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Ontology driven decision support for the diagnosis of mild cognitive impairment

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ABSTRACT

In recent years, mild cognitive impairment (MCI) has attracted significant attention as an indicator of high risk for Alzheimer's disease (AD), and the diagnosis of MCI can alert patient to carry out appropriate strategies to prevent AD. To avoid subjectivity in diagnosis, we propose an ontology driven decision support method which is an automated procedure for diagnosing MCI through magnetic resonance imaging (MRI). In this approach, we encode specialized MRI knowledge into an ontology and construct a rule set using machine learning algorithms. Then we apply these two parts in conjunction with reasoning engine to automatically distinguish MCI patients from normal controls (NC). The rule set is trained by MRI data of 187 MCI patients and 177 normal controls selected from Alzheimer's Disease Neuroimaging Initiative (ADNI) using C4.5 algorithm. By using a 10-fold cross validation, we prove that the performance of C4.5 with 80.2% sensitivity is better than other algorithms, such as support vector machine (SVM), Bayesian network (BN) and back propagation (BP) neural networks, and C4.5 is suitable for the construction of reasoning rules. Meanwhile, the evaluation results suggest that our approach would be useful to assist physicians efficiently in real clinical diagnosis for the disease of MCI.

1. Introduction

Mild cognitive impairment (MCI) is currently thought of as a transition phase between normal aging and dementia, especially Alzheimer's disease (AD). MCI refers to the clinical state of individuals who have impaired memory but are otherwise functioning well and do not meet clinical criteria of dementia. By cognitive impairment, we typically refer to a person's ability to remember, read, write, solve problems, perform calculations, and navigate around their environment. A common indicator of the early onset of AD involves an insidious progression of forgetfulness. For a discussion on the progressive development of dementia see Vickland and Brodaty [1] in which the 7 tier model applies a taxonomy for dementia with prevalence statistics.

With the rapid aging of society, the cognitive impairment and dementia have high incidence and this seriously impacts on the elderly's health and quality of life. At the Mayo Alzheimer's Disease Research Center (ADRC), studies manifest that when subjects are followed for 6 years, approximately 80% of patients with MCI will convert to AD [2]. Obviously, people with MCI have been the high-risk group for AD, therefore recognition of MCI serves as an important tool for the

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investigation of treatments aimed at managing AD and improving the quality of life (QoL) for both patients with dementia and carers.

AD can be diagnosed clinically with reasonable accuracy at the dementia stage when there is impairment in a patient's function at a social level. However, diagnosing the early onset of AD represents a difficult clinical decision and is frequently a matter of clinical judgment. Generally, the identification of MCI can be made by neuropathological confirmation of individuals who have been studied in life and meet criteria for MCI. The diagnostic criteria for MCI, as formulated by ADRC, are as follows [3]:

1. Memory complaint by patient, family or physician.
2. Normal activities of daily living.
3. Normal general cognitive function.
4. Objective impairment in one area of cognitive function as evidenced by scores >1.5 SD of age-appropriate norms or abnormal memory function for age.
5. Clinical dementia rating score of 0.5.
6. Not demented.

As can be seen from the above, clinicians diagnose MCI mainly based on their observations and experience, and it is usually difficult to complete accurate diagnosis due to the very mild symptoms of cognitive impairment. Recently brain informatics may be able to provide some reliable information of MCI detection. Brain structure changes associated with MCI have been researched widely, for example, the cortical thickness of MCI patients has been found significantly reduced because of the gray matter atrophy according to structural magnetic resonance imaging (MRI) studies [4]; and distributed and progressive changes of white matter fibers have been found in diffusion tensor imaging (DTI) studies [5]. Present findings suggest that most DTI-derived changes in MCI are largely secondary to gray matter atrophy [6]. In order to make prior diagnosis of disease and shun subjectivity and superficiality, an objective method able to diagnose MCI automatically using MRI may provide significant diagnostic benefits.

Studies have shown that a computer-based system, which intelligently filters and assesses relevant parameters, may foster an objective and correct diagnosis [7]. Decision-support, which takes computer as a tool, can help physicians diagnose more objectively as it can analyze data derived from medical tests and then present results to physicians using an appropriate visualization to enable diagnosis more easily and efficiently. Therefore, clinicians who are less well trained or experienced may also identify MCI with the help of decision-support tools. Accordingly, a knowledge-based decision support for identifying MCI is needed to support neurologists in the automatic classification of NC and MCI patients.

Ontology expressed using the Web Ontology Language (OWL) and playing a central role in the development of the Semantic Web [8] provides an explicit specification of conceptualizations and relationships among them in specific domains of interest [9]. Ontology is often used in decision support system as a tool of knowledge representation [10] and it provides convenience of knowledge acquisition, knowledge sharing, and knowledge reuse [11,12]. The main advantages of applying ontology technologies are as follows: (1) knowledge can be managed organically and hierarchically. (2) Semantic representation of knowledge provides the ability to share data across heterogeneous medical information systems. (3) It can be realized the decidability and consistency on expressed knowledge.

In our proposed method, we calculate the mean values of cortical thickness in different anatomical regions of brain as features, anatomical regions correspond to 90 non-cerebellar regions-of-interest (ROI) using the automatic anatomical labeling (AAL). AAL provided by the Montreal Neurological Institute (MNI) is an anatomical parcellation including 116 areas (45 anatomical volumes in each hemisphere and 26 areas of cerebellum) [13]. Then these features are stored into a domain ontology. We use ontology technique to manage and represent specialized knowledge explicitly to assist physicians distinguishing MCI patients from NC with the help of reasoning rules.

