1 **Machine Learning methods for predicting conversion**
2 **from Mild Cognitive Impairment to Alzheimer's**
3 **disease. A systematic review**

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ABSTRACT

Background: Increase in life-span in our society is a double-edged sword that entails a growing number of patients with neurocognitive disorders, Alzheimer's disease being the most prevalent. Advances in medical imaging and computational power, enable new methods for early detection of neurocognitive disorders with the goal of preventing or reducing cognitive decline. Computer-aided image analysis and early detection of changes in cognition is a promising approach for patients with mild cognitive impairment, sometimes a prodromal stage of Alzheimer's disease.

Methods: We conducted a systematic review following PRISMA guidelines of studies where Machine Learning was applied to neuroimaging data in order to predict whether patients with Mild Cognitive Impairment might develop Alzheimer's disease or remain stable. After removing duplicates, we screened 452 studies and selected 116 for a qualitative analysis.

Results: Most studies used Magnetic Resonance Image (MRI) and Positron Emission Tomography (PET) data but also Magnetoencephalography. The datasets were mainly extracted from the Alzheimer's disease Neuroimaging Initiative (ADNI) database with some exceptions. Regarding the algorithms used, the most common was Support Vector Machine with a mean accuracy of 75.4%, but Convolutional Neural Networks achieved higher a mean accuracy of 78.5%. Studies combining MRI and PET achieved overall better classification accuracy than studies that only selected one neuroimaging technique. In general, the more complex models such as those based on Deep Learning, combined with multimodal and multidimensional data (neuroimaging, clinical, cognitive, genetic, and behavioral) achieved the best performance.

Conclusions: Although performance of the different models still has room for improvement, the results are promising and this methodology has a great potential as a support tool for clinicians and healthcare professionals.

KEYWORDS: Alzheimer's disease; Conversion; Machine Learning; Magnetic Resonance; Mild Cognitive Impairment; PRISMA; Positron Emission Tomography; Prediction

1 BACKGROUND

The increase in life-span experienced in Western societies has largely been drive by medical and technological advances (1), however, this improvement has resulted in an increasing number of people diagnosed with neurocognitive disorders. In 2010, dementia was associated with \$604 billion dollars of healthcare expenses in United States of America (2). Every year, ten million new cases of dementia are registered and by 2050 it is estimated that 135 million people will have some degree of dementia (3). Age is the main risk factor for dementia; the prevalence is 1-2% at the age of 65 but reaches 30% at the age of 85. From all neurodegenerative disorders, about 60-90% are characterized as Alzheimer's Disease (AD) subtype (depending on the diagnostic criteria used) (4), for which there is yet no cure.

Patients are typically diagnosed when the symptoms of cognitive decline have already manifested. In such cases, the diagnosis was determined too late, failing to implement preventive protocols to reduce cognitive decline. Pharmacological and non-pharmacological treatments have proven to be effective in reducing cognitive and behavioral symptoms in early stages of the disease (5). In light of these treatments, recent studies have focused on detecting patients with cognitive impairment that have not reached dementia in order to delay or prevent its development. The last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes a specific category for this type of patients called Mild Neurocognitive Disorder, analogous to the Mild Cognitive Impairment (MCI) whose main characteristic is having minor memory impairment (4) (throughout this review, MCI will be used instead of Mild Neurocognitive Disorder as it is more frequent in the scientific literature). MCI can, in some cases, be a prodromal stage of dementia, especially for AD (6).

In late stages, AD is easily detectable with neuroimaging techniques and cerebrospinal fluid evaluations for the presence of neurofibrillary clews, beta-amyloid and tau proteins (7), and temporal cortex atrophy (4). In early stages, however, when these biomarkers have not clearly emerged, early detection of the disease or its progression from MCI to AD remains challenging. Conventional neuroimaging techniques such as Magnetic Resonance Image (MRI) or Positron Emission Tomography (PET) have had limited utility so far in early detection for individual patients (8,9). However, the scientific community now has access to thousands of neuroimaging longitudinal datasets from

71 healthy, MCI, and AD subjects along with other variables (i.e. demographic, genetic,
72 and cognitive measurements, etc.) stored in public databases such as the Alzheimer
73 Disease Neuroimaging Initiative (ADNI) (<http://adni.loni.usc.edu>). These datasets can
74 be compared and analyzed to perform classification and automatic detection of AD and
75 MCI progression (10,11) using newly developed computer-aided techniques like
76 Machine Learning (ML) algorithms.

77 The ML paradigm consists of training an algorithm with a dataset; in this case,
78 neuroimaging results together with other clinical variables, to extract common factors
79 that help classify subjects according to a variable of interest. In the case of an early
80 diagnosis of AD and distinction from a stable MCI condition, for example, the
81 algorithm learns to classify the data according to the specific diagnosis and extracts
82 which factors have been the most relevant for the differentiation between the groups.
83 Subsequently, the trained algorithm can be used to classify a specific individual for
84 which we do not know the diagnosis and thus manage to assist in the therapeutic
85 approach (12–14). This technique can be applied to any disease that occurs with
86 morphological changes or with characteristic neural patterns. See Arbabshirani, Plis,
87 Sui, & Calhoun (15) for a review of the same objective and methodology but applied to
88 autism, attention deficit disorder, and schizophrenia.

89 Recent work has demonstrated that ML algorithms are able to classify images from AD,
90 MCI, and healthy participants with very high accuracy levels (16,17). Although such
91 classification has provided valuable information about AD biomarkers, for this
92 technology to have more substantial clinical impact by empowering a clinician to
93 administer a customized treatment protocol, it is necessary to determine and predict
94 whether a MCI patient will progress to AD or remain stable. The goal of this systematic
95 review is to analyze the existing classification methods based in ML algorithms applied
96 to neuroimaging data in combination with other variables for predicting MCI to AD
97 conversion.

99 2 METHODS

100 To perform this systematic review we followed the Preferred Reporting Items for
101 Systematic Reviews and Meta-Analysis (PRISMA) guidelines (18,19). A systematic
102 search was done to find studies that included ML methods to predict MCI to AD
103 progression using neuroimaging techniques. Progression to AD from MCI is established
104 when, during a follow-up period (3 years for ADNI and 1 year for AddNeuroMed
105 databases), a patient that was initially classified as MCI, is diagnosed with Alzheimer
106 (progressive MCI or pMCI) based on clinical criteria (MMSE and CDR scales, and
107 NINCDS/ADRDA criteria for probable AD (20,21)). Patients are considered “stable
108 MCI” (sMCI), when they were diagnosed as MCI at baseline and the diagnosis
109 remained as MCI during the follow-up.

110 Only articles written in English and published between January 2010 and May 2021
111 (included) were selected. Articles published before 2010 were not included because the
112 technological (e.g., computational power, graphical processing units) and
113 methodological (e.g., ML and deep learning algorithm development) gap between those
114 studies and the current standards makes them hardly comparable. In fact, even the
115 comparison between articles published in early vs. late 2010s present methodological
116 gaps, these differences are not only due to better methods but mainly to technological
117 advances that were not possible before 2010 and at the beginning of the decade, and the
118 growth of the ADNI database.

119 We performed an advanced search concatenating terms with Boolean operators in
120 PubMed, PsycINFO and Web of Science databases as follows: (*"computational*
121 *neuroscience" OR "artificial intelligence" OR "machine learning" OR "deep learning"*
122 *OR "neural network*") AND ("neuroimag*") AND ("Alzheimer*" OR "AD dementia")*
123 *AND ("mild cognitive impairment" OR "MCI") AND ("conversion" OR "predict*" OR*
124 *"follow-up")*

125 After removing duplicates, the eligibility criteria were applied by two independent
126 reviewers (SG and RVS) to select only the articles that included: 1) prediction of MCI
127 to AD conversion; 2) use of neuroimaging data; 3) classification methods based on ML
128 algorithms; and 4) accuracy results.

Once the selection of studies was concluded, the following data was extracted for each study: 1) first author and year of publication; 2) groups; 3) sample size and mean age; 4) database; 5) neuroimaging technique used and variables selected; 6) classification method; 7) validation method; 8) accuracy achieved and 9) Area Under the ROC Curve.

We also analyzed the risk of bias of the selected studies. The aspects considered in the analysis of bias were based on the Cochrane guidelines for systematic reviews (22) but the exact criteria were adapted by taking into account the particular methodology and goals of the studies, focused on creating and validating a classification model in large datasets. The criteria used are detailed in Table 1.

Table 1

Risk of bias analysis criteria

Risk of bias	Score	Criteria
Database	Low (0)	Use of validated and widely used dataset for the study of biomarkers of Alzheimer's Disease (AD) including several years of follow-up with information of stable and progressive MCI patients
	Medium (1)	Use of similar database with less widespread usage
	High (2)	The participants were selected by the authors and no validated database was used
Validation of the classification method	Low (0)	The study validates the classification method with a test sample and/or and independent sample
	Medium (1)	It uses a different validation method
	High (2)	There is no validation of the classification method
Mathematical development of the algorithms	Low (0)	Explanation of their theoretical basis or architecture for Neural Networks
	Medium (1)	The authors refer to literature but do not develop their mathematical notation or architecture
	High (2)	No information about the model

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141 We also performed an interpretability analysis based on the framework proposed by
142 Kohoutová et al. (23). These authors developed three levels of assessment for the
143 interpretability of ML models in neuroimaging based on the model, the feature, and the
144 biology; also, each level has several sublevels. *Model-level* assessment consists on
145 evaluating the model as a whole and testing it in different contexts and conditions. The
146 sublevels include sensitivity and specificity, generalizability, behavioural analysis,
147 representational analysis, and analysis of confounds. *Feature-level* assessment consists
148 on evaluating the significance of individual features used in prediction, including
149 stability, feature importance, and visualization. Finally, the *biology-level* assessment is a
150 validation of the model based on its neurobiological plausibility and it has two
151 sublevels: literature (relationship with the model with previous literature) and invasive
152 studies (the possibility of using more invasive methods).

153 We assessed whether the studies included in the review complied with each of the
154 sublevels but we did not include behavioural analysis, representational analysis, and
155 invasive studies sub-levels. *Behaviour analysis* sub-level was not considered because
156 the only “behaviour” of the model is to classify subjects, and the behaviour is measured
157 as accuracy, which is included in the sensitivity and specificity sublevels.
158 *Representational analysis* compares the model with other models, other brain regions or
159 other experimental settings; in our review, the main goal of almost all studies was to
160 find neural patterns that predict AD and therefore it is common to use the whole brain
161 as a feature. Also, there is only one experimental setting aimed to find maximum
162 classification accuracy so it cannot be compared to similar experiments in the same
163 study, only with similar literature (which represents another sub-level). Finally, the
164 *invasive studies* sub-level is not applicable because the long-term objective of these
165 investigations is to find a non-invasive method of predicting AD as soon as possible.

