Chapter 16
Neuroimage Classification for Early Diagnosis of Alzheimer's Disease

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ABSTRACT

Diagnostic criteria for neurological and psychiatric disorders are typically based on clinical and psychometric assessment, which might not be effective for early detection of the disease onset. For brain disorders such as Alzheimer's Disease (AD), neuroimaging can potentially play an important role in the development of imaging-based biomarkers. Following voxel-wise univariate neuroimage analysis methods, machine learning and pattern recognition based neuroimage analysis techniques have been increasingly adopted in neuroimaging studies of neurological and psychiatric disorders, aiming to provide tools that classify individuals, based on their neuroimaging scans, rather than detect statistical group difference. The machine learning based methods, optimally combining information of multiple measures derived from images, have demonstrated promising performance in diagnosis of AD and early prediction of conversion of Mild Cognitive Impairment (MCI) individuals. This chapter introduces the general framework of such techniques with a focus on structural MRI analyses and their applications to studies of AD.

INTRODUCTION

The diagnosis of brain disorders such as Alzheimer's Disease (AD) has relied on behavioral manifestation and psychometric assessment. However, the brain alternation induced by a brain disorder might occur long before the disease is clinically detectable. Since such alternation might be detectable with modern neuroimaging techniques (Gomez-Isla, et al., 1996), there has been a keen interest in the neuroimaging community to develop imaging-based biomarkers for achieving an early diagnosis of neurological and psychiatric diseases. In particular, structural magnetic resonance imaging (MRI), functional MRI, positron emission tomography (PET), including FDG-PET

DOI: 10.4018/978-1-4666-0059-1.ch016

and Pittsburgh compound B (PiB)-PET, as well as other imaging modalities are being investigated as surrogate markers of neurological and psychiatric pathology (Alexander, Chen, Pietrini, Rapoport, & Reiman, 2002; Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Chan, et al., 2003; De-Leon, et al., 1991; deToledo-Morrell, et al., 1997; Dickerson, et al., 2001; N. Fox, et al., 1996; Fox, Freeborough, & Rossor, 1996; Golomb, et al., 1993; Grundman, et al., 2002; Jack, et al., 2000; Jack, et al., 2003; Jacobs & Cherry, 2001; Jagust, Haan, Reed, & Eberling, 1998; Mega, et al., 1999; Rosen, et al., 2003; Scheltens, Fox, Barkhof, & De Carli, 2002; Stoub, et al., 2005; Y. Wang, Fan, Bhatt, & Davatzikos, 2011; Xu, et al., 2000). We focus on studies of AD based on structural MRI, although most of the techniques are generally applicable to different applications and independent on imaging modalities.

MRI can potentially play an important role in diagnosis of AD. The neuroimaging literature is rich in studies measuring volumes of Regions of Interest (ROIs) for detecting anatomical changes rendered by AD (Chetelat & Baron, 2003). The ROIs under investigation are often selected based on *a prior* knowledge or hypothesis. Apparently, the ROI analysis methods are limited in the absence of *a prior* knowledge. Moreover, the regional hypothesis might be biased and lead to a suboptimal detection of brain abnormality due to the complicated brain structure.

To achieve a systematic brain investigation, whole brain univariate voxel-wise analysis techniques have been proposed, including deformation-, tensor- and voxel-based morphometry, aiming to characterize brain regional volume differences at voxel level in structural MRI images (Ashburner, et al., 2003; Ashburner & Friston, 2000, 2001). A number of studies have demonstrated that whole brain voxel-wise analysis methods are able to capture structural brain abnormalities among different patient populations (Ashburner & Friston, 2000; Chung, et al., 2001; Davatzikos, Genc, Xu, & Resnick, 2001; Good, et al., 2001; Granert, et al., 2011; Thompson, et al., 1997; Wright, et al., 1995). These techniques have also been used to measure aging effect (Baron, et al., 2001; Tisserand, et al., 2002), human creativity (Takeuchi, et al., 2010) and smoking cue reactivity (Zhang, et al., 2011). In these applications, whole brain voxel-wise analysis techniques has proved advantages of fully automated and unbiased whole brain analysis. However, the focus of voxel-wise univariate analysis has been on group-wise comparison.

Following the whole brain univariate voxel-wise analysis methods, machine learning based neuroimage analysis methods, particularly high-dimensional pattern classification, have been proposed to achieve individual classification or diagnosis based on neuroimages. Applications included but not limited to detecting schizophrenia, distinguishing autistic spectrum disorder, and early detection of AD (Davatzikos, Resnick, Wu, Parmpi, & Clark, 2008; Ecker, et al., 2010; Gerardin, et al., 2009; Kühn, Bodammer, & Brass, 2010; Misra, Fan, & Davatzikos, 2009; Yoon, et al., 2007).

A typical machine learning based neuroimage analysis method consists of three major components (i.e., feature extraction, feature selection, and feature based classification) (Shen, et al., 2007). The most crucial among them is the feature extraction, owing to the fact that features play a key role in the classification. Once discriminative features have been extracted, feature selection and feature based classification can be straightforwardly applied using suitable methods developed in machine learning research community. For instance, principal component analysis (PCA) or feature selection techniques can be used for feature dimensionality reduction (Guyon & Elisseeff, 2003; Liu, et al., 2004), whereas for classification, Support Vector Machine (SVM) is typically adopted (Vapnik, 1998).

As machine learning based neuroimage analysis methods have been applied to a variety of neuroimaging applications for years, techniques