In conclusion, this approach enables the classification of NC and MCI patients based on cortical thickness in 'real-world' clinical conditions. The ontology and rule set are both flexible and extensible; these traits provide our approach with the capability to generalize to many other classification problems. The encouraging results suggest that the system can be used effectively in auxiliary diagnosis of MCI.

This paper is organized as follows: the following section describes related work which addresses the use of cortical thickness in detecting MCI and Ontology-Based Modeling (OBM) for representing clinical knowledge. Section 3 introduces the ontology-based decision support approach in detail including descriptions of data processing, feature extraction, and knowledge modeling. Section 4 presents some numerical results when using different machine learning algorithms in this approach, followed by the conclusions in Section 5.

2. Related work

Recently, many researchers have focused on the automatic identification and diagnosis of AD [14,15]. For instance, a method using the scale-invariant feature transforms in magnetic resonance images to diagnose AD has presented in [14] with the accuracy of 86%. Cho et al. [16] proposed to classify AD and NC using cortical thickness data which has demonstrated good results (with 82% sensitivity and 93% specificity). Although these methods for AD diagnosis are effective, it also should not be ignored that the diagnosis of MCI is conducive to early detection and early treatment of AD. Studies have shown that MCI patients have a certain degree of reduction in cortical thickness [17–19]. The cortical thickness of the MCI patient decreased significantly when compared to that in NC, mainly in the medial temporal lobe region and in some regions of the frontal and the parietal cortices [20]. Yao et al. [4] indicate most significant changes in MCI patients appeared in the prefrontal gyrus, the somatosensory cortex, the Wernicke's area and the superolateral temporal lobe when compare to these areas in NC. Thus cortical thickness could provide potentially powerful information to assist in the diagnosis of MCI. Approaches of classifying MCI and NC using cortical thickness have been

summarized in [21] which presents that the highest sensitivity is 65%. These approaches can automatically discriminate MCI patients and NC based on cortical thickness, but they are always based on a large set of medical image information, which is too complex to manage and integrate in a manual way.

Ontology is mainly used as semantic description and data integration or management of domain knowledge in medical practice [22–24], therefore, it is often applied in knowledge-driven decision support systems to assist in clinical diagnosis [12] as much knowledge should be managed reasonably in decision support systems [25]. For example, Esposito et al. [26] have implemented an ontology-based system that can support neuroradiologists in cases of multiple sclerosis, in which ontology is used to represent the semantic structure of expert knowledge and to provide a comprehensible formulation of the generated outcomes. A system proposed by Dasmahapatra et al. [27] uses ontology to model varied nature of expertise by describing concepts and relationships for breast cancer. Farooq et al. [28] develop an ontology driven adaptive questionnaire for cardio-vascular (CV) screening using standardized questionnaires for CV and family history acquired from Harvard medical school. Lee et al. [29] propose a novel five-layer fuzzy ontology and then extend the fuzzy ontology model to construct the fuzzy diabetes ontology (FDO) with diabetes domain, the expert system based on FDO has been shown to work effectively in diabetes decision-support.

Inspired by their work, we propose an ontology-based decision support approach which manages MCI-related knowledge in the way of ontological knowledge representation, performs MCI diagnosis, and eventually supports medical staff in their decision-making.

3. Materials and methodology

The framework of our proposed approach is set out in Fig. 1. This framework is composed of the data processing and features obtaining process, a MCI knowledge repository and an inference mechanism. The structure operates as follows (the details of every procedure will be depicted in the following sub-section):

- Initially, the cortical thickness of each ROI is calculated after the human magnetic resonance image is obtained.
- Secondly, we combine the three modules of MCI related concepts, 90 non-cerebellar ROI, and trail details and then store them into the MCI ontology. The rule set is trained by a large set of data through method of data mining in advance.
- Finally, we implement the inference engine to infer if the subject is a MCI patient by considering the computed data.

3.1. *Data processing and features extraction*

This section addresses the processing of the data and the features extraction. Following data description, image preprocessing and cortical thickness measurement is considered. And then features extracted from magnetic resonance image are discussed. After that, we address knowledge modeling with the nature of descriptive knowledge and procedural knowledge [26]. We conclude this section with a discussion around knowledge reasoning. The experimental results are presented in the following section.

3.1.1. *Data description*

The source dataset used in this research is from the ADNI database (http://adni.loni.ucla.edu/). The ADNI was 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), non-profit organizations and private pharmaceutical companies [30]. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (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 early Alzheimer's disease progression is intended to aid researchers and clinicians in the development of new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The image acquisition parameters have been described in *Alzheimer's Disease Neuroimaging Initiative* (http://www.adni-info.org/).

The study employed 364 subjects, MRI scans were acquired from 187 MCI patients and 177 normal controls coming from ADNI, all of the subjects' age is from 60 to 88 and the ratio of their sex is 1:1.

3.1.2. *Image preprocessing and cortical thickness measurement*

Magnetic resonance images of all subjects used in this research were preprocessed with the volume and surface pipeline of FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) [4]. The cortical thickness was obtained from the following steps:

- Images were corrected for non-uniformity artifacts using the N3 algorithms [31].
- The registered and corrected volumes were segmented into white matter, gray matter, cerebrospinal fluid and background using an advanced neural net classifier [32].
- The white and gray matter surfaces were then fitted using deformable models [33].
- After surface reconstruction, cortical thickness was measuring by *tlink* method [33,34] which can be used for getting distance between the white and pial surfaces.

