USE OF PATTERN CLASSIFICATION TO IDENTIFY MILD COGNITIVE IMPAIRMENT AND PREDICT COGNITIVE DECLINE

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Yue Cui

To my father, Dexiang Cui, and my mother, Jihong Yue

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List of Abbreviations

$A\beta_{1-42}$	Amyloid-β 1 to 42 peptide
AAL	Automated Anatomical Labeling
AD	Alzheimer's disease
ADLs	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
aMCI	Amnestic mild cognitive impairment
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOE	Apolipoprotein E
APP	Amyloid precursor protein
AUC	Area under a receiver operating characteristic curve
BMI	Body mass index
BNT	Boston Naming Test
BSIT	Brief Smell Identification Test
BVRT	Benton Visual Retention Test
CAD	Computer-aided diagnosis
CDR	Clinical Dementia Rating
CI	Curvature index
CSF	Cerebrospinal fluid

CT	Computer-assisted tomography
CV	Cortical volume
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI	Diffusion tensor imaging
EPI	Echo-planar imaging
FA	Fractional anisotropy
FAQ	Functional Assessment Questionnaire
FAS	Controlled Oral Word Association Test
FDG-PET	Fluorodeoxyglucose positron emission tomography
FI	Folding index
FLAIR	Fluid attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
FN	False negative
FNIRT	FMRIB's Nonlinear Image Registration Tool
FP	False positive
FS	FreeSurfer
FSL	FRMIB Software Library
FS+LDDMM	FreeSurfer-initialized Large-Deformation Diffeomorphic Metric Mapping
GC	Gaussian curvature

GDS	Geriatric Depression Scale
GM	Gray matter
ICV	Intracranial volume
IRB	Institutional Review Board
L	Left hemisphere
LDDMM	Large Deformation Diffeomorphic Metric Mapping
LM	Logical Memory
LOOCV	Leave-one-out cross-validation
MAS	Memory and Ageing Study
MC	Mean curvature
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MPRAGE	Magnetization prepared rapid gradient-echo
MRI	Magnetic resonance imaging
mRMR	Minimum redundancy maximum relevance
MRS	Magnetic resonance spectroscopy
naMCI	Non-amnestic mild cognitive impairment
NART	National Adult Reading Test
NC	Normal control
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association

NM	Neuropsychological measure
PASW	Predictive Analytics SoftWare
PET	Positron emission tomography
PiB	Pittsburgh Compound B
p-tau$_{181p}$	Tau phosphorylated at threonine 181
R	Right hemisphere
RAVLT	Rey Auditory Verbal Learning Test
RBF	Radial basis function
RFE	Recursive Feature Elimination
ROC	Receiver operating characteristic
ROI	Region of interest
SA	Surface area
SD	Standard deviation
SPARE-AD	Spatial Pattern of Abnormality for Recognition of Early AD
SPECT	Single photon emission computed tomography
SPHARM	Spherical harmonics
SPM	Statistical Parametric Mapping
SPSS	Statistical package for social science
STAND	Structural Abnormality index
SV	Subcortical volume
SVM	Support vector machine
T	Tesla
TA	Cortical thickness average

TBSS	Tract-based spatial statistics
TE	Echo delay time
TMT	Trail Making Test
TN	True negative
TP	True positive
TR	Repetition time
TS	Cortical thickness standard deviation
t-tau	Total tau
VBM	Voxel-based morphometry
WM	White matter
WMPM	White matter parcellation map

Abstract

Alzheimer's disease (AD) is the most common cause of dementia in older people, with the prevalence doubling for every 5-year interval beyond the age of 65. The combination of our ageing society and the broad-reaching and devastating impacts of AD make research into this disease an urgent priority. A desirable aim of such research is to develop means of making early and accurate diagnoses of individuals who either have or are at increased risk of developing AD. This will allow for timely interventions that may be effective in managing or treating AD. There is a cognitive continuum from normal ageing to dementia, with mild cognitive impairment (MCI) being a syndrome widely considered to be a prodromal stage of dementia.

In this thesis, pattern classification algorithms were used for the identification of MCI and prediction of decline from normal cognition to MCI, and MCI to AD. Three studies were conducted: (1) identification of amnestic MCI among community-dwelling elderly adults, (2) prediction of the transition from normal cognition to MCI in community-dwelling elderly adults, and (3) prediction of the conversion from amnestic MCI to AD in a clinic-based sample. Due to there being only subtle brain changes in the very early stages of cognitive decline, early diagnosis is particularly challenging. The first study investigated the automated detection of MCI using a combination of spatial atrophy and white matter alterations, as changes in both brain structure and the capacity for

information flow within and between structures are important contributors to cognitive dysfunction. Additionally, numerous socio-demographic, lifestyle, health and other factors were implicated in the misclassification of individuals. The second study used neuropsychological test scores and neuroimaging morphological measures to identify cognitively normal individuals at increased risk of developing MCI, and appears to be the first study to use pattern classification methods for this purpose. The third study investigated conversion from MCI to AD using multimodal data that included cerebrospinal fluid (CSF) protein concentrations, neuroimaging, and neuropsychological test scores. The classification and prediction schema used in these studies comprised feature extraction, feature selection and classification stages. Using an automated feature extraction process, measurements of brain structures were computed from neuroimages. In addition to these, cognitive data obtained from neuropsychological assessments and CSF biomarker data were also used. Meaningful features, which enabled optimal differentiation between cognitive groups, were then identified from the range of neuroimage, neuropsychological and CSF biomarker features using a feature selection process. In the classification stage, non-linear support vector machines were then used to train classifiers and test classification performance.

These pattern classification methods achieved a high level of performance in all three studies. In addition, performance was enhanced by using a combination of multiple data modalities over any one modality alone. The use of the scheme to identify discriminating markers enhances the current understanding of AD progression. Also importantly, the scheme has the potential to detect MCI in the early stages of its development. Early detection would enable interventions designed to prevent or slow the development of AD and other dementias to begin as soon as possible.