166

167 **3 RESULTS**

168 As shown in Figure 1, the workflow followed for the article selection included the four
169 phases (identification, screening, eligibility, and inclusion) proposed by the PRISMA
170 guidelines (18,19). The 452 articles remaining after eliminating duplicates were

171 screened and, after applying the exclusion criteria, 117articles were selected for the
172 review.

173 The risk of bias analysis is shown in Figure 2 and Table 2. The overall risk of bias of all
174 the studies was considered low. From the 117 articles selected at the eligibility stage,
175 only one study (24) was not included in the qualitative analysis because of the high risk
176 of bias. The sample size in this study was seven subjects, and it did not include any
177 validation method. Therefore, the final number of studies included in the qualitative
178 analysis was 116.

179

Figure 1

PRISMA workflow for study selection.

Note. This diagram shows the PRISMA workflow followed for the sample selection adapted from Moher et al. (18).
WOS: Web Of Science; AD: Alzheimer's disease; MCI: Mild Cognitive Impairment.

Figure 2

Risk of bias analysis

Table 2

Risk of bias analysis for individual studies

<i>Author (year)</i>	<i>Algorithm</i>	<i>Validation</i>	<i>Database</i>	<i>Total bias</i>
Plant et al. (2010) (25)	0	0	2	2
Chincarini et al. (2011) (26)	0	0	0	0
Costafreda et al. (2011) (27)	1	0	1	2
Filipovych et al. (2011) (28)	0	0	0	0
Hinrichs et al. (2011) (8)	0	0	0	0
Westman et al. (2011) (29)	0	0	1	1
Wolz et al. (2011) (30)	1	0	0	0
Zhang et al. (2011) (31)	0	0	0	0
Batmanghelich et al. (2012) (32)	0	0	0	0
Cheng et al. (2012) (33)	0	0	0	0
Cho et al. (2012) (34)	0	0	0	0
Gray et al. (2012) (35)	0	0	0	0
Li et al. (2012) (36)	1	0	0	1
Toussaint et al. (2012) (37)	1	0	0	1
Wee et al. (2012) (38)	0	0	0	0
Ye et al. (2012) (39)	1	0	0	1
Zhang et al. (2012) (9)	0	0	0	0
Adaszewski et al. (2013) (40)	1	0	0	1
Aguilar et al. (2013) (41)	1	0	1	2
Babu et al. (2013) (42)	0	0	0	0
Casanova et al. (2013) (43)	0	0	0	0
Cheng et al. (2013) (44)	0	0	0	0

<i>Author (year)</i>	<i>Algorithm</i>	<i>Validation</i>	<i>Database</i>	<i>Total bias</i>
Liu, M. et al. (2013) (45)	0	0	0	0
Liu, X. et al. (2013) (46)	0	0	0	0
Wee et al. (2013) (47)	0	0	0	0
Young et al. (2013) (48)	1	0	0	1
Apostolova et al. (2014) (49)	1	0	0	1
Guerrero et al. (2014) (50)	0	0	0	0
Lebedev et al. (2014) (51)	0	0	0	0
Liu, M. et al. (2014) (52)	0	0	0	0
Liu, F. et al. (2014) (53)	0	0	0	0
Min et al. (2014) (54)	0	0	0	0
Suk et al. (2014) (55)	0	0	0	0
Tong et al. (2014) (56)	0	0	0	0
Cabral et al. (2015) (57)	0	0	0	0
Cheng et al. (2015) (58)	0	0	0	0
Cheng et al. (2015) (59)	0	0	0	0
Moradi et al. (2015) (60)	0	0	0	0
Raamana et al. (2015) (61)	0	0	0	0
Ritter et al. (2015) (62)	1	0	0	1
Salvatore et al. (2015) (63)	0	0	0	0
Xu et al. (2015) (64)	0	0	0	0
Ardekani et al. (2016) (65)	1	1	0	2
Cappeci et al. (2016) (24)	0	2	2	4
Collij et al. (2016) (66)	0	0	2	2
Li et al. (2016) (67)	2	0	0	2
Liu et al. (2016) (68)	0	0	0	0
López et al. (2016) (69)	0	0	0	0
Suk et al. (2016) (70)	0	0	0	0
Thung et al. (2016) (71)	0	0	0	0
Vasta et al. (2016) (72)	0	0	0	0
Zhang et al. (2016) (73)	0	0	0	0
Zhang et al. (2016) (74)	0	0	0	0
Çitak-Er et al. (2017) (75)	0	0	0	0
Hojjati et al. (2017) (76)	0	0	0	0
Long et al. (2017) (77)	0	0	0	0
Mathotaarachchi et al. (2017) (78)	0	0	0	0
Suk et al. (2017) (79)	0	0	0	0
Tong et al. (2017) (80)	0	0	0	0
Choi et al. (2018) (81)	0	0	0	0

<i>Author (year)</i>	<i>Algorithm</i>	<i>Validation</i>	<i>Database</i>	<i>Total bias</i>
Donnelly-Kehoe et al. (2018) (82)	1	0	0	1
Gao et al. (2018) (83)	1	0	0	1
Gómez-Sancho et al. (2018) (84)	0	0	0	0
Hojjati et al. (2018) (85)	1	0	0	1
Khanna et al. (2018) (86)	0	0	0	0
Lin et al. (2018) (87)	0	0	0	0
Liu et al. (2018) (88)	0	0	0	0
Liu et al. (2018) (89)	0	0	0	0
Lu et al. (2018) (90)	0	0	0	0
Minhas et al. (2018) (91)	0	0	0	0
Popuri et al. (2018) (92)	2	0	0	2
Sorensen et al. (2018) (93)	0	0	0	0
Sun et al. (2018) (94)	0	0	0	0
Wu et al. (2018) (95)	0	0	0	0
Yan et al. (2018) (96)	0	0	0	0
Basaia et al. (2019) (97)	0	0	0	0
Cheng et al. (2019) (98)	0	0	0	0
Collazos-Huertas et al. (2019) (99)	1	0	0	1
Elahifasae et al. (2019) (100)	0	0	0	0
Ezzati et al. (2019) (101)	1	0	0	1
Gupta et al. (2019) (102)	0	0	0	0
Lee et al. (2019) (103)	0	0	0	0
Lee et al. (2019) (104)	0	0	0	0
Lei et al. (2019) (105)	0	0	0	0
Li et al. (2019) (106)	0	0	0	0
Li et al. (2019) (107)	0	0	0	0
Oh et al. (2019) (108)	0	0	0	0
Pan et al. (2019) (109)	0	0	0	0
Pusil et al. (2019) (110)	0	0	2	2
Spasov et al. (2019) (111)	0	0	0	0
Wang et al. (2019) (112)	1	0	0	1
Wee et al. (2019) (113)	0	0	0	0
Xu et al. (2019) (114)	0	0	0	0
Zhou et al. (2019) (115)	0	0	0	0
Zhu et al. (2019) (116)	0	0	0	0
Abrol et al. (2020) (117)	0	0	0	0
Gao et al. (2020) (118)	0	0	0	0
Giorgio et al. (2020) (119)	1	0	0	1

<i>Author (year)</i>	<i>Algorithm</i>	<i>Validation</i>	<i>Database</i>	<i>Total bias</i>
Khatri et al. (2020) (120)	0	0	0	0
Lin et al. (2020) (121)	0	0	0	0
Lin et al. (2020) (122)	0	0	0	0
Pan et al. (2020) (123)	0	0	0	0
Ramon-Julvez et al. (2020) (124)	1	0	0	1
Xiao et al. (2020) (125)	0	0	0	0
Xu et al. (2020) (126)	0	0	2	2
Yang et al. (2020) (127)	1	0	0	1
Yee et al. (2020) (128)	0	0	0	0
Zhou et al. (2020) (129)	0	0	0	0
Bae et al. (2021) (130)	0	0	0	0
Mofrad et al. (2021) (131)	1	0	0	1
Mofrad et al. (2021) (132)	1	0	0	1
Pan et al. (2021) (133)	0	0	0	0
Shen et al. (2021) (134)	0	0	0	0
Syaifullah et al. (2021) (135)	1	0	0	1
Wen et al. (2021) (136)	1	0	0	1
Zhang et al. (2021) (137)	0	0	0	0
Zhu et al. (2021) (138)	0	0	0	0
<i>Total</i>	<i>28/234</i>	<i>3/234</i>	<i>13/234</i>	<i>43/702</i>

Note. This table shows the results of the bias analysis performed based on Higgins et al. (22) with the punctuations specified in Table 1.

The studies selected for the qualitative analysis are presented in Table 3 following the structure explained in the data extraction section (study, cohort, sample [mean age], database, features and neuroimaging technique, classification method, validation method, results [% accuracy], and AUC ROC).

Magnetic Resonance was the most common kind of neuroimaging used (in 76 out of 116 studies), followed by Positron Emission Tomography (PET, 11 studies), 26 studies included data from both techniques (MRI and PET), two studies used Magnetoencephalography (MEG) data and one study used MRI and MEG data.

Regarding the source of the datasets, 107 out of 116 studies used the ADNI database in any of its versions (ADNI-1, 2, 3 or GO) to obtain samples of healthy, MCI and AD subjects. Of the remaining eight studies, three used data from AddNeuroMed (<https://consortiapedia.fastercures.org/consortia/anm/>) database, one used the Australian

Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) database, and four collected their own data. Li et al. (108) used both ADNI and AIBL.

Although almost all studies used the same database, the cohorts selected varied across them. Most articles (66 out of 116 studies) divided their participants in four groups: healthy controls, stable MCI patients (sMCI), progressive MCI patients (pMCI), and AD patients. 21 articles selected three cohorts of MCI, AD, and healthy subjects, although in order to predict the conversion to AD, they had to distinguish between pMCI and sMCI patients. The remaining 29 studies used different groups of participants: 21 only sMCI and pMCI, six had healthy controls and MCI with two of them separating sMCI and pMCI, Wee et al. (113) differentiated between early and late MCI and Li et al. (106) did not specify the cohorts selected.

The sample size also varied across studies, Wee et al. (38) has the smallest sample with 27 subjects and Bae et al. (130) has the largest sample with 3940 subjects, the mean sample size was 546 participants. The sample size follows an ascendant trend across years, which may be attributed to the increased data availability in the ADNI database. The mean age ranged from 56 to 79 years old. Although 30 studies did not include the mean age of the sample, they used an ADNI database and therefore the age range might be similar to the rest of the studies. The variations in age between studies may be due to differences in participant selection and the moment when the study was conducted (since the ADNI database has been incorporating more data over the years).

As for feature selection, the most common were whole brain volumes, selected in 70 articles, and intensity measurements of glucose metabolism, selected in 31 PET studies, also 16 studies included genetic features (APOE4 genotype). Other selected features were neuropsychological test results (18 out of 116 studies) and demographic variables such as age (15 out of 116 studies). 42 studies only used one type of feature such as 3D MRI data or whole brain grey matter volumes and 74 studies selected two or more different types of features. As for the algorithm results regarding the most useful areas to discriminate between AD patients and healthy subjects or sMCI, those were mainly located in the temporal, parietal and frontal lobes. In particular, the most relevant regions were the hippocampus, amygdala, entorhinal cortex, precuneus, cingulate gyrus, and rostral and caudal areas of the medial frontal lobe.