3.1.3. *Features extracted from cortical thickness*

Following data preprocessing the cortical thickness of 327,682 vertexes for each subject were obtained. These measurements correspond to 90 non-cerebellar ROI. Here, the mean value of each 90 non-cerebellar ROI was calculated as standby data. In order to select or extract features from the obtained cortical thickness, statistical analysis was performed. Researches documented in [17,35–37] have observed that age and gender have a certain effect in variation of cortical thickness. In our work, we avoided the influence of age and gender by using general linear regression model.

In the 90 non-cerebellar ROI, every ROI of patients with MCI when compared to the same area of NC has a different level of brain atrophy [4]. We chose the mean values of ROI with

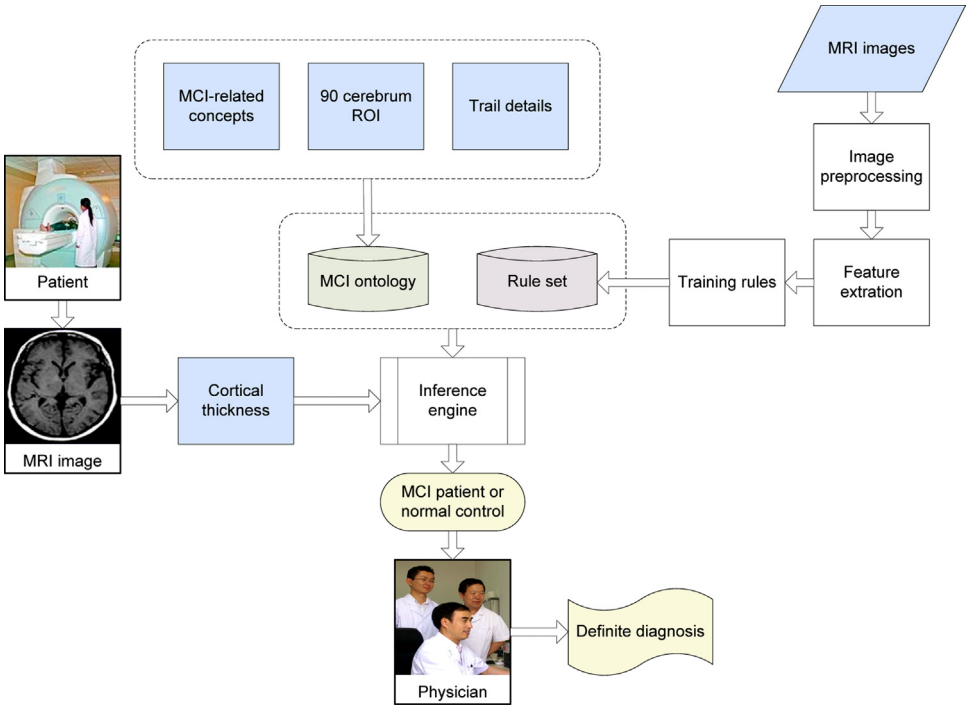


Fig. 1 – The framework of decision support for MCI diagnosis.

relatively serious atrophy as features. Independent sample t-tests were used to accomplish selection. Through independent sample t-tests (99% confidence interval), we compared statistical significance between two groups for each ROI and picked out brain regions with significant difference. Thus 46 areas of AAL that have relatively serious encephalatrophy in the 90 non-cerebellar ROI were selected and listed in Table 1. The mean values of these areas are used as features in the creation of the rule set.

3.2. *Knowledge modeling*

Essentially, this procedure can be divided into two parts: descriptive and procedural knowledge [26]. Descriptive knowledge relates to the structure of the domain knowledge and includes domain concepts with their properties and relations. Procedural knowledge addresses the rule set which is trained by a method of data mining.

For descriptive knowledge we elicited knowledge referring to terms from the Systematized Nomenclature of Medicine Clinical Terms which is a set of comprehensive clinical terminologies and encoded them into the domain ontology. The procedural knowledge describes logical relations that can provide more explicit information to enable the drawing of conclusions from descriptive knowledge. The architecture developed to address these demands is set out in Fig. 2.

3.2.1. *Descriptive knowledge*

The ontology has been created with a view to sharing across domains. To enable this objective the descriptive knowledge

Table 1 – The areas of relatively serious encephalatrophy in the all 90 non-cerebellar ROI.

	AAL brain partitions		
Left cerebral hemisphere	Calcarine_L;	Temporal_Sup_L;	Cingulum_Post_L;
	Lingual_L;	Temporal_Mid_L;	ParaHippocampal_L;
	Insula_L;	Temporal_Inf_L;	Occipital_Mid_L;
	Fusiform_L;	Frontal_Mid_L;	Frontal_Sup_Orb_L;
	Angular_L;	Parietal_Sup_L;	Frontal_Inf_Tri_L;
	Heschl_L;	Frontal_Sup_L;	Frontal_Sup_Medial_L;
	Precuneus_L;	Cingulum_Mid_L;	Temporal_Pole_Mid_L;
	Parietal_Inf_L;	SupraMarginal_L;	Temporal_Pole_Sup_L;
Right cerebral hemisphere	Olfactory_R;	Temporal_Sup_R;	ParaHippocampal_R;
	Rectus_R;	Temporal_Mid_R;	Frontal_Mid_Orb_R;
	Angular_R;	Temporal_Inf_R;	Frontal_Sup_Medial_R;
	Precuneus_R;	Occipital_Mid_R;	Frontal_Sup_Orb_R;
	Fusiform_R;	Parietal_Sup_R;	Temporal_Pole_Sup_R;
	Calcarine_R;	Parietal_Inf_R;	Frontal_Med_Orb_R;
	Frontal_Sup_R;	Cingulum_Post_R;	Temporal_Pole_Mid_R;
	Frontal_Mid_R;		

