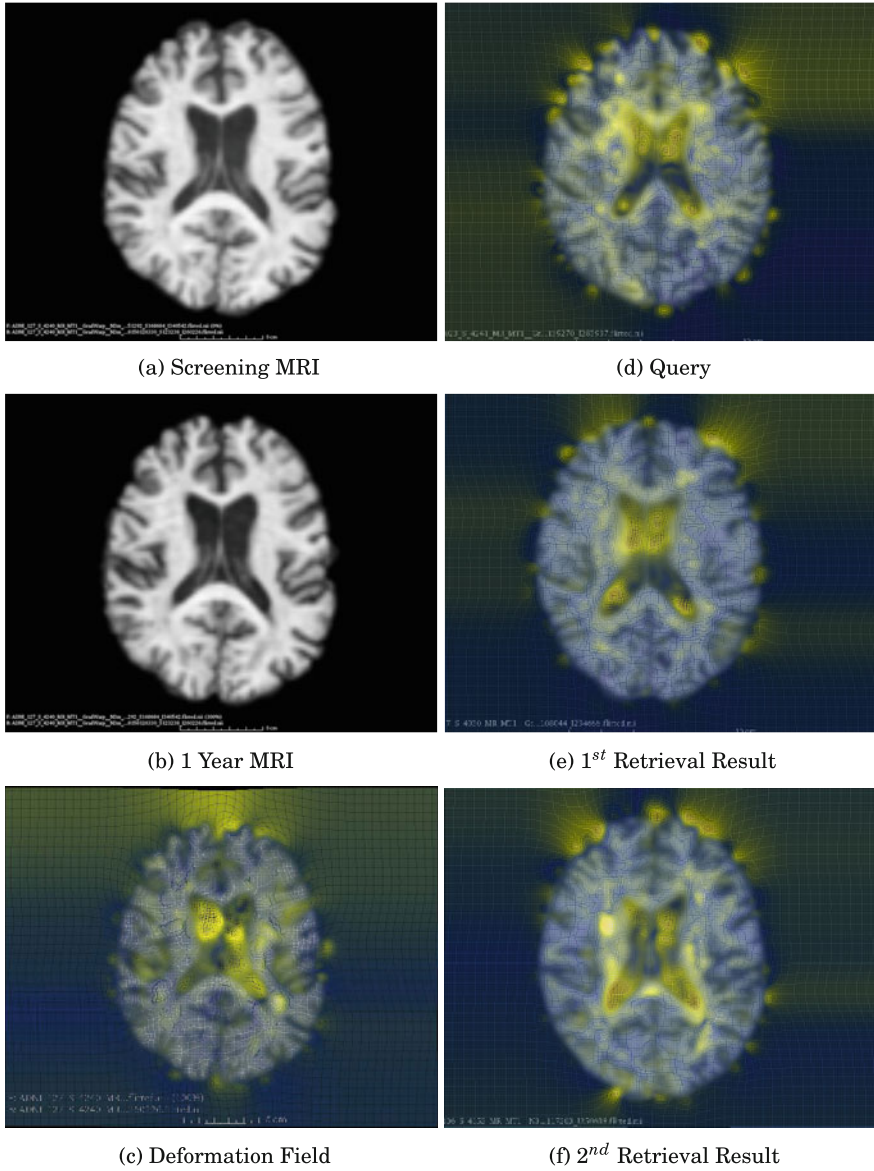


Fig. 2.3 *First column* an example of the longitudinal screening scan (a) the follow up scan in 1 year (b), and their deformation field (c) after registration. *Second column* an example of deformation-based query (d) and the two top ranked retrieval results (e, f) with the most similar longitudinal changes. Figure reproduced with permission from [39]

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