Regarding the ML methods used to classify the patients and detect probable MCI to AD progression, the most popular were those based in Support Vector Machine (SVM). SVM was used in 60 out of the 116 studies; this method is a supervised ML algorithm that has demonstrated its utility in neuroimaging-based applications, especially in classification of future clinical outcomes (139). SVM takes every measurement from every subject as a single point in a multidimensional space, with the number of dimensions being the total number of features of that particular dataset (for example, 93 grey matter volumes from regions of interest). The algorithm then finds the maximal margin separating hyperplane that optimally differentiates groups of data points representing different classes (e.g. pMCI vs. sMCI, or AD vs. HC). The data instances closest to the group boundaries are the support vectors and are, by definition, the ones that determine the position of the hyperplane. The mapping into a higher dimensional space is done by a kernel function, usually polynomial or Gaussian (27). The SVM algorithm is trained with labelled data (indicating whether the data belongs to a healthy person, sMCI, pMCI, or AD patient, for example) to generate this multidimensional space. Once the model has been trained we can introduce a new subject with MCI and it will be classified in the multidimensional space into the boundaries of one of the previously defined groups (i.e. sMCI, AD, etc.). For example, if the new patient is classified as belonging to the AD group, we can infer that this subject is more likely to develop a future AD due to being more similar to subjects in that group. The different groups for classification will depend on the specific methodology of each study.

The combination of SVM with other methods allows better feature selection and to avoid overfitting of data, this will facilitate the generalization of the model (i.e. achieving high accuracy when applied to different datasets). For example, Thung et al. (71) used SVM with multiple kernels (linear, Gaussian, and polynomial) after feature selection with least squares and logistic elastic net regressions and also matrix completion with label-guided low-rank matrix completion method. On the other hand, Toussaint et al. (37) used non-linear SVM with Gaussian Radial Basis Function kernel but only after a two-sample t-test and a spatial independent component analysis, performed for the detection of glucose metabolism and characteristic region patterns of AD patients. Other classification methods used were Random Forest or Neural Networks that can have different architectures but the most commonly used for image classification tasks were Convolutional Neural Networks, applied in 16 studies.

As for validation methods, Cross-Validation was selected in 72 studies, with different numbers of folds and/or iterations. Cross-Validation consists in dividing the sample in two sets, one to train the algorithm (training set) and another one for validation (testing set). This partition can be done several times changing the train/test split of the data, and the accuracy of each iteration can be averaged to obtain a more robust quantification of the model performance instead of just validating the model on one test sample. Another validation method is the Leave-One-Out Cross Validation, selected in 13 studies. In this case, the model is trained with all the data except for one data point, then it tries to classify the data point left out and does the same with the rest of the sample in subsequent iterations. The train/test method was selected in 27 studies with different percentages of data partitions. Finally, three studies validated the model on an independent test set and Ardekani et al. (65) used “out of bag” as validation method.

The results of ML classification algorithms can be assessed based on their sensitivity (percentage of correctly detected pMCI patients or true positive ratio) and specificity (percentage of healthy or sMCI subjects correctly identified or true negative ratio), or accuracy (percentage of correctly classified subjects). By changing the decision threshold of the classifier we can compensate the ratio between true positive/true negative and generate a graphic representation of that ratio, or what is known as the Receiver Operating Characteristic (ROC) curve (140). The calculation of the area under the ROC curve (AUC ROC) represents a good quantitative index for the comparison of classification models, since it indicates the ability of the model to predict both the presence and non-presence of disease, or in this case, the progression or lack of progression from MCI to AD (141). An AUC ROC of one implies a perfect classification of every subject in the sample. The maximum accuracies achieved by every study in the prediction of AD conversion from MCI patients or the accuracy of the method in discriminating between a progressive/stable MCI are shown in the “Results” column of Table 3; the AUC coefficient is presented when available.

Mean accuracy of studies that used MRI as neuroimaging technique was 74.5% and 76.9% for studies that selected PET scans. The combination of both techniques achieved even better results with a mean accuracy of 77.5%. AUC results follow a similar pattern with a mean AUC of 0.79, 0.80 and 0.80 for MRI, PET and MRI+PET respectively. López et al. (69) used MRI and MEG and achieved an accuracy of 100 and

an AUC of 0.97 but with a sample of 33 subjects and finally Pusil et al. (110) (with 54 subjects) and Xu et al. (126) (with 129 subjects) used MEG with accuracies of 100% and 87% respectively.

Considering the two most popular classification methods (SVM and CNN), mean accuracies were 75.4% for SVM and 78.5% for CNN. The best results with the SVM algorithm were obtained again by Pusil et al. (110) with 100% accuracy, but using a small sample of 54, making the model hardly generalizable. In studies with bigger samples, Guerrero et al. (50) had the highest accuracy results (97.2% with 511 subjects) followed by Lin et al. (122) (97.3% with 164 subjects). Finally, although 43 studies did not report AUC ROC values, the highest reported was 0.98 in Lin et al. (122) followed by 0.98 in Hojjati et al. (85) with 80 subjects. The lowest accuracy reported was found in the study by Plant et al. (25) (50%), who included a small sample size (64) and is the oldest study of all the analyzed, making the comparison between studies difficult. The second lowest accuracy was achieved by Sorensen et al. (93) (55% with 400 subjects), in this case, the study was part of a data science (Kaggle) competition where data was already preprocessed for all participants and couldn't be manipulated by the authors. About the lowest AUC ROC reported, it was found in Liu et al. (46) (0.53 and 414 subjects) using SVM, and in Pan et al. (123) (0.59 with 787 subjects) with CNN.

Table 3*Studies selected following PRISMA guidelines*

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Plant et al. (2010) (25)	HS AD MCI	18 (64.8) 32 (68.8) 24 (69.7)	Sample collected for the study	MRI: whole-brain volume measures	SVM Bayes VFI	Train/test method: AD + HS as train set and MCI as test set.	pMCI vs sMCI: SVM: 50 Bayes: 58.3 VFI: 75	NA
Chincarini et al. (2011) (26)	HS AD sMCI pMCI	189 (76.6) 144 (75.5) 166 (75.7) 136 (75.1)	ADNI-1	MRI: GM volumes	SVM	20-fold Cross Validation	NA	0.74
Costafreda et al. (2011) (27)	HS AD MCI	88 (73.6) 71 (74.9) 103 (74.1)	AddNeuro Med	MRI: 3D hippocampal morphometric measures	SVM with RBF kernel	4-fold Cross Validation	pMCI vs sMCI: 80	NA
Filipovych et al. (2011) (28)	HS AD sMCI pMCI	63 (75.2) 54 (77.4) 174 (74.5) 68 (76.2)	ADNI-1	MRI: whole-brain GM density	Semi-supervised SVM	<i>Leave-one-out</i> Cross Validation	pMCI: 79.4 sMCI: 51.7	0.69
Hinrichs et al. (2011) (8)	HS AD MCI	66 (76.2) 48 (76.6) 119 (75.1)	ADNI-1	MRI and PET: scan data, APOE4 genotype, CSF assays, and cognitive tests	MK-SVM	Train/test method: AD + HS as train set and MCI as test set	pMCI vs sMCI: NA	0.79
Westman et al. (2011) (29)	HS AD MCI	112 (73) 117 (76) 122 (75)	AddNeuro Med	MRI: whole-brain volume, age, and education	OPLS	Train/test method: sample of 51 subjects	pMCI vs sMCI: 73	NA
Wolz et al. (2011) (30)	HS AD sMCI pMCI	231 (76) 198 (75.7) 238 (74.8) 167 (74.6)	ADNI-1	MRI: hippocampal volume, cortical thickness, tensor-based morphometry, and manifold-based learning	SVM LDA	Train/test method: 95/5 partition	pMCI vs sMCI: SVM: 60 LDA: 68	NA
Zhang et al. (2011) (31)	HS AD sMCI pMCI	52 (75.3) 51 (75.2) 56 (75.3) 43 (75.3)	ADNI-1	MRI and PET: volume, intensity, and CSF ($A\beta_{42}$, t-tau y p-tau) measures	SVM	10-fold Cross Validation	pMCI: 91.5 sMCI: 73.4	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Batmanghelich et al. (2012) (32)	sMCI pMCI	139 (NA) 99 (NA)	ADNI-1	MRI: WM, GM and CSF	Logistic model trees + Laplacian SVM	5-fold Cross Validation	pMCI vs sMCI: 61.5	NA
Cheng et al. (2012) (33)	HS AD sMCI pMCI	52 (75.3) 51 (75.2) 56 (75.3) 43 (75.3)	ADNI-1	MRI and PET: GM and WM volume, intensity and CSF ($A\beta_{42}$, t-tau y p-tau) measures	Domain Transfer SVM	Train/test method: AD + HS as train set and MCI as test set with 10-fold Cross Validation Train/test method: 50/50 partition	pMCI vs sMCI: 69.4	0.74
Cho et al. (2012) (34)	HS AD sMCI pMCI	160 (76.2) 128 (76) 131 (74.1) 72 (74.8)	ADNI-1	MRI: cortical thickness	LDA	Train/test method: 50/50 partition	pMCI vs sMCI: 70	NA
Gray et al. (2012) (35)	HS AD sMCI pMCI	54 (NA) 50 (NA) 64 (NA) 53 (NA)	ADNI-1	PET: signal intensity and relative change over 12 month	SVM with RBF kernel	Train/test method: 75/25 partition with 1000 iterations	pMCI vs sMCI: 63.1	0.66
Li et al. (2012) (36)	HS AD sMCI pMCI	40 (73.7) 37 (74.8) 36 (75.3) 39 (75.6)	ADNI-1	MRI: static and dynamic cortical thickness and clustering coefficient	SVM	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 81.7	NA
Toussaint et al. (2012) (37)	HS AD sMCI pMCI	80 (76.4) 80 (76) 40 (76.4) 40 (76.4)	ADNI-1	PET: glucose metabolic signal and clinical measures	Two-sample t-test + spatial ICA + SVM with RBF kernel	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 80	NA
Wee et al. (2012) (38)	HS MCI	17 (72.1) 10 (74.2)	ADNI-1	MRI and PET: WM structural connectivity and GM functional connectivity	Mk-SVM	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 96.3	0.95
Ye et al. (2012) (39)	sMCI pMCI	177 (NA) 142 (NA)	ADNI-1	MRI: GM and WM volumes, cortical thickness, demographic, genetic, and cognitive measures	SVM	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: NA	0.85
Zhang et al. (2012) (9)	HS AD sMCI pMCI	50 (75.3) 45 (75.4) 48 (74.7) 43 (75.8)	ADNI-1	MRI and PET: volume, intensity and CSF ($A\beta_{42}$, t-tau y p-tau) measures	M3TL	10-fold Cross Validation	pMCI vs sMCI: 73.9	0.80