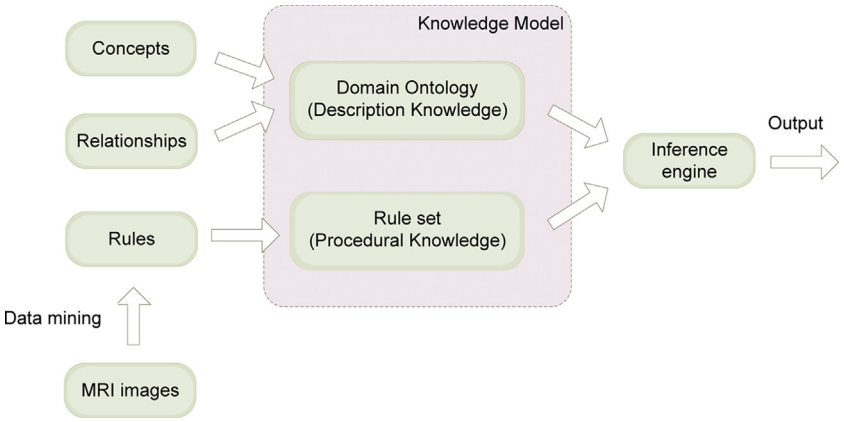


Fig. 2 – Knowledge modeling architecture.

is tripartite: the 90 non-cerebellar ROI, MCI related concepts and trial details. The part of trial details is used to present methods of data processing in our work. The structure of the ontology is shown in Fig. 3; the three aspects in the category level indicate contents of the MCI domain ontology, the terms which are shown within the rectangle in the class level of the structure are class terms of this ontology, and the low level is composed of individuals of the MCI domain ontology.

Initially the definitions of the basic terms used in reasoning are necessary, other terms are defined to enable the process of data processing; additionally, these terms are designed to facilitate ontology reuse in related domains of interest. These terms are defined in ontology as classes, there follows the definition of the properties and their related literal values, and the relationships between the terms have been specified as object properties and data properties. For example, each of the 90 non-cerebellar ROI has a data property "*hasValue*", the data type of this property is *double*, and the data value is the average of this area's cortical thickness, which serves as the basis of medical diagnosis. The core concepts of the ontology

