Automated Detection of Depression from Brain Structural Magnetic Resonance Imaging Scans

by

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Doctor of Philosophy (Engineering)

Deakin University
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Abstract

Depression is a major issue worldwide and is seen as a significant health problem. Detection of depression from brain structural magnetic resonance imaging (sMRI) scans is relatively new in mental health diagnosis and hence remains a challenge. The brain volumetric changes at a structural level appear to have the utmost importance in depression biomarker studies. However, the significance of various brain sMRI volumetric features in the detection of depression at an individual level is yet to be investigated. Thus, the establishment of a brain sMRI-based depression detection system that can detect depression-related brain abnormalities would assist medical experts in their decision-making process. In this thesis, we investigate the feasibility of depression detection at an individual level using the brain volumetric features. An automated sMRI-based depression detection system is proposed whose components include acquisition and preprocessing, feature extraction, feature selection, and classification. The core focus of this thesis is on the establishment of a new feature selection algorithm that quantifies the most relevant brain volumetric feature for depression detection at an individual level. In addition, we also investigate and propose the best techniques for use in each of the other components. Finally, optimization of the employed algorithms is performed to ensure that the performance of the proposed system is enhanced.

This thesis first reviews the existing methods for the automated detection of depression from brain sMRI data, and introduces a generic structure for representing and describing the methods developed for the detection of depression. The image acquisition, pre-processing and segmentation procedures for the system are next described for the extraction of sMRI brain regions of interest. Finally, the volumetric features are calculated using a volume calculation method. In this thesis, we employed a dataset consisting of 115 brain sMRI images belonging to 88 healthy controls and 27 depressed subjects with 44 sMRI volumetric features. The features include the volume calculated from the whole brain (WB), white matter (WM), gray matter (GM), and the hippocampus etc.

Limitation of the available works on feature selection in the field of depression motivated us to focus on this area. Our initial investigation on the existing feature selection algorithms assisted us to develop a robust feature selection algorithm.
Using an ensemble-based approach, this algorithm is called ‘degree of contribution’ (DoC). A key aspect of this algorithm is the calculation of the degree of contribution of brain sMRI volumetric features for detection of depression. The DoC is the score of features importance and serves as feature ranking. The algorithm involves four stages: feature ranking, subset generation, subset evaluation, and DoC analysis. From the designed experiments, the proposed DoC algorithm demonstrates great potential for application in the feature selection of sMRI volumetric features. DoC outperformed four well-known existing feature selection algorithms (IG, OneR, SVM and ReliefF) in terms of the average classification accuracy. DoC also outperformed OneR, SVM and ReliefF and was comparable to IG in terms of its stability measure. From the DoC score, it was determined that the most discriminant volumetric features of depression were those from the left-brain region.

Different classifiers were also investigated for the classification component. We presented a comparison of the classification performances through a number of factors. The proposed DoC algorithm achieved its best performance when paired with the K-Nearest Neighborhood classifier. This combination generated reduced-size subsets of features and could yield the high classification accuracy. The highest average classification accuracy was 91.67% and was achieved using a combination of DoC-KNN. This result outperformed that of the existing works in depression detection. The performance result highlighted the potential of depression detection from sMRI volumetric attributes, and validated the developed sMRI-based depression system. This thesis also demonstrated the importance of accurate feature selection and the associated impact on the final classification results.

The thesis is concluded with a brief discussion on the developed system and its various system components. Future recommendations on how to further improve the work, especially the proposed system, are also included.
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# Nomenclatures