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Adaszewski et al. (2013) (40)	HS AD sMCI pMCI	137 (NA) 108 (NA) 61 (74) 142 (74)	ADNI-1 ADNI-GO	MRI: whole-brain GM volume	SVM	Train/test method: AD + HS subset as train set and bootstrapping with 100 permutations	pMCI: 63.7 sMCI: NA	NA
Aguilar et al. (2013) (41)	HS AD sMCI pMCI	110 (73) 116 (74.4) 98 (74.7) 21 (72.9)	AddNeuro Med	MRI: volume and cortical thickness	OPLS SVM Decision Trees ANN	10-fold Cross Validation	pMCI vs sMCI: OPLS: 74.7 SVM: 70.9 Decision Trees: 67.4 ANN: 70.1	0.83 0.81 0.80 0.75
Babu et al. (2013) (42)	HS sMCI pMCI	232 (76) 236 (74.9) 167 (74.6)	ADNI-1	MRI: GM volumes	PBL- McqRBFN	Train/test method: 95/5 partition	pMCI vs sMCI: 79	NA
Casanova et al. (2013) (43)	HS AD sMCI pMCI	188 (75.9) 171 (75.5) 182 (75.2) 153 (75)	ADNI-1	MRI: GM volumes	RLR	10-fold Cross Validation	pMCI vs sMCI: 61.5	NA
Cheng et al. (2013) (44)	HS AD sMCI pMCI	52 (NA) 51 (NA) 56 (NA) 43 (NA)	ADNI-1	MRI and PET: volume, intensity, APOE4 genotype, and CSF (A β ₄₂ , t-tau y p-tau) measures	SM2TLC	10-fold Cross Validation	pMCI vs sMCI: 77.8	0.81
Liu, M. et al. (2013) (45)	sMCI pMCI	185 (74.9) 164 (74.9)	ADNI-1	MRI: GM volumes	MTSRC	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 74.1	0.75
Liu, X. et al. (2013) (46)	HS AD sMCI pMCI	138 (76) 86 (75) 93 (75) 97 (75)	ADNI-1	MRI: volume and cortical thickness	SVM EN LDA	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: SVM: 66 EN: 68 LDA: 68	0.53 NA 0.68
Wee et al. (2013) (47)	HS AD sMCI pMCI	200 (75.8) 198 (75.7) 111 (75.3) 89 (74.8)	ADNI-1	MRI: cortical thickness and correlation of cortical thickness between pairs of ROIs	Mk-SVM	10-fold Cross Validation	pMCI vs sMCI: 75	0.84
Young et al. (2013) (48)	HS AD sMCI pMCI	73 (75.9) 63 (75.2) 96 (75.6) 47 (74.5)	ADNI-1	MRI and PET: volume, intensity, APOE4 genotype, and CSF (A β ₄₂ , t-tau y p-tau) measures	Gaussian Process	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 74.1	0.80

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Apostolova et al. (2014) (49)	HS AD MCI	111 (NA) 95 (NA) 182 (NA)	ADNI-1	MRI: hippocampal volumes and demographic, APOE genotype, and CSF measures	SVM	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 68	0.68
Guerrero et al. (2014) (50)	HS AD sMCI pMCI	175 (76.3) 106 (75.4) 114 (75.1) 116 (74.7)	ADNI-1 ADNI-GO	3D MRI data	SVM	Train/test method: Unknown partition	pMCI vs sMCI: 97.2	NA
Lebedev et al. (2014) (51)	HS AD MCI	225 (75.9) 185 (75.2) 165 (75.5)	ADNI-1	MRI: cortical thickness, demographic variables, and APOE4 genotype	RF	Independent test set	pMCI vs sMCI: 82.3	0.83
Liu, M. et al. (2014) (52)	HS AD sMCI pMCI	229 (76) 198 (75.7) 236 (74.9) 167 (74.9)	ADNI-1	MRI. whole-brain GM density	SVM	10-fold Cross Validation	pMCI vs sMCI: 70.7	NA
Liu, F. et al. (2014) (53)	HS AD MCI	52 (75.3) 51 (75.2) 99 (75.3)	ADNI-1	MRI and PET: volume and intensity measures	Mk-SVM	10-fold Cross Validation	pMCI vs sMCI: 67.8	0.70
Min et al. (2014) (54)	HS AD sMCI pMCI	128 (76.1) 97 (75.9) 117 (75.1) 117 (75.2)	ADNI-1	MRI: multi-atlas GM volume measures	SVM	10-fold Cross Validation	pMCI vs sMCI: 72.4	0.67
Suk et al. (2014) (55)	HS AD MCI	101 (75.9) 93 (75.5) 204 (74.9)	ADNI-1	MRI and PET: volume and intensity measures	DBM	10-fold Cross Validation	pMCI vs sMCI: 75.9	0.75
Tong et al. (2014) (56)	HS AD sMCI pMCI	231 (76) 198 (75.7) 238 (74.9) 167 (74.6)	ADNI-1	MRI: intensity patches	Multiple instance- Graph	<i>Leave-one-out</i> Cross Validation	pMCI vs sMCI: 70.4	NA
Cabral et al. (2015) (57)	sMCI pMCI	56 (NA) 44 (NA)	ADNI-1	PET: voxel intensities	Linear-SVM SVM-RBF Gaussian Naïve Bayes	10-fold Cross Validation	pMCI vs sMCI: Linear-SVM: 71-89 SVM-RBF: 75-85 Gaussian Naïve Bayes: 73-81	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Cheng et al. (2015) (58)	HS AD sMCI pMCI	52 (NA) 51 (NA) 56 (NA) 53 (NA)	ADNI-1	MRI and PET: volume, intensity and CSF ($A\beta_{42}$, t-tau y p-tau) measures	M2TL	10-fold Cross Validation	pMCI vs sMCI: 80.1	0.85
Cheng et al. (2015) (59)	HS AD sMCI pMCI	52 (NA) 51 (NA) 56 (NA) 43 (NA)	ADNI-1	MRI and PET: volume, intensity, APOE4 genotype, and CSF ($A\beta_{42}$, t-tau y p-tau) measures	Domain Transfer SVM	10-fold Cross Validation	pMCI vs sMCI: 79.4	0.85
Moradi et al. (2015) (60)	HS AD sMCI pMCI	231 (NA) 200 (NA) 100 (NA) 164 (NA)	ADNI-1	MRI: GM volumes, age, and cognitive measures	RF	10-fold Cross Validation	pMCI vs sMCI: 81	0.90
Raamana et al. (2015) (61)	HS AD sMCI pMCI	159 (NA) 136 (NA) 130 (NA) 56 (NA)	ADNI-1	MRI: cortical thickness	Variational Bayes probabilistic MKL	Train/test method: 95/5 partition	pMCI vs sMCI: 64	0.68
Ritter et al. (2015) (62)	sMCI pMCI	151 (74.1) 86 (74.6)	ADNI-1	MRI and PET: cortical thickness, intensity measurements, neuropsychological tests, clinical variables, and demographic data	SVM with RBF kernel Classification tree RF	30 iterations of 10-fold Cross Validation	pMCI vs sMCI: SVM: 61-64 Classification Tree: 61-64 RF: 60-61	NA
Salvatore et al. (2015) (63)	HS AD sMCI pMCI	162 (76.3) 137 (76) 134 (74.5) 76 (74.8)	ADNI-1	MRI: GM and WM volumes	SVM	20-fold Cross Validation	pMCI vs sMCI: 66	NA
Xu et al. (2015) (64)	HS AD MCI	117 (75.4) 113 (75.6) 110 (75.2)	ADNI-1	MRI and PET: Volume and intensity measures	wmSRC	10-fold Cross Validation	pMCI vs sMCI: 77.8	0.80
Ardekani et al. (2016) (65)	sMCI pMCI	78 (NA) 86 (NA)	ADNI-1	MRI: hippocampal volumetric integrity, APOE genotype, demographic data, and neuropsychological tests	RF	Out-of-bag method	pMCI vs sMCI: 82.3	0.83
Collij et al. (2016) (66)	HS AD MCI	100 (61.7) 100 (63.1) 60 (62.7)	Sample collected for the study	MRI: whole-brain arterial spin labelling perfusion maps	SVM	Train/test method: 50/50 partition	pMCI vs sMCI: 70.8	0.77