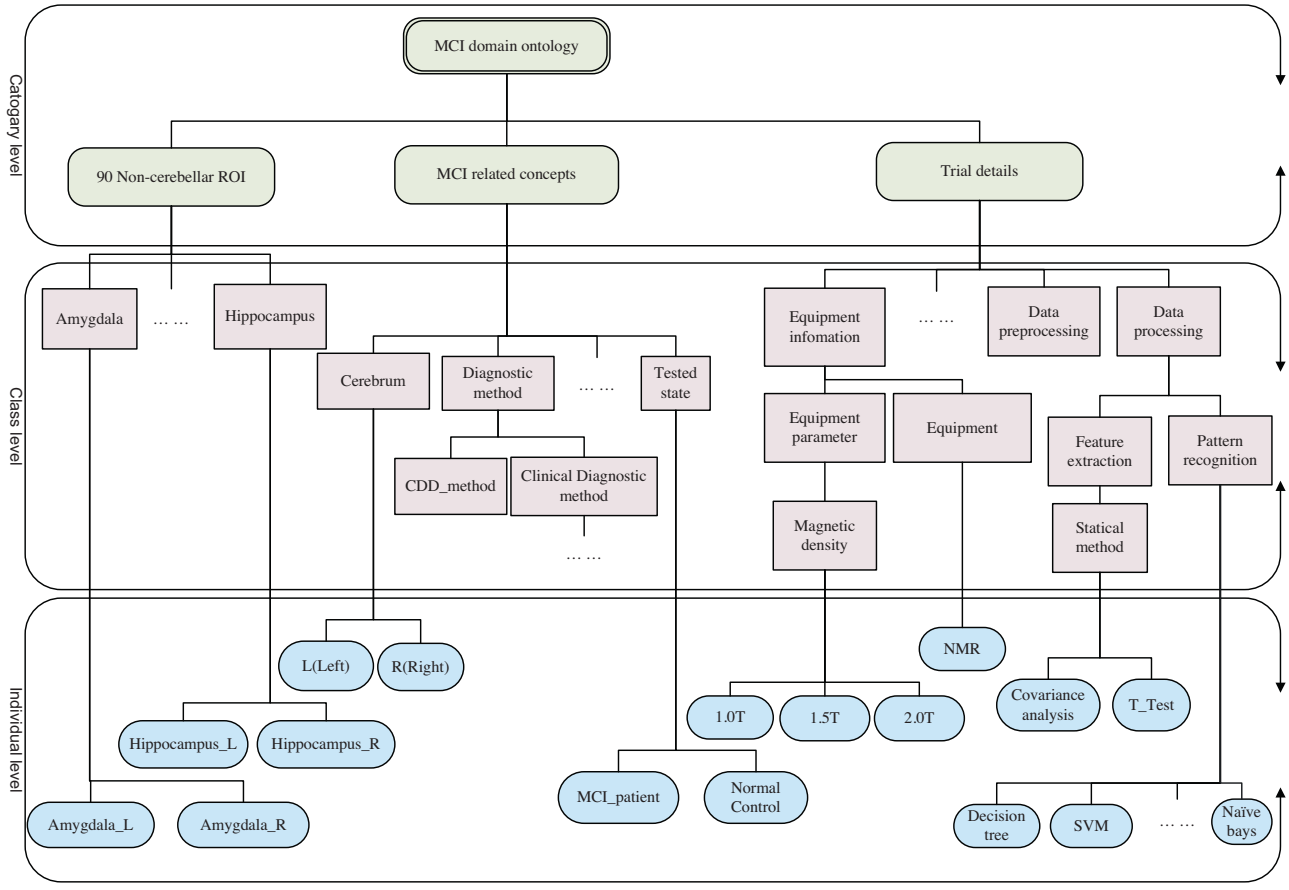


Fig. 3 – The structure of MCI domain ontology.

Table 2 – Several key classes and corresponding individuals.

Class	Individuals
Amygdala	Amygdala_L, Amygdala_R
Angular	Angular_L, Angular_R
Calcarine	Calcarine_L, Calcarine_R
OccipitalSup	OccipitalSup_L, OccipitalSup_R
...	...
Subject	subject1, subject2
Cerebrum	L, R
Tested_state	MCI_patient, Normal Control

Table 3 – Objective properties of the ontology.

Objective properties	Domain	Range
hasInformation	Subject	Patient_information
hasMCI	Subject	Tested_state
hasNeuroimaging	Subject	Neuroimaging
onCerebrum	Cortical_thickness_average	Cerebrum

are some terms related to reasoning (Table 2), each of which is formalized by means of concepts and individuals. The domain ontology concepts, which can be used to define the domain or range according to relations between them, are linked by object properties listed in Table 3. Attributes of concepts are also described here as data properties (see Table 4).

3.2.2. *Procedural knowledge*

To avoid superficial, subjective and biased evaluation, the procedural knowledge did not adopt expert knowledge, but was obtained by training a large set of data through classification algorithm. In this research we selected the C4.5 algorithm who can build a decision tree from a training set; the generated decision tree consists of decision nodes and leaves. A decision node generally specifies criteria based on one of attributes and a leaf specifies a class value [38]. A path from the root to a leaf node corresponds to a rule, and the entire decision tree corresponds to a set of expression rules.

The motivation for this selection includes: (1) the C4.5 algorithm can handle continuous and discrete data with a relatively small amount of calculation. (2) It is rapid in training and executing, and the processes require reasonable storage [39]. (3) The rules produced by C4.5 algorithm is easy to understand and analyze, they are often presented by an appropriate IF-THEN statement. (4) The C4.5 algorithm selects the appropriate feature of each node of the tree, in order to separate and group the testing samples properly [40]. That is, in our research this algorithm merely selects features which are most relevant to differentiate NC and patients with MCI. (4) According to the experimental results the C4.5 demonstrates good performance using in this approach. Due to these advantages, the C4.5 algorithm has been adopted in our study.

Table 4 – Data properties of the ontology.

Data properties	Domain	Data type
nameValue	Subject	String
hasValue	Cortical_thickness_average	Double
magneticValue	Magnetic_field_density	Float
equipmentName	Equipment_type	String

Table 5 – The parameters of C4.5 algorithm setting in WEKA.

Option and description	Value
confidenceFactor – The confidence factor used for pruning	0.25
minNumObj – The minimum number of instances per leaf	2
numFolds – The amount of data used for reduced-error pruning	3
reducedErrorPruning – Whether reduced-error pruning is used instead of C.4.5 pruning	True
seed – Used for randomizing the data when reduced-error pruning is used	1
subtreeRaising – Whether to consider the subtree raising operation when pruning	True

We used J48 in WEKA (Waikato Environment for Knowledge Analysis, version 3.7.9) [41,42], a tool of Data Mining, for the rule generation. Some parameters were set for getting a better performance, which details in Table 5. Part of decision tree constructed by C4.5 algorithm is presented in Fig. 4. There followed the creation of the rule set using the IF-THEN logic structure to implement the concepts and properties as defined in the domain ontology. Take one of the rules for instance: [IF "*left middle frontal gyrus*" > 2.417068 THEN *Subject* = ⟨normal control⟩]. This rule is depicted as follow:

String rules = "[rule1: (?subject rdf: type base:Subject)

(?f1 rdf: type base:FrontalMid)
(?f1 base:hasValue?value1) greaterThan(?value1,2.417068)
(?f1 base:onCerebrum?cerebrum1)
(?cerebrum1 rdfs: label "R")
(?testedstate rdf:type base:Tested_state)
(?testedstate base:hasStatus "2")
->(?subject base:hasMCI?testedstate)]"

3.3. *Knowledge reasoning*

Knowledge reasoning based on the inference engine is constructed to enable the processing of the formalized knowledge. It is the process of concatenating the descriptive knowledge with the procedural knowledge and it is designed to approximate to human reasoning capabilities in the drawing conclusions from existing data. After one subject's data is put into inference engine which is implemented using Jena API, the engine can output if this subject has MCI on the base of the rule-set, at the same time the input data of subject is recorded in the domain ontology so as to look up, just as Fig. 5.