## Abbreviations:

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<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention deficient hyperactivity disorder</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the receiver operating characteristic curve</td>
</tr>
<tr>
<td>BD</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>CFS</td>
<td>Correlation-based feature selection</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CV</td>
<td>Cross validation</td>
</tr>
<tr>
<td>DARTEL</td>
<td>Diffeomorphic anatomical registration through exponentiated lie algebra</td>
</tr>
<tr>
<td>DoC</td>
<td>Degree of contribution</td>
</tr>
<tr>
<td>DPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and statistical manual</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>EBS</td>
<td>Entropy-based segmentation</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>ELUDE</td>
<td>Efficient Longitudinal Upload of Depression in the Elderly</td>
</tr>
<tr>
<td>FBM</td>
<td>Feature-based morphometry</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FSS</td>
<td>Feature subset selection</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full-width at half-maximum</td>
</tr>
<tr>
<td>GA</td>
<td>Genetic Algorithm</td>
</tr>
<tr>
<td>GM</td>
<td>Gray matter</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HMRF</td>
<td>Hidden Markov Random Field</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
</tr>
<tr>
<td>IG</td>
<td>Information Gain</td>
</tr>
<tr>
<td>JCI</td>
<td>Jaccard Index</td>
</tr>
<tr>
<td>KNN</td>
<td>K-Nearest Neighbourhood</td>
</tr>
<tr>
<td>LASSO</td>
<td>Least Absolute Shrinkage and Selection Operator</td>
</tr>
<tr>
<td>LDDMM</td>
<td>Large Deformation Diffeomorphic Metric</td>
</tr>
<tr>
<td>LICA</td>
<td>Lattice Independent Component Analysis</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild Cognitive Impairment</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>MI</td>
<td>Mutual Information</td>
</tr>
<tr>
<td>MIRIAD</td>
<td>Multisite Imaging Research In the Analysis of Depression</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>NB</td>
<td>Naïve Bayes</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal Cortex</td>
</tr>
<tr>
<td>OneR</td>
<td>One Rule</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component Analysis</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PLSC</td>
<td>Partial Least Squares Correlation</td>
</tr>
<tr>
<td>RBF</td>
<td>Radial Basis Function</td>
</tr>
<tr>
<td>RF</td>
<td>Random Forest</td>
</tr>
<tr>
<td>RFE</td>
<td>Recursive Feature Elimination</td>
</tr>
<tr>
<td>ROI</td>
<td>Regions of Interest</td>
</tr>
<tr>
<td>RT</td>
<td>Random Tree</td>
</tr>
<tr>
<td>RVM</td>
<td>Relevance Vector Machine</td>
</tr>
<tr>
<td>RVR</td>
<td>Relevance Vector Regression</td>
</tr>
<tr>
<td>SA</td>
<td>Simulated Annealing</td>
</tr>
<tr>
<td>SBE</td>
<td>Sequential Backward Elimination</td>
</tr>
<tr>
<td>SBFS</td>
<td>Sequential Floating Backward Search</td>
</tr>
<tr>
<td>SBS</td>
<td>Sequential Backward Selection</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SFFS</td>
<td>Sequential Floating Forward Search</td>
</tr>
<tr>
<td>SFS</td>
<td>Sequential Forward Selection</td>
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<tr>
<td>Symbol</td>
<td>Definition</td>
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<td>-------------------------------------------------</td>
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<tr>
<td>SGPFC</td>
<td>Subgenual prefrontal cortex</td>
</tr>
<tr>
<td>sMRI</td>
<td>Structural magnetic resonance imaging</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>SPHARM</td>
<td>Spherical harmonic</td>
</tr>
<tr>
<td>SU</td>
<td>Symmetrical uncertainty</td>
</tr>
<tr>
<td>SVM</td>
<td>Support Vector Machine</td>
</tr>
<tr>
<td>T1-w</td>
<td>T1-weighted</td>
</tr>
<tr>
<td>T2-w</td>
<td>T2-weighted</td>
</tr>
<tr>
<td>TCP</td>
<td>Transductive conformal predictors</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel-based morphometry</td>
</tr>
<tr>
<td>WB</td>
<td>Whole brain</td>
</tr>
<tr>
<td>WM</td>
<td>White matter</td>
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</tbody>
</table>

Symbols:

- $Acc_{Thresh}$: Accuracy threshold
- $Sp$: Spearman rank correlation coefficient
- $s$: second
- $ms$: milisecond
List of Publications

Journal Publications


Conference Publications


(Selected for publication in the International Journal of Bioscience, Biochemistry and Bioinformatics (IJBBB, ISSN: 2010-3638))


CHAPTER ONE

Introduction

Depression is the most common mental disorder worldwide and currently the fourth largest contributor to the burden of disease, as reported by the World Health Organization [1]. By 2020, it is estimated that depression will remain a leading cause of disability, second only to cardiovascular disease [1]. Depression is a complex phenomenon with many sub-types and more than one etiology. It is a long-term recurrent disease in most people, with significant morbidity, mortality, and psychosocial impairment. Depression is associated with widely varying psychological and physiological features, and this heterogeneity is acknowledged within depression classification systems [2].