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Li et al. (2016) (67)	HS AD sMCI pMCI	42 (65.6) 25 (69.4) 10 (66.5) 21 (68.6)	ADNI-1	MRI: GM whole-brain and seed-based functional connectivity	SVM	<i>Leave One Out</i> Cross Validation	pMCI vs sMCI: 80.6	NA
Liu et al. (2016) (68)	HS AD sMCI pMCI	97 (75.9) 128 (76.1) 117 (75.1) 117 (75.2)	ADNI-1	MRI: GM density maps	SVM	10-fold Cross Validation	pMCI vs sMCI: 79.2	0.83
López et al. (2016) (69)	sMCI pMCI	21 (72.7) 12 (75.7)	Sample collected for the study	MRI and MEG: MEG power data on each ROI and hippocampal volumes, age, gender, cognitive reserve, neuropsychological testing score, and APOE genotype	HLR	Train/test method: 75/25 partition	pMCI vs sMCI: 100	0.97
Suk et al. (2016) (70)	HS AD sMCI pMCI	52 (75.3) 51 (75.2) 56 (75) 43 (75.7)	ADNI-1	MRI and PET: GM, CSF, and intensity measures	DW-S2MTL	10-fold Cross Validation	pMCI vs sMCI: 73	NA
Thung et al. (2016) (71)	sMCI pMCI	53 (75.7) 60 (75.2)	ADNI-1	MRI: whole-brain GM volume and changes in 4 years of follow-up	Mk-SVM	10-fold Cross Validation	pMCI vs sMCI: 78.2	0.84
Vasta et al. (2016) (72)	HS AD sMCI pMCI	47 (78.2) 55 (75.9) 89 (75.4) 32 (75.5)	ADNI-1	MRI: hippocampal volumes	SVM Naive Bayes Neural Network	Train/test method: AD + HS as train set and MCI as test set	pMCI vs sMCI: SVM: 66.1 Naïve Bayes: 65.3 Neural Network: 66.9	NA NA NA
Zhang et al. (2016) (73)	sMCI pMCI	62 (75.4) 71 (74.8)	ADNI-1	MRI: whole ventricular tensor-based morphometry	SVM	5-fold Cross Validation	pMCI vs sMCI: 96.7	0.97
Zhang et al. (2016) (74)	AD HS MCI	194 (NA) 228 (NA) 388 (NA)	ADNI-1	MRI: multivariate hippocampal surface TBM and radial distance	AdaBoost	<i>Leave One Out</i> Cross Validation	pMCI vs sMCI: 77	0.75
Çitak-Er et al. (2017) (75)	sMCI pMCI	165 (70.9) 140 (73.1)	ADNI-1	MRI: GM volumes	Linear SVM Polynomial-SVM LR	10-fold Cross Validation	pMCI vs sMCI: Linear-SVM: 73.1 Poly-SVM: 78.7 LR: 76.1	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Hojjati et al. (2017) (76)	sMCI pMCI	62 (73) 18 (73.6)	ADNI-1	MRI: connectivity matrix	SVM	9-fold Cross Validation	pMCI vs sMCI: 91.4	0.95
Long et al. (2017) (77)	HS AD sMCI pMCI	135 (76.2) 65 (75.6) 132 (75.2) 95 (75.1)	ADNI-1	MRI: whole-brain GM and WM	SVM	10-fold Cross Validation	pMCI vs sMCI: with GM: 85.9 with WM: 68.7	GM: 0.89 WM: 0.68
Mathotaarachchi et al. (2017) (78)	sMCI pMCI	230 (71.4) 43 (73.2)	ADNI-1	PET: intensity, demographic, and AOPE4 genotype measures	RUSRF	10-fold Cross Validation	pMCI vs sMCI: 84	0.91
Suk et al. (2017) (79)	HS AD sMCI pMCI	226 (NA) 186 (NA) 226 (NA) 167 (NA)	ADNI-1	MRI: GM volume	CNN	10-fold Cross Validation	pMCI vs sMCI: 74.8	0.75
Tong et al. (2017) (80)	HS AD sMCI pMCI	229 (75.9) 191 (75.3) 129 (74.6) 171 (74.5)	ADNI-1	MRI: global grading biomarker, age, and cognitive measures	SVM	10-fold Cross Validation	pMCI vs sMCI: 81	0.87
Choi et al. (2018) (81)	HS AD sMCI pMCI	182 (73.4) 139 (74.3) 92 (70.3) 79 (72.3)	ADNI-2	PET: voxel volumes of FDG and florbetapir (AV-45) images	CNN	10-fold Cross Validation	pMCI vs sMCI: 84.2	0.89
Donnelly-Kehoe et al. (2018) (82)	HS AD sMCI pMCI	100 (NA) 100 (NA) 100 (NA) 100 (NA)	ADNI-1	MRI: brain morphometry, demographic data, and MMSE	RF SVM AB	Train/test method: 75/25 partition	NA	0.75 0.76 0.63
Gao et al. (2018) (83)	HS AD MCI	94 (76.3) 58 (74.2) 147 (74.8)	ADNI-1	MRI and PET: hippocampal texture features, medical history, and neuropsychological tests	GPR PLS	Train/test method: AD + HS as train set and MCI as test set + follow-up	pMCI vs sMCI: GPR:82.2 PLS:85.5	NA
Gómez-Sancho et al. (2018) (84)	HS AD sMCI pMCI	413 (NA) 326 (NA) 173 (NA) 274 (NA)	ADNI-1	MRI: regional volumetry, surface area, and cortical thickness	SVM RLR	10-fold Cross Validation	pMCI vs sMCI: SVM: 61-62.5 RLR: 61.1-65	0.64-0.68 0-65-0.70

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Hojjati et al. (2018) (85)	sMCI pMCI	62 (73) 18 (73.6)	ADNI-1	MRI: whole-brain cortical thickness, volumes, and connectivity matrix	SVM	9-fold Cross Validation	pMCI vs sMCI: 97	0.98
Khanna et al. (2018) (86)	HS MCI	315 (NA) 609 (NA)	ADNI-1	MRI and PET: volume, clinical, and SNP measures	GBM	10 iterations of a 10-fold Cross Validation	C-index (it's a generalization of the AUC ROC calculation for binary classification): 0.86	
Lin et al. (2018) (87)	HS AD sMCI pMCI	229 (NA) 188 (NA) 139 (NA) 169 (NA)	ADNI-1	MRI: hippocampal measures and whole-brain cortical volume, surface area, and cortical thickness	LASSO + ELM	<i>Leave One Out</i> Cross Validation	pMCI vs sMCI: 79.9	0.86
Liu et al. (2018) (88)	HS AD sMCI pMCI	230 (77.1) 200 (76.6) 160 (76.2) 120 (75.9)	ADNI-1	MRI: whole-brain hierarchical structural network	Multiple Kernel Boost	10-fold Cross Validation	pMCI vs sMCI: 72.8	0.72
Liu et al. (2018) (89)	HS AD MCI	126 (76) 186 (75.4) 395 (74.9)	ADNI-1	MRI and PET: volume, intensity, and CSF ($A\beta_{42}$, t-tau y p-tau) measures	Multi-hyper graph Learning	10-fold Cross Validation	pMCI vs sMCI: 74.7	0.72
Lu et al. (2018) (90)	HS AD sMCI pMCI	360 (73.4) 238 (75) 409 (74) 217 (74)	ADNI-1	MRI and PET: volume, intensity, and CSF ($A\beta_{42}$, t-tau y p-tau) measures	Deep NN	10-fold Cross Validation	pMCI vs sMCI: 82.9	NA
Minhas et al. (2018) (91)	sMCI pMCI	54 (74.1) 65 (74.7)	ADNI-1	MRI: whole-brain volumes, surface area, cortical thickness, and neuropsychological measures	SVM	5-fold Cross Validation	pMCI vs sMCI: 84.3	0.89
Popuri et al. (2018) (92)	sHS uHS pSH pMCI sMCI eDAT sDAT	360 (75.4) 52 (78.9) 18 (78.2) 205 (74.8) 431 (75) 133 (76.6) 238 (75.8)	ADNI-1	PET: glucose metabolic signal	FPDS	Independent test set	Classification of DAT+/DAT-: pMCI = 67.9 sMCI = 70.4	pMCI vs sMCI at 2, 3 and 5 years: 0.81 0.80 0.77