4. Experimental results and evaluation

To obtain an unbiased estimation of the rule-set generated according to the C4.5 algorithm and ensure the accuracy of the generated model without overfitting occurred, a 10-fold cross validation process was adopted in our research.

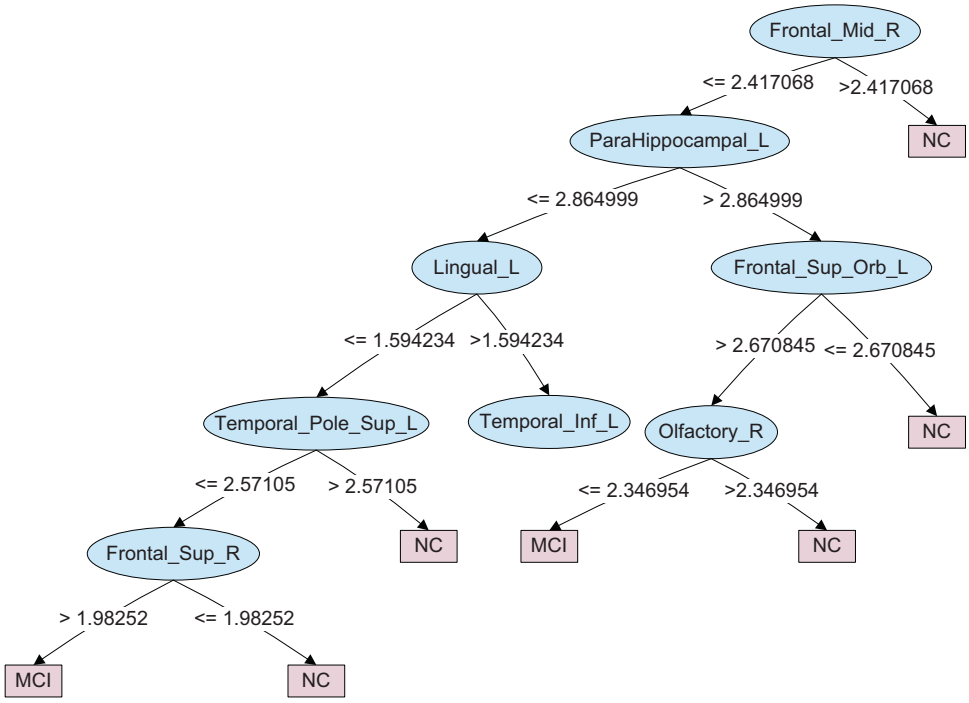


Fig. 4 – Part of decision tree constructed by C4.5 algorithm.

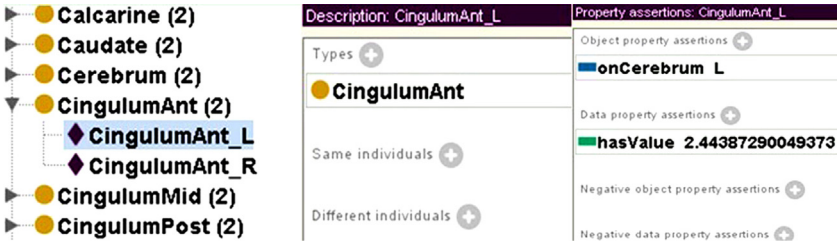


Fig. 5 – The data recorded in the domain ontology after reasoning.

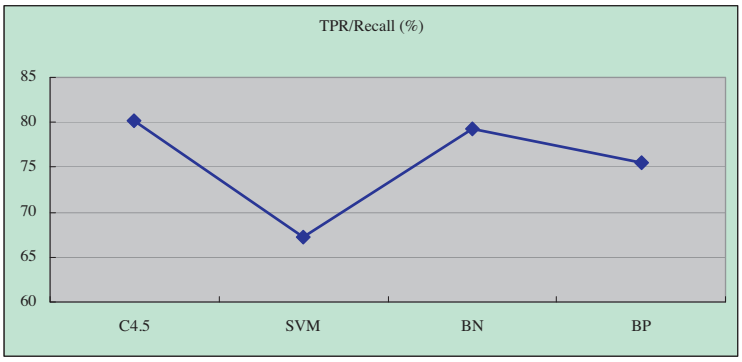
Simultaneously, we trained other popular classification algorithms (including Bayesian network, back propagation neural networks, and support vector machine) instead of C4.5. Default parameters of these algorithms were used except J48 (see Table 5), for example, *RadioBaseFunction* was selected as kernel function in SVM and *SimpleEstimator* was used in Bayesian network. We have compared C4.5 algorithm with other classification algorithms, and the accuracy (the mean of 10-fold cross validation) for each algorithm is synthesized in Fig. 6 and Table 6. To evaluate the performance of each algorithm for MCI diagnosis, we computed the number of true positives *TP* (i.e. the number of diseased individuals which were correctly identified by the classifier), the number of true negatives *TN* (i.e. the number of healthy individuals which were correctly identified by the classifier), the number of false positives *FP* (i.e. the number of healthy individuals which were not correctly identified by the classifier), the number of false negatives *FN* (i.e. the number of diseased individuals which were not correctly identified by the classifier) in [21] (to comprehend these statistic metrics visually, please see Table 7).