A recent epidemiological study by Bromet et al. [3] indicated that approximately 121 million people worldwide have been affected by depression. Suicide is the worst consequence of depression, with up to 850,000 deaths reported every year [3]. Suicide rates have been shown to increase with age for both males and females: from 1 death per 100,000 young people aged 12 to 14 years, to 5 deaths per 100,000 people aged 15 to 17 years and 13 deaths per 100,000 people aged 18 to 24 years [3]. Despite efforts devoted to the recognition and treatment of depression, new data suggests that the prevalence of depression may be on the rise, particularly in younger people [4].

Current clinical diagnosis of depression is based on one’s judgement as to whether or not set symptomatic criteria are being met. Thus, the diagnosis procedure depends on the patient’s understanding and cooperation, as well as the investigator’s skill in obtaining information [5]. Some widely used screening tests for the evaluation of depression include the Hamilton Rating Scale for Depression [6], the Diagnostic Interview Schedule [7], and the Hospital Anxiety and Depression Scale [8]. Furthermore, a mental status examination is routinely conducted to assess the patients’ level of cognitive ability, their appearance, emotional mood, speech and thought patterns at the time of evaluation [9]. Finally, following a positive screen for depression, tests such as the Montgomery-Asberg Depression Rating Scale [10], the Inventory of Depressive Symptomatology [11, 12], and the Quick Inventory of Depressive Symptomatology [13] may be used to assess the severity of depression.
Early detection is key to better prognosis and appropriate treatment. There are still concerns that depression is poorly detected and that reliable severity measures are needed [14, 15]. Despite several biomarkers associated with depression, there are no specific medical tests to objectively diagnose depression. In current practices, further tests are only requested to rule out the possibility that the symptoms of depression are not being caused by other medical illnesses [16, 17]. Stigma and patient denial, clinical experience, time limitations, and reliability of psychometrics are barriers to the clinical diagnoses of depression. The efficiency of antidepressants is largely based on trial, and individuals can take weeks to respond, if at all. Previous research has shown that approximately 33–41% of those who committed suicide had contacted mental health services in the year prior to their death and 20% within the month prior to their death [18]. Thus, more effective ways of detecting depression would reduce time to intervention and suicidal behavior. The establishment of an automated system to detect depression-related abnormalities would assist medical experts in their decision-making process.

A structural magnetic resonance imaging (sMRI) is a widely used neuroimaging technique in research as well as in clinical practice. An sMRI offers anatomical detail and high sensitivity to pathological changes [19]. It can demonstrate certain patterns of change in the brain that may be present at a structural level. The acceptance of sMRI in clinical research and practice demonstrates its potential and usability in clinical diagnostics. However, the use of sMRI in depression diagnosis is in its infancy. Available studies that reported the detection of depression at an individual level include: Costafreda et al. [20], Nouretdinov et al. [21], Gong et al. [22], Mwangi et al. [23, 24], and Bao et al. [25]. Existing sMRI neuroimaging studies of patients with depression at a group level analysis reported certain patterns of brain changes that may be present at structural levels [26-34]. sMRI volumetric features of various brain regions that have drawn a lot of attention include volume changes in the hippocampus, amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DPFC), subgenual prefrontal cortex (SGPFC), putamen, caudate and also in the volume of cerebrospinal fluid (CSF) [19]. Volumetric analysis refers to the measurement of the volume of selected brain regions. It is conducted by summing all voxels within the traced regions of interest (ROIs). The volume measure is calculated after manual or semi-automated segmentation. For example, the hippocampus volume in the scanning space is
measured by multiplying the number of voxels of the hippocampal mask by the voxel size of the image.