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Sorensen et al. (2018) (93)	HS AD sMCI pMCI	100 (NA) 100 (NA) 100 (NA) 100 (NA)	ADNI-1	MRI: brain volumetry, cortical thickness, WM hipointensities, MMSE, age, and hippocampal sub-regional volumetry	Linear SVM RBF SVM	Train /test method: 60/40 partition	pMCI vs sMCI: Linear SVM: 55.6 RBF SVM: 55	NA NA
Sun et al. (2018) (94)	HS AD sMCI pMCI	162 (76.3) 137 (76) 134 (74.5) 76 (74.8)	ADNI-1	MRI: GM densities	LASSO + SVM	Train /test method: 50/50 partition	pMCI vs sMCI: 65.4	0.68
Wu et al. (2018) (95)	HS sMCI pMCI	150 (75.6) 150 (75.3) 157 (75.3)	ADNI-1	MRI: 3D volumes	GoogleNet CaffeNet	5-fold Cross Validation	GoogleNet/CaffeNet in: pMCI: 84.7/92.3 sMCI: 67.3/72	NA
Yan et al. (2018) (96)	sMCI pMCI	50 (NA) 29 (NA)	ADNI-1	PET: 3D Images	ResNet	10-fold Cross Validation	pMCI vs sMCI: 82	0.81
Basaia et al. (2019) (97)	HS AD sMCI pMCI	352 (74.5) 294 (75.1) 510 (72.3) 253 (73.8)	ADNI-1	MRI: WM, GM, and CSF measures	CNN	Independent test set	pMCI vs sMCI: 74.9	NA
Cheng et al. (2019) (98)	HS AD MCI	112 (NA) 102 (NA) 192 (NA)	ADNI-1	MRI: GM volumes and CSF measures	SVM	10-fold Cross Validation	pMCI vs sMCI: 76.3	0.81
Collazos-Huertas et al. (2019) (99)	sMCI pMCI	325 (75) 245 (75)	ADNI-1	MRI: volumes and cortical thickness	SVM KNN	5-fold Cross Validation	pMCI vs sMCI: SVM: 76.1 KNN: 77.8	NA NA
Elahifasae et al. (2019) (100)	HS AD sMCI pMCI	229 (76) 198 (57.5) 236 (74.9) 167 (74.9)	ADNI-1	MRI: GM density	KDA	10-fold Cross Validation	pMCI vs sMCI: 65.9	0.71
Ezzati et al. (2019) (101)	HS AD sMCI pMCI	424 (74.3) 249 (74.7) 372 (72.8) 235 (73)	ADNI-1	MRI: whole-brain volumes, APOE4 genotype, and demographic measures	Ensemble Learning	10-fold Cross Validation	MCI to AD at 6, 12, 24, 36, and 48 months: 63.8%, 68.9%, 74.9%, 75.3%, and 77%, respectively	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Gupta et al. (2019) (102)	HS AD sMCI pMCI	38 (76.7) 38 (77.1) 36 (74.2) 46 (76.7)	ADNI-1	MRI and PET: whole-brain volume, intensity and CSF ($A\beta_{42}$, t-tau y p-tau) measures	Mk-SVM	10-fold Cross Validation	pMCI vs sMCI: 94.9	0.94
Lee et al. (2019) (103)	HS AD sMCI pMCI	415 (NA) 338 (NA) 558 (NA) 307 (NA)	ADNI-1	MRI: brain phenotypes, demographic and neuropsychological data, APOE4 genotype, and CSF measures	rDNN	5-fold Cross Validation	pMCI vs sMCI at 6, 12, 18 and 24 months: 81, 81, 79 and 80 respectively	NA
Lee et al. (2019) (104)	HS AD sMCI pMCI	229 (76) 198 (75.4) 214 (75) 160 (74.9)	ADNI-1	MRI: GM volumes	rDNN + SVM	10-fold Cross Validation	pMCI vs sMCI: 88.5	0.96
Lei et al. (2019) (105)	HS AD sMCI pMCI	152 (NA) 91 (NA) 98 (NA) 104 (NA)	ADNI-1	MRI: GM volumes and neuropsychological measures	SVR	10-fold Cross Validation	pMCI vs sMCI: 78	NA
Li et al. (2019) (106)	NA	803 (NA)	ADNI-1/2/GO and AIBL	MRI: hippocampal volumes, cognitive, demographic and neuropsychological measures	NN	Train in ADNI-1 and test in ADNI-2&GO	MCI to AD prediction (C-index): 0.86	
Li et al. (2019) (107)	HS AD sMCI pMCI	165 (76.4) 142 (76.1) 95 (74.9) 126 (73.4)	ADNI-1	MRI: cortical thickness and volumes	SVM with RBF kernel	10-fold Cross Validation	pMCI vs sMCI: 69.8	0.70
Oh et al. (2019) (108)	HS AD sMCI pMCI	230 (76) 198 (75.6) 101 (74.1) 166 (74.8)	ADNI-1	MRI data	CNN	5-fold Cross Validation	pMCI vs sMCI: 73.9	NA
Pan et al. (2019) (109)	HS AD sMCI pMCI	90 (76.1) 94 (75.8) 44 (77.6) 44 (75.9)	ADNI-1	PET: intensities and connectivity measures	SVM	10-fold Cross Validation	pMCI vs sMCI: 72.3	0.72
Pusil et al. (2019) (110)	sMCI pMCI	27 (71.2) 27 (74.8)	Sample collected for the study	MEG: Brain connectivity matrix	MCFS + SVM with RBF kernel	Train /test method: 80/20 partition	pMCI vs sMCI: 100	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Spasov et al. (2019) (111)	HS AD sMCI pMCI	184 (74.6) 192 (75.6) 228 (72.2) 181 (73.7)	ADNI-1	MRI: brain volumes, demographic, neuropsychological, and genetic (APOE4) measures	CNN	Train/test method: 90/10 partition	pMCI vs sMCI: 86	0.93
Wang et al. (2019) (112)	HS AD MCI	71 (72.5) 48 (75) 60 (72.6)	ADNI-2	MRI: morphometry and WM structural connectivity	LR	10-fold Cross Validation	pMCI vs sMCI: 59	0.65
Wee et al. (2019) (113)	HS AD MCI eMCI lMCI	ADNI-1/ADNI-2: 242/300 (76.9/75.6) 355/261 (76.3/75.3) 415/NA (75.9) NA/314 (72.9) NA/208 (73.7)		MRI: Cortical thickness	Graph NN	10-fold Cross Validation	Conversion from: eMCI to AD: 79.2 lMCI to AD: 65.2	NA
Xu et al. (2019) (114)	HS AD sMCI pMCI	165 (76.4) 142 (76.1) 95 (74.9) 126 (73.4)	ADNI-1	MRI: Cortical thickness	SVM with RBF kernel	10-fold Cross Validation	pMCI vs sMCI: 63.7	0.67
Zhou et al. (2019) (115)	HS AD sMCI pMCI	204 (76.1) 171 (75.5) 205 (75.1) 157 (74.8)	ADNI-1	MRI and PET: GM volumes, average intensities and SNP measures	Multi-modal Classifier	10-fold Cross Validation	pMCI vs sMCI: 74..3	0.75
Zhu et al. (2019) (116)	HS AD MCI	101 (75.8) 93 (75.4) 202 (75.1)	ADNI-1	MRI and PET: GM volumes and average intensities	SVM	10-fold Cross Validation	pMCI vs sMCI: 72.6	0.73
Abrol et al. (2020) (117)	HS AD sMCI pMCI	237 (74.3) 157 (75.1) 245 (72.1) 189 (74.2)	ADNI-1 ADNI-2 ADNI-3 ADNI-GO	MRI: 3D brain volumes	ResNet	Train/test method: 80/20 partition	pMCI vs sMCI: 75.1	0.78
Gao et al. (2020) (118)	HS sMCI pMCI	847 (56.9) 129 (74.8) 168 (74.8)	ADNI-1	MRI: 3D brain volumes	Age prediction + AD-NET	5-fold Cross Validation	pMCI vs sMCI: 76	0.81
Giorgio et al. (2020) (119)	HS MCI	317 (NA) 272 (NA)	ADNI-1	MRI and PET: GM density; genetic, and cognitive measures	GMLVQ	10-fold Cross Validation	pMCI vs sMCI: 81.4	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
Khatri et al. (2020) (120)	HS AD MCI	57 (75.6) 53 (74.4) 77 (74.1)	ADNI-1	MRI: cortical thickness, surface area, GM volumes, MMSE, APOE4 data, and levels of A β 42, T-tau and P-tau in CSF	SVM with RBFk Linear SVM ELM	10-fold Cross Validation	pMCI vs sMCI: SVM-RBFk: 71.3 Linear SVM: 75.7 ELM: 83.4	NA NA 0.85
Lin et al. (2020) (121)	HS AD sMCI pMCI	200 (73.9) 102 (75.7) 205 (71.8) 110 (73.9)	ADNI-1	MRI and PET: volume, cortical thickness, intensity measures, APOE4 presence, and levels of A β 42, T-tau and P-tau in CSF	LASSO + ELM with Gaussian kernel	10-fold Cross Validation	pMCI vs sMCI: 84.7	0.89
Lin et al. (2020) (122)	sMCI pMCI	124 (70.8) 40 (71.6)	ADNI-1	MRI: GM densities	SVM	4-fold Cross Validation	pMCI vs sMCI: 97.3	0.98
Pan et al. (2020) (123)	HS AD sMCI pMCI	262 (NA) 237 (NA) 173 (NA) 115 (NA)	ADNI-1	MRI: 3D brain volumes	CNN + EL	5-fold Cross Validation on independent test set	pMCI vs sMCI: 62	0.59
Ramon-Julvez et al. (2020) (124)	HS AD sMCI pMCI	181 (NA) 191 (NA) 227 (NA) 179 (NA)	ADNI-1	MRI data and Jacobian determinant of diffeomorphic transformations	CNN	10-fold Cross Validation	pMCI vs sMCI: 89	0.94
Xiao et al. (2020) (125)	HS AD sMCI pMCI	50 (77.8) 51 (75.8) 45 (71.9) 51 (72.5)	ADNI-1	MRI: GM volumes	LR	10-fold Cross Validation	pMCI vs sMCI: 72.9	NA
Xu et al. (2020) (126)	HS MCI	53 (69.6) 76 (73.7)	Sample collected for the study	MEG: brain connectivity matrix	MG2G Embedding model	Train/validation/test method: 85/10/5 partition	HS vs pMCI vs sMCI: 82 pMCI vs sMCI: 87	0.75-0.96
Yang et al. (2020) (127)	sMCI pMCI	280 (72) 70 (71.7)	ADNI-1	PET: GM densities	CNN + SVM	Train/test method: unknown partition	pMCI vs sMCI: 78.6	NA
Yee et al. (2020) (128)	sHS uHS pSH pMCI sMCI eDAT	359 (75.4) 51 (79) 19 (78.1) 210 (75) 427 (75) 135 (76.6)	ADNI-1	PET: intensity measures	CNN	5-fold Cross Validation	pMCI vs sMCI: 74.7	0.81

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
	sDAT	237 (75.7)						
Zhou et al. (2020) (129)	HS AD sMCI pMCI	226 (75.8) 186 (75.3) 205 (75.1) 157 (74.7)	ADNI-1	MRI and PET: GM volumes and intensity measures	SVM	10-fold Cross Validation	pMCI vs sMCI: 74-76	0.74-0.76
Bae et al. (2021) (130)	HS AD sMCI pMCI	2084 (76.5) 1406 (76.2) 222 (72.2) 228 (74.2)	ADNI-1	MRI: 3D brain volume and neuropsychological measures	CNN	Train/validation/ test method: 70/15/15 partition	pMCI vs sMCI: 82.4	NA
Mofrad et al. (2021) (131)	sMCI pMCI	333 (NA) 134 (NA)	ADNI-1	MRI: hippocampal entorhinal cortex, ventricles, and neuropsychological measures	Ensemble Learning	15-fold Cross Validation	pMCI vs sMCI: 77	NA
Mofrad et al. (2021) (132)	sMCI pMCI	279 (NA) 279 (NA)	ADNI-1 and AIBL	MRI: hippocampal and ventricle measures	Ensemble Learning	15-fold Cross Validation	pMCI vs sMCI: 78	NA
Pan et al. (2021) (133)	HS AD sMCI pMCI	242 (73.6) 237 (75) 360 (71.7) 166 (73.9)	ADNI-1	PET: 3D images	CNN	5-fold Cross Validation repeated 2 times	pMCI vs sMCI: 83	0.87
Shen et al. (2021) (134)	HS AD sMCI pMCI	150 (NA) 143 (NA) 89 (NA) 86 (NA)	ADNI-1	MRI and PET: Volume, cortical thickness, intensity measures, APOE4 presence and levels of A β 42, T-tau and P-tau in CSF	SVM	10-fold Cross Validation	pMCI vs sMCI: 75-78	0.76-0.80
Syaifullah et al. (2021) (135)	HS AD MCI	543 (NA) 359 (NA) 544 (NA)	NA-ADNI	MRI and PET data and MMSE	SVM	Train/test method: 50/50 partition	pMCI vs sMCI: 87.9	NA
Wen et al. (2021) (136)	HS AD MCI sMCI	46 (72.7) 46 (74.4) 97 (72.9) 54 (72.6)	ADNI-1	MRI: GM density	SVM	10-fold Cross Validation	pMCI vs sMCI: 80	NA

Author (year)	Groups	Sample size (mean age)	Database	Neuroimaging technique and features	Classification method	Validation method	Results (% accuracy)	AUC ROC
	pMCI	24 (74.2)						
Zhang et al. (2021) (137)	HS AD sMCI pMCI	275 (76.2) 280 (76.1) 251 (77.6) 162 (75.1)	ADNI-1	MRI: 3D brain volumes	CNN	Train/validation/ test method: 70/15/15 partition	pMCI vs sMCI: 78.8	0.87
Zhu et al. (2021) (138)	HS AD sMCI pMCI	275 (76.2) 280 (76.1) 251 (77.6) 162 (75.1)	ADNI-1	MRI: GM, WM and CSF measures, demographic data and APOE genotype	Temporally Structured- SVM	10-fold Cross Validation	pMCI vs sMCI: 85.4	0.86

Note. AB = Ada-Boost; AD = Alzheimer's Disease; AD-NET = Age-Adjust Neural Network; AIBL = Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging; ANN = Artificial Neural Network; AUC = Area Under the Curve; CNN = Convolutional Neural Network; DAT = Dementia Alzheimer Type; DBM = Deep Boltzmann Machine; DW-S2MTL = Deep weighted subclass-based sparse multi-task learning; EL = Ensemble Learning; eDAT = early DAT; ELM = Extreme Learning Machine; eMCI = early MCI; EN = Elastic Nets; F-FDG = Fluorine 18 fluorodesoxyglucose; FPDS = FDG-PET; GM = Grey Matter; GMB = Gradient Boosting Model; GPR = Gaussian Process Regression; HS = Healthy Subjects; HLR = Hierarchical Logistic Regression; ICA = Independent Component Analysis; KDA = Kernel Discriminant Analysis; IMCI = late MCI; LR = Logistic Regression; M2TL = Multimodal manifold-regularized transfer learning; M3TL= Multi-Modal Multi-Task Learning; MCI = Mild Cognitive Impairment; MCFS = Multi-Cluster Feature Selection; MG2G = Multiple Graph2Gauss; MKL = Multi Kernel Learning; MMSE = Mini Mental State Examination; MTSRC = Multi-task Sparse Representation Classifier; NA = Not Applicable; nl-SVM-RBFk = non-linear SVM with Radial Basis Function kernel; NN = Neural Network; OPLS = Orthogonal Partial Least Squares; PBL-McqRBFN = Projection Based Learning for Meta-cognitive q-Gaussian Radial Basis Function Network; PLS = Partial Least Squares; pMCI = progressive MCI; rDNN = randomized Deep Neural Network; Res-Net = Deep Residual Neural Network; RF = Random Forest; RLR = Regularized Logistic Regression; RUSRF = Random Under Sampled Random Forest; sDAT = stable DAT; SM2TLC = sparse multimodal manifold-regularized transfer learning classification; sMCI = stable MCI; SNN = Spiking Neural Network; SNP = Single Nucleotide Polymorphisms; ss = sample selection; SVM = Support Vector Machine; VFI = Voting Feature Intervals; WM = White Matter; wmSRC = weighted multi-modality sparse representation-based classification.