Table 6 – The accuracy of several classification algorithms.

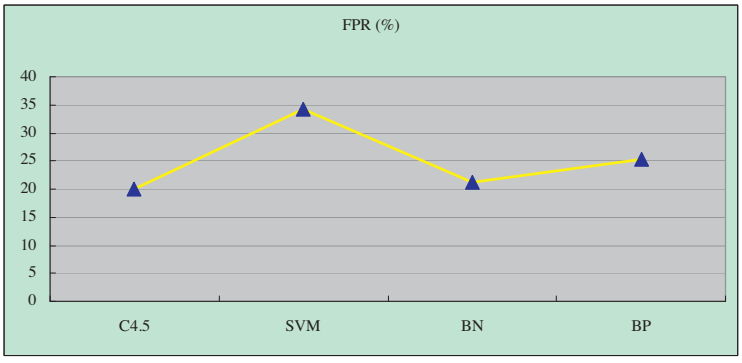
Algorithm	Kappa statistic	Training time (s)
C4.5	0.6021	0.16
SVM	0.3357	0.28
BN	0.5129	0.05
BP	0.5049	10.28

Table 7 – A confusion matrix for binary classification.

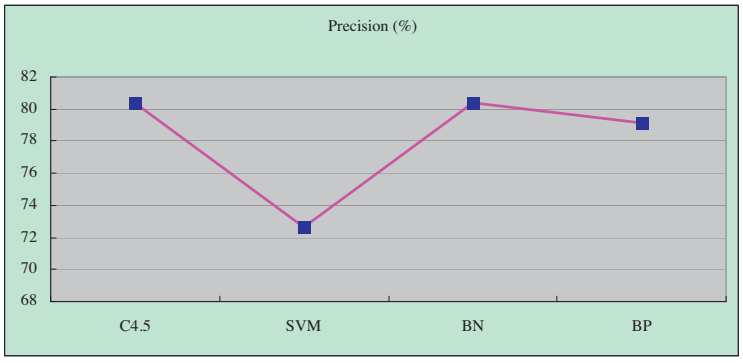
Correct classification	Obtained classification	
	C1	C2
C1	TP (true positives)	FN (true negatives)
C2	FP (false positives)	TN (false negatives)



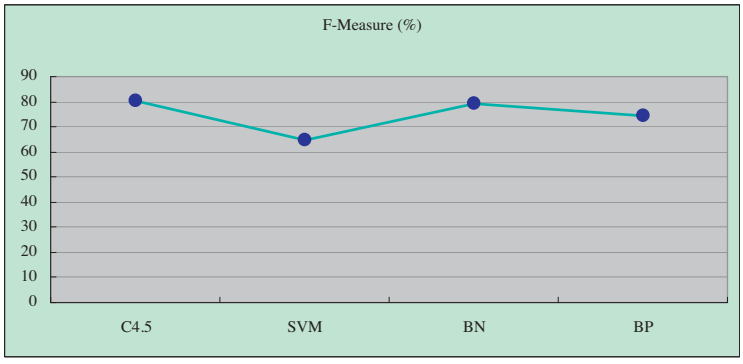
(a) The true positive rate (TPR)/Recall



(b) The false positive rate (FPR)



(c) Precision



(d) F-Measure

Fig. 6 – The comparison of four classifiers' parameters.

Table 8 – The result of other three schemes compared to C4.5 using paired t-test.

C4.5	SVM	BN	BP
75.73% (v/ /*)	67.33% (0/0/1)	75.74% (0/1/0)	77.38% (0/1/0)

We then employed the following statistical measures to evaluate the diagnostic power of the various methods used for comparison:

- The true positive rate (TPR) defined as: $TP/(TP+FN)$ which we also term as sensitivity.
- The false positive rate (FPR) defined as: $FP/(TN+FP)$ which is 1-specificity.
- Precision defined as: $TP/(TP+FP)$.
- Recall defined as: $TP/(TP+FN)$ whose computing method is same to TPR.
- F-Measure which is the weighted harmonic mean of precision and recall.
- The Kappa statistic defined as: $2(TN*TP - FP*FN)/((TN+FN)*(FN+TP)+(FP+TP)*(TN+FP))$.
- The training time used on establishing the model.

Among these metrics, we expect higher values of TPR, Precision, Recall, F-measure, and Kappa statistic, and lower value of FPR because these results indicate a better classification. The Kappa statistic which measures the agreement of prediction with the true class is expected to have a value close to 1.0 (1.0 signifies complete agreement). The results are shown in Fig. 6 and support the conclusion that it gets a higher TPR, Recall, F-measure, and equal Precision with a Bayesian network while using C4.5 algorithm, it also has a lower FPR here than other three classification algorithms. The value of Kappa statistic when using C4.5 is 0.6021 which is the most close to 1.0, but the training time of Bayesian Network is about 0.11 s shorter than that of C4.5 (see Table 6).