1.1 Research Problems and Significance

While the biomarkers for depression from brain sMRI volumetric changes have been identified, the influence of this discovery for depression diagnosis on clinical practice is very limited. There has been little efforts to formulate a detection system that could automatically diagnose depression for clinical applications. Thus, a system needs to be architecturally developed, and relevant techniques for the system components must be identified and evaluated. To be diagnostically effective, an sMRI-based depression detection system must be able to reliably distinguish a depressed person from a healthy one at an individual level [35]. Such detection requires processes including image acquisition and pre-processing, feature extraction and selection, and classification.

One of the components of the detection system is feature selection. Feature selection identifies the most useful features, and reduces the features dimensionality whilst preserving the most significant aspects of the data [36]. Although feature selection has considerable impact on the success or failure of the classification process, it is clear that there is still a need to investigate the best feature selection algorithms for individual depression detection. Thus, an investigation is required to evaluate the existing feature selection algorithms for depression detection. Reported studies on the investigation of feature selection from sMRI depression data have used statistical analysis (analysis of variance (ANOVA) [4] and a significant t-test [5]). Using sMRI data, Costafreda et al. [20] used analysis of variance (ANOVA) to filter the whole-brain voxels to select the areas of maximum group difference between patients and controls. Mwangi et al. [23] implemented a t-test to filter voxel-based morphometry (VBM) for identification of the voxels that differed most in major depressive disorder (MDD) patients versus healthy controls. They also investigated a wrapper feature selection method called Recursive Feature Elimination (RFE). Currently, there is no feature selection algorithm specifically developed for depression detection.

To the best of our knowledge, no systematic study has been carried out to explore the relationship between the features extracted from brain sMRI data of depressed
subjects (particularly brain sMRI volumetric features) and the feature selection methods. The available individual depression detection studies based on sMRI [20, 23-25] have utilized some brain sMRI non-volumetric features, for example, voxel intensities, brain shape, and voxel morphometry. The brain sMRI volumetric features have yet to be explored for individual depression detection. To use brain sMRI volumetric features for individual depression detection, there is a need to identify the applicability of these features for depression detection, and then identify the most relevant and discriminant features that contribute towards accurate depression detection.

Another important component in a depression detection system is the classification model. Thus far, very limited works have been reported on identifying a suitable classification algorithm for the detection of depression. The Support Vector Machine (SVM) classifier was employed by Costafreda et al. [20], Gong et al. [22], and Bao et al. [25]. In addition to the SVM classifier, Bao et al. [25] also investigated the K-Nearest Neighbor classifier for predicting treatment remission in major depression. Nouretdinov et al. [21] proposed a general probabilistic classification method for structural and functional MRIs to investigate diagnostic and prognostic prediction in depression. The proposed classification method is known as transductive conformal predictors (TCP). Mwangi et al. [24] used regression analysis based on relevance vector regression (RVR) which is a sparse Bayesian leaning method to predict brain disease. In another published study, Mwangi et al. [23] investigated both the relevance vector machine (RVM) and the SVM machine learning for diagnostic purposes. The stated studies only evaluated the performance of a single classifier for the detection of depression. Therefore, it is necessary to investigate the performance of various classification algorithms in detecting depression and identifying reliable classifiers for the depression domain. Upon establishment of various system components, the final stage is optimization of the classification model to guarantee that the system will detect depression efficiently.

1.2 Research Objectives

The objectives of the research presented in this thesis are as follows:
1. To propose a generic architecture for an automated sMRI-based depression detection system that contributes to the formulation of the system components, techniques, requirements, issues and challenges.

2. To investigate the feasibility of using brain sMRI volumetric features for detecting individual levels of depression.

3. To investigate feature selection algorithms for an automated sMRI-based depression detection system.

4. To evaluate and compare the performances of the classification algorithms and identify a suitable algorithm for application in the sMRI-based depression detection system.

5. To develop a stable and reliable feature selection algorithm for the weighting, ranking and subset selection of brain sMRI volumetric features dedicated to the depression detection problem.