Finally, the interpretability analysis are presented in Table 4. Most of the studies presented results of *specificity and sensitivity* (113 out of 116), about half of them (60 out of 116) made an *analysis of confounds*, but only Lebedev et al. (51), Li et al. (106) and Syaifullah et al. (135) complied with the *generalizability* sublevel, testing their model in different datasets. All of the studies performed a *stability* measurement of their model, and 25 did not specify which features were the most *important* for the classification task. On the other hand, less than half of the studies (51 out of 116) presented their results along with some kind of *visualization* of the most relevant brain areas for the prediction of MCI conversion. Finally, the comparison of the results with the existing *literature* was done in all of the studies except for four of them.

Table 4

Analysis of the interpretability based on Kohoutová et al.(23)

Author (year)	Model			Feature			Biology
	SEN/SPE	GN	AC	ST	IMP	VIS	LIT
Plant et al. (2010) (25)	✓	-	✓	✓	✓	-	✓
Chincarini et al. (2011) (26)	✓	-	✓	✓	✓	-	✓
Costafreda et al. (2011) (27)	✓	-	✓	✓	✓	✓	✓
Filipovych et al. (2011) (28)	✓	-	-	✓	✓	✓	✓
Hinrichs et al. (2011) (8)	✓	-	-	✓	✓	✓	✓
Westman et al. (2011) (29)	✓	-	-	✓	✓	✓	✓
Wolz et al. (2011) (30)	✓	-	-	✓	✓	✓	✓
Zhang et al. (2011) (31)	-	-	-	✓	✓	✓	✓
Batmanghelich et al. (2012) (32)	✓	-	-	✓	✓	-	✓
Cheng et al. (2012) (33)	✓	-	-	✓	-	-	✓
Cho et al. (2012) (34)	✓	-	-	✓	✓	✓	✓
Gray et al. (2012) (35)	✓	-	✓	✓	✓	✓	✓
Li et al. (2012) (36)	✓	-	-	✓	✓	✓	✓
Toussaint et al. (2012) (37)	✓	-	✓	✓	✓	✓	✓
Wee et al. (2012) (38)	✓	-	✓	✓	✓	✓	✓
Ye et al. (2012) (39)	✓	-	-	✓	✓	-	✓
Zhang et al. (2012) (9)	✓	-	-	✓	✓	✓	✓

Author (year)	Model			Feature			Biology
	SEN/SPE	GN	AC	ST	IMP	VIS	LIT
Adaszewski et al. (2013) (40)	✓	-	-	✓	✓	✓	✓
Aguilar et al. (2013) (41)	✓	-	-	✓	✓	-	✓
Babu et al. (2013) (42)	✓	-	-	✓	✓	-	✓
Casanova et al. (2013) (43)	✓	-	-	✓	✓	-	✓
Cheng et al. (2013) (44)	✓	-	-	✓	-	-	✓
Liu, M. et al. (2013) (45)	✓	-	-	✓	-	-	✓
Liu, X. et al. (2013) (46)	✓	-	-	✓	✓	✓	✓
Wee et al. (2013) (47)	✓	-	-	✓	✓	-	✓
Young et al. (2013) (48)	✓	-	-	✓	-	-	-
Apostolova et al. (2014) (49)	✓	-	✓	✓	✓	-	✓
Guerrero et al. (2014) (50)	✓	-	✓	✓	✓	-	✓
Lebedev et al. (2014) (51)	✓	✓	-	✓	✓	✓	✓
Liu, M. et al. (2014) (52)	✓	-	-	✓	✓	✓	✓
Liu, F. et al. (2014) (53)	✓	-	-	✓	-	-	-
Min et al. (2014) (54)	✓	-	✓	✓	-	-	-
Suk et al. (2014) (55)	✓	-	✓	✓	✓	-	✓
Tong et al. (2014) (56)	✓	-	✓	✓	✓	✓	✓
Cabral et al. (2015) (57)	✓	-	-	✓	✓	✓	✓
Cheng et al. (2015) (58)	✓	-	✓	✓	-	-	-
Cheng et al. (2015) (59)	✓	-	✓	✓	✓	✓	✓
Moradi et al. (2015) (60)	✓	-	-	✓	✓	-	✓
Raamana et al. (2015) (61)	✓	-	✓	✓	-	✓	✓
Ritter et al. (2015) (62)	✓	-	-	✓	✓	-	✓
Salvatore et al. (2015) (63)	✓	-	-	✓	✓	✓	✓
Xu et al. (2015) (64)	✓	-	✓	✓	-	-	✓
Ardekani et al. (2016) (65)	✓	-	✓	✓	✓	-	✓
Collij et al. (2016) (66)	✓	-	✓	✓	✓	✓	✓
Li et al. (2016) (67)	✓	-	✓	✓	✓	✓	✓
Liu et al. (2016) (68)	✓	-	✓	✓	-	-	✓

Author (year)	Model			Feature			Biology
	SEN/SPE	GN	AC	ST	IMP	VIS	LIT
López et al. (2016) (69)	✓	-	-	✓	✓	-	✓
Suk et al. (2016) (70)	✓	-	✓	✓	✓	✓	✓
Thung et al. (2016) (71)	✓	-	✓	✓	✓	-	✓
Vasta et al. (2016) (72)	✓	-	✓	✓	✓	-	✓
Zhang et al. (2016) (73)	✓	-	-	✓	✓	-	✓
Zhang et al. (2016) (74)	✓	-	-	✓	✓	-	✓
Çitak-Er et al. (2017) (75)	✓	-	-	✓	✓	✓	✓
Hojjati et al. (2017) (76)	✓	-	✓	✓	✓	✓	✓
Long et al. (2017) (77)	✓	-	-	✓	✓	-	✓
Mathotaarachchi et al. (2017) (78)	✓	-	✓	✓	✓	✓	✓
Suk et al. (2017) (79)	✓	-	✓	✓	✓	✓	✓
Tong et al. (2017) (80)	✓	-	-	✓	✓	✓	✓
Choi et al. (2018) (81)	✓	-	✓	✓	✓	-	✓
Donnelly-Kehoe et al. (2018) (82)	✓	-	✓	✓	✓	-	✓
Gao et al. (2018) (83)	✓	-	-	✓	✓	-	✓
Gómez-Sancho et al. (2018) (84)	✓	-	-	✓	✓	-	✓
Hojjati et al. (2018) (85)	✓	-	-	✓	✓	✓	✓
Khanna et al. (2018) (86)	-	-	✓	✓	✓	-	✓
Lin et al. (2018) (87)	✓	-	-	✓	✓	✓	✓
Liu et al. (2018) (88)	✓	-	-	✓	✓	✓	✓
Liu et al. (2018) (89)	✓	-	✓	✓	-	-	✓
Lu et al. (2018) (90)	✓	-	-	✓	-	-	✓
Minhas et al. (2018) (91)	✓	-	-	✓	-	-	✓
Popuri et al. (2018) (92)	✓	-	✓	✓	✓	-	✓
Sorensen et al. (2018) (93)	✓	-	-	✓	-	-	✓
Sun et al. (2018) (94)	✓	-	✓	✓	✓	✓	✓
Wu et al. (2018) (95)	✓	-	✓	✓	-	-	✓
Yan et al. (2018) (96)	✓	-	-	✓	-	-	✓
Basaia et al. (2019) (97)	✓	-	✓	✓	-	-	✓

Author (year)	Model			Feature			Biology
	SEN/SPE	GN	AC	ST	IMP	VIS	LIT
Cheng et al. (2019) (98)	✓	-	✓	✓	✓	-	✓
Collazos-Huertas et al. (2019) (99)	✓	-	✓	✓	✓	-	✓
Elahifasae et al. (2019) (100)	✓	-	✓	✓	✓	✓	✓
Ezzati et al. (2019) (101)	✓	-	✓	✓	-	-	✓
Gupta et al. (2019) (102)	✓	-	-	✓	✓	-	✓
Lee et al. (2019) (103)	✓	-	✓	✓	✓	-	✓
Lee et al. (2019) (104)	✓	-	-	✓	✓	✓	✓
Lei et al. (2019) (105)	✓	-	-	✓	✓	✓	✓
Li et al. (2019) (106)	✓	✓	✓	✓	✓	✓	✓
Li et al. (2019) (107)	✓	-	✓	✓	-	-	✓
Oh et al. (2019) (108)	✓	-	✓	✓	✓	✓	✓
Pan et al. (2019) (109)	✓	-	-	✓	-	-	✓
Pusil et al. (2019) (110)	✓	-	-	✓	✓	-	✓
Spasov et al. (2019) (111)	✓	-	-	✓	✓	-	✓
Wang et al. (2019) (112)	✓	-	✓	✓	-	-	✓
Wee et al. (2019) (113)	✓	-	✓	✓	✓	✓	✓
Xu et al. (2019) (114)	✓	-	✓	✓	✓	✓	✓
Zhou et al. (2019) (115)	✓	-	✓	✓	✓	✓	✓
Zhu et al. (2019) (116)	✓	-	✓	✓	✓	✓	✓
Abrol et al. (2020) (117)	✓	-	✓	✓	✓	✓	✓
Gao et al. (2020) (118)	✓	-	-	✓	-	-	✓
Giorgio et al. (2020) (119)	✓	-	-	✓	✓	-	✓
Khatri et al. (2020) (120)	✓	-	✓	✓	✓	✓	✓
Lin et al. (2020) (121)	✓	-	-	✓	✓	-	✓
Lin et al. (2020) (122)	✓	-	✓	✓	✓	✓	✓
Pan et al. (2020) (123)	-	-	-	✓	✓	-	✓
Ramon-Julvez et al. (2020) (124)	✓	-	-	✓	-	-	✓
Xiao et al. (2020) (125)	✓	-	-	✓	-	-	✓
Xu et al. (2020) (126)	✓	-	-	✓	✓	✓	✓

Author (year)	Model			Feature			Biology
	SEN/SPE	GN	AC	ST	IMP	VIS	LIT
Yang et al. (2020) (127)	✓	-	✓	✓	-	-	✓
Yee et al. (2020) (128)	✓	-	✓	✓	✓	✓	✓
Zhou et al. (2020) (129)	✓	-	✓	✓	✓	✓	✓
Bae et al. (2021) (130)	✓	-	-	✓	✓	✓	✓
Mofrad et al. (2021) (131)	✓	-	✓	✓	✓	-	✓
Mofrad et al. (2021) (132)	✓	-	✓	✓	✓	-	✓
Pan et al. (2021) (133)	✓	-	✓	✓	✓	✓	✓
Shen et al. (2021) (134)	✓	-	✓	✓	✓	-	✓
Syaifullah et al. (2021) (135)	✓	✓	✓	✓	✓	-	✓
Wen et al. (2021) (136)	✓	-	✓	✓	✓	-	✓
Zhang et al. (2021) (137)	✓	-	✓	✓	✓	-	✓
Zhu et al. (2021) (138)	✓	-	✓	✓	✓	✓	✓
Total (116)	113	3	60	116	91	51	112

Note. This table shows an interpretability analysis performed for each study selected in our review following the framework proposed in Kohoutová et al. (23). Presence (✓) or absence (-) of the different sublevels assessments. Behavioural Analysis, Representational Analysis and Invasive studies sub-levels are not applicable to this type of studies by its definition. SEN = Sensitivity; SPE = Specificity; GN = Generalizability; AC = Analysis of confounds; ST = Stability; IMP = Importance; VIS = Visualization; LIT = Literature.