We created a standard experiment in WEKA (version 3.7.9) that runs several machine learning algorithms against the dataset (mentioned in Section 3.1.1) and then analyzed the results to determine if C4.5 is (statistically) better than the other algorithm. We also adopted 10-fold cross validation, additionally, in order to get statistically meaningful results, the default number of iterations is 10. This means 100 calls of one classifier with training data and tested against test data. This experiment consisted of 100 runs, for 4 schemes (C4.5, SVM, BN, BP), for 1 dataset, for a total of 400 results. We chose C4.5 algorithm as the baseline scheme and used paired t-test (95% confidence interval) to make a comparison of the 4 schemes which is displayed in Table 8. The annotation v or * indicates that a specific result is statistically better (v) or worse (*) than the baseline scheme at the significance level specified (currently 0.05) [42]. At the bottom of each column after the first column is a count (xx/yy/zz) of the number of times that the scheme was better than (xx), the same as (yy), or worse than (zz) the baseline scheme on the datasets used in the experiment [42]. In this experiment, the results of SVM are statistically worse than the baseline established by C4.5 (0/0/1), and the results of both BN and BP are the same as C4.5 (0/1/0) on this dataset. Simultaneously, each two of the four schemes were compared with each other (Table 9). The number in brackets represents the number of significant wins for the column with regard to the row and a 0 means that the scheme in the corresponding column did not score a significant win with regard to the scheme in the row [42]. The first row (– 1 1 1) of Table 9 indicates that C4.5, BN, and BP are better than SVM. It is worth noting that BN and BP are better than C4.5 when the iteration is 10 (C4.5 – 75.73%, BN – 75.74%, BP – 77.38%), but they do not score a significant win in statistical when compared to C4.5 (see the number in the brackets of Table 9).

Table 9 – The summary test of the four schemes.

	SVM	BP	BN	C4.5
SVM	–	1(1)	1(1)	1(1)
BP	0(0)	–	0(0)	0(0)
BN	0(0)	0(0)	–	0(0)
C4.5	0(0)	1(0)	1(0)	–

The classification accuracies of BN and BP are a little higher than C4.5 algorithm when the number of iterations is 10, but considering all respects including statistical significant and the ability of integrating into ontology-based knowledge model, the C4.5 algorithm would be the most suitable for the problem this research addresses.

5. Discussion and conclusion

The paper has addressed knowledge-based decision support for the identification of MCI to enable automation of decision-support for clinicians in the classification of NC and MCI. We have combined the mean values of cortical thickness as features and knowledge reasoning which includes domain ontology and rule set. The usage of knowledge reasoning is to present specialized knowledge explicitly to assist physicians distinguishing MCI patients from NC. Standard medical knowledge and data processing methods of MCI have been encoded into domain ontology to enable sharing and reuse in similar domains of interest. The ontology has been designed to be hierarchical, simple and intuitive, the goal is to enable a data structure that is machine readable and also can be understood by a non-technical human audience. Moreover, we train the rule set using the C4.5 algorithm for the ontology as this algorithm demonstrates a higher degree of accuracy in classification and additionally simplifies understanding of inference rules due to the use of IF-THEN statements. Researchers may extend our ontology to represent all the domain knowledge of MCI as required.

In this paper, we use cortical thickness as the diagnostic indicator because of the gray matter atrophy in MCI patient. Automatic classification of patients with MCI from structural MRI using different methods have been summarized in [21] which evaluated the performance of ten approaches (five voxel-based methods, three methods based on cortical thickness and two methods based on the hippocampus) using a data set (76 MCI patients and 162 NC) from the ADNI database, and our results (0.802 sensitivity and 0.799 specificity) is better than the results (the highest sensitivity reaches 0.73) [21]. But it is worth mentioning that the reduction of cortical thickness is not the only indicator of MCI, functional Magnetic Resonance

Imaging (fMRI) and DTI could also be used to distinguish MCI patients from NC. Koch et al. [43] had proved that analysis of fMRI using different methods can identify patients with MCI efficiently. Changes in white matter reflect changes in the brain's structural connectivity pattern, so it can also give a good result when using individual structural connectivity networks to distinguish MCI patients from NC have also got a good result [44]. Integrating information from DTI and fMRI achieved an improved classification performance too, and the classification accuracy can reach 96.3% [45]. With regard to the accuracy in [45] that is higher than our results, we think that the reason may lies in the following several aspects: (1) the data used in [45] came from the Duke-UNC Brain Imaging and Analysis Center (BIAC), not ADNI, the performance may be affected by the data because of individual difference; (2) the number of the subjects we chose is much more than that in [45] which involved only 27 participants: 10 individuals with MCI, and 17 normal controls; (3) we used different mode of cross-validation for the estimation of classification accuracy, k-fold cross-validation that we have employed would be more precise when compared to leave-one-out cross-validation in [45].

The experimental results demonstrate that the posited approach is potentially usable in 'real-world' diagnostic situations. While the research has addressed a number of issues with our proposed approach:

- The accuracy of diagnosis has room for improvement. The sensitivity (0.802) can be only used to assist physician but it is not enough to be used to diagnose MCI alone.
- The rule set in our approach is fixed, but decision tree generated by C4.5 algorithm is sensitive to the training data. Considering physical difference of groups in different regions, the rule set should be adapted to different groups of people. So it is more appropriate to make the rule set update dynamically.

Notwithstanding existing the aforementioned issues and challenges, we prove that our approach could classify NC and MCI patients effectively based on cortical thickness in 'real-world' clinical conditions, and could be used in clinical diagnosis of MCI. Moreover, the ontology and rule-set can be both flexible and extensible; this provides the capability for the posited approach to generalize to many other classification problems.

Conflict of interest statement

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication, and no financial relationship with the organization that sponsored the research exits in the submission of this manuscript. The experiments comply with the current laws of China.

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