6. To develop a classification model to implement the new feature selection algorithm in order to achieve the maximum accuracy rate.

1.3 Research Contributions

The thesis contributions are as follows:

1. **Architecture of brain sMRI based depression detection system.** This thesis presents the architecture of an sMRI based depression detection system. It investigates related concepts, and identifies the required system components. The presented architecture is mapped into a generic architecture of a diagnosis system to demonstrate its applicability. Also, the mapping assists to perform a gap analysis in this research field.

2. **Brain sMRI volumetric features.** The thesis introduces potential features, one of which being the brain sMRI volumetric features, for utilization in the detection of depression at an individual level. We identify the weight, ranking, and selection of discriminant features of the brain sMRI volumetric features that assist in accurately classifying depression.

3. **Feature selection algorithms.** The thesis investigates feature selection algorithms to select features in brain sMRI data. First, an empirical comparison of the existing/baseline feature selection algorithms is performed to identify the performances and characteristics of different feature selection
algorithms when implemented on brain sMRI volumetric features. Subsequently, a new feature selection algorithm is devised. The proposed algorithm incorporates an ensemble-based approach to the existing/baseline feature selection algorithms. The new feature selection algorithm is compared with other existing algorithms to demonstrate that its performance is superior to others. In the thesis, we investigate the use of feature selection with regard to stability and classification performance.

4. Classification algorithms. The thesis presents an investigation to help determine the best classifier to use in the sMRI based depression detection system. An experimental procedure is devised and an empirical comparison is conducted for the identification of the classifier. Identification of the best classifier for the sMRI-based depression detection system is extremely important. This will ensure the validity and robustness of the system to accurately classify those who do or do not have depression.

5. Optimization of the classification model. The thesis also presents the proposed classification component for implementing the new feature selection algorithm. After establishing the system components, optimization of the classification model is carried out at the final stage. This stage is important in order to guarantee that the overall system can efficiently detect depression. At this stage, we can define the best classifier and an optimum feature subset that can be implemented to accurately classify our subjects into their diagnostic categories.

1.4 Thesis Organization

This thesis has been formulated according to the development steps of the sMRI-based depression detection system. The chapters of this thesis are derived from various papers published during the PhD candidature. This chapter (Chapter 1) is the Introduction chapter. The remainder of the thesis is organized as follows:

Chapter 2: Literature Review. This chapter provides an overview on depression and an in-depth review of existing depression detection research specifically in brain sMRI. This chapter is derived from the following publication:

- K. Kipli, A. Kouzani, and L. Williams, "Towards automated detection of depression from brain structural magnetic resonance images,"
This chapter also surveys one of the main components in developing a depression detection system, which is feature selection. A feature selection algorithm will be the core contribution of this thesis. Four broad categories of the feature selection methods are described and the main components of feature selection are presented and discussed. Advantages and disadvantages of the methods are also explored along with current issues and challenges in feature selection.

Chapter 3: Proposed Brain sMRI-based Depression Detection System. Chapter 3 presents the proposed architecture of the sMRI based depression detection formulated from a survey of the literature. The chapter describes the different components involved in depression detection, and discusses the most common algorithms used to tackle these problems. This chapter is based on the following publications:


Chapter 4: Image Acquisition, Pre-processing and Feature extraction. This chapter presents specific methods that are employed to implement the first three components of the proposed sMRI-based depression detection system, including image acquisition, pre-processing and feature extraction.

Chapter 5: Feature Selection. This chapter introduces the feature selection techniques and discusses the different aspects of feature selection for depression detection. We discuss the motivations to perform feature selection, and describe various approaches to accomplish this. We also introduce the feature selection techniques that will be used in our experiments. For each of the feature selection techniques, we perform a comparative evaluation of feature selection techniques, assess accuracy of classification and investigate whether techniques are suitable for the depression domain. Building on the outcome of our evaluation of the feature selection techniques, the next chapter will introduce the proposed sMRI-based depression detection system, which will be evaluated using the feature selection techniques described above.