4 DISCUSSION

In this systematic review, we analysed 116 studies, conducted over the last ten years, which used neuroimaging data to predict conversion to AD from MCI using ML algorithms. The complexity of neuroimaging results and the amplitude of the deterioration and symptoms present in multiple areas and functions in AD, make its prediction practically impossible in patients with MCI by simply visualizing an image or result of MRI, PET, or other neuroimaging techniques. Nevertheless, using the publicly available neuroimaging data collected over the last decades, together with the newly developed ML algorithms, researchers can not only distinguish the brains of AD patients and healthy people with high accuracy, but also predict MCI patient's disease progression (i.e., whether a MCI patient will progress to AD or remain stable in the future). This information is highly valuable for clinicians in order to achieve more accurate

prognosis and therefore set treatment plans that can slow down the development of the disease and prevent higher degrees of cognitive impairment.

The 116 studies analysed reached different levels of accuracy using classification methods based on ML algorithms. Only 24 studies focused exclusively on predicting MCI conversion, most studies also tried to find the main differences between healthy controls and AD patients. The specific search for AD biomarkers is much more abundant in the literature than predicting progression from a MCI or even from healthy subjects (142). In any case, in the studies that carried out both tasks and in studies that focused on the prediction of AD conversion, the distinction between controls and AD was always more accurate than the distinction between pMCI vs. sMCI, showing the difficulty of finding biomarkers before functional impairment/dementia appears.

One of the main challenges of this review was to compare studies with highly variable methodologies including different samples, preprocessing techniques, types of neuroimaging data, and also different classification and validation methods. Still, studies that achieved higher levels of accuracy have in common the use of multimodal and multidimensional data combined with increasingly complex classification methods. Easy-to-implement algorithms, such as those based on SVM, are leaving room to more complex algorithms based on Deep Learning paradigms such as Neural Networks, capable of identifying dementia-associated subtle changes of brain morphology in a way able to increase the number of correctly classified subjects. All methods seemed to benefit from the inclusion of demographic variables and cognitive measurements, and even genetic variables if these were available. Nevertheless, in order for these techniques to be able to help clinicians in their everyday practice, a balance is needed between the most advanced data and algorithms that achieve the higher performance, and the data and methods that might be available in the clinical practice. In this sense, future studies might need to focus more on achieving high performance using large datasets with more essential (and easily obtainable) data such as structural MRI, demographic, and cognitive results.

Regarding the sample, most studies use the public available data from the ADNI database. This database is still incorporating new data and the most recent studies even use ADNI-2 and ADNI-3 (113,117). The main problem of the studies performed ten years ago, is their smaller sample size. Furthermore, even if two studies report similar accuracies, a study with a bigger sample size will have results that are more generalizable. For example, Plant et al. (25) and Popuri et al. (92) obtained similar accuracies of 75% and 79% of correct classifications respectively, but Popuri et

al. (92) used a sample about 30 times larger. Upon review of the recent developments in the field, it is apparent that as these patient populations continue to age and their disease progression matures and is clinically diagnosed, the inclusion of their ongoing neuroimaging data will enrich these public databases thereby enabling improved validation of classification methods. Nevertheless, it should be noted that a follow-up of two or three years, might not be long enough to detect progression to AD. Therefore, subjects considered as stable MCI or even as healthy subjects might, in fact, progress to AD in the long term. This problem will always be present with the inclusion of new cases in the ADNI database, but the follow-ups recorded will be increasingly long-lasting, thus being more useful. On the other hand, in order for these methods to be clinically useful, the models have to be tested, not only in big samples, but also in more variable and diverse groups of people, other than the ADNI sample. This approach is highlighted by Lebedev et al. (51), for example, who applied the model to the ADNI and then to the AddNeuroMed cohort, achieving similar performance and accuracy results in both, making it more robust for future clinical implementation.

Another interesting result from the inclusion of neuroimaging data in ML algorithms is the possibility of finding out which brain regions are more relevant to predict the conversion from MCI to AD. In this sense, the highlighted regions as informed by the algorithms (hippocampus, amygdala, entorhinal cortex, precuneus, cingulate gyrus, and medial frontal lobe) have been widely validated by the scientific literature as relevant in the progression to AD (8,34,35,143–147). This coincidence between the literature and the algorithm results supports the notion that the classification methods can detect differences between groups based on relevant neuroimaging features.

In terms of accuracy, although the algorithms are useful and able to discriminate the brain characteristics of AD, the performance of the algorithms are far from being specific enough to leave complete diagnosis in the hands of automated methods, so the judgment of a clinical professional will remain crucial in the near future. Nevertheless, the automated methods discussed above present a low-cost approach that can be useful as a first approximation, a method to discriminate ambiguous cases, and as a support tool for large datasets.

Clinical research is moving towards a broader and more open context where professionals from very different disciplines might be interested in these types of studies. As such, it is important to present the results from complex neuroimaging classification studies as clearly as possible. The framework to interpret ML models provided by Kohoutová et al. (23) is a helpful starting point

for this purpose. Most or all of the studies reviewed here included information about the specificity and sensitivity (model level), the stability of the models, and the most important features selected (feature level), along with a comparison with the previous literature (biology level). However, there are some important issues that should be addressed in future studies such as the inclusion of visualizations of the most relevant brain areas to predict MCI conversion, an adequate analysis of confounds, and generalization methods. These specific improvements would provide more comprehensive and comparable studies.

5 LIMITATIONS

Regarding the limitations of the review, it is worth mentioning that we did not include methodological details such as the preprocessing methods to obtain the neuroimaging results, or the mathematical development of the algorithms. This information could have provided a better understanding of each model performance and how the data is classified to differentiate between groups, but these deep methodological analyses were out of the scope of this review given its more clinically-oriented focus.

6 CONCLUSIONS

The recent trend in research to find diagnostic automation methods presents great potential in the early detection of neurodegenerative diseases. Since structural changes appear before the clinical symptoms manifest, there is a valuable period of time in which the morphological and functional changes in the brain can be detected and, therefore, used to predict and provide clinical treatment to slow down the future development of a neurological disease.

Research in this field is still rapidly advancing, new increasingly complex algorithms continue to be developed, and access to higher levels of computational capacity is also increasing, as well as the precision and resolution of neuroimaging techniques. In the future, we can expect faster, more precise, and more efficient classification methods that may be directly incorporated into the neuroimaging techniques themselves that enable the generation of a diagnostic hypothesis with a simple scan of a patient's brain. However, the challenge to translate this knowledge to daily practice remains. This challenge will be overcome on one hand by increasing the generalizability of the classification methods as they are applied to more diverse samples; and,

on the other, by finding the trade-off between the higher precision achieved when including complex information and a sufficient performance using only the clinical data commonly available for the clinicians. Thus, future studies should focus on obtaining good results using data easily available in the clinical practice (structural MRI, demographic data, and cognitive results, for example), and making their models as much generalizable as possible using more diverse and inclusive samples.

7 LIST OF ABBREVIATIONS

- AUC: Area Under the Curve
- AD: Alzheimer's Disease
- ADNI: Alzheimer's Disease Neuroimage Initiative
- HC: Healthy Controls
- MCI: Mild Cognitive Impairment
- ML: Machine Learning
- MRI: Magnetic Resonance Image
- PET: Positron Emission Tomography
- pMCI: Progressive Mild Cognitive Impairment
- ROC: Receiver Operating Characteristic
- sMCI: Stable Mild Cognitive Impairment
- SVM: Support Vector Machine

8 DECLARATIONS

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476 SG conceived the original idea for the review, designed the search strategy, performed the
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478 contributed to the subsequent reviews and final version. RVS supervised the review process,
479 made an independent article screening, revised the manuscript, and contributed to writing of the
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484 **9 REFERENCES**

485 1. Menéndez G. La revolución de la longevidad : cambio tecnológico, envejecimiento
486 poblacional y transformación cultural. Rev Ciencias Soc. 2017;

487 2. Prince M, Wimo A, Guerchet M, Gemma-Claire A, Wu Y-T, Prina M. World Alzheimer
488 Report 2015: The Global Impact of Dementia - An analysis of prevalence, incidence, cost
489 and trends. Alzheimer's Dis Int. 2015;

490 3. Dementia.

- 491 4. APA. American Psychiatric Association, 2013. Diagnostic and statistical manual of
492 mental disorders (5th ed.). American Journal of Psychiatry. 2013.
- 493 5. Robinson L, Tang E, Taylor J-P. Dementia: timely diagnosis and early intervention. *BMJ*.
494 2015 Jun;350(jun15 14):h3029–h3029.
- 495 6. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. International
496 Psychogeriatric Association Expert Conference on mild cognitive impairment. *Lancet*
497 (London, England). 2006;
- 498 7. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta*
499 *Neuropathologica*. 1991.
- 500 8. Hinrichs C, Singh V, Xu G, Johnson SC. Predictive markers for AD in a multi-modality
501 framework: An analysis of MCI progression in the ADNI population. *Neuroimage*. 2011
502 Mar;55(2):574–89.
- 503 9. Zhang D, Shen D. Multi-modal multi-task learning for joint prediction of multiple
504 regression and classification variables in Alzheimer’s disease. *Neuroimage*. 2012
505 Jan;59(2):895–907.
- 506 10. Pellegrini E, Ballerini L, Hernandez M del CV, Chappell FM, González-Castro V,
507 Anblagan D, et al. Machine learning of neuroimaging for assisted diagnosis of cognitive
508 impairment and dementia: A systematic review. *Alzheimer’s Dement Diagnosis, Assess*
509 *Dis Monit*. 2018;
- 510 11. Samper-González J, Burgos N, Fontanella S, Bertin H, Habert MO, Durrleman S, et al.
511 Yet another ADNI machine learning paper? Paving the way towards fully-reproducible
512 research on classification of Alzheimer’s disease. In: *Lecture Notes in Computer Science*
513 (including subseries *Lecture Notes in Artificial Intelligence* and *Lecture Notes in*
514 *Bioinformatics*). 2017.
- 515 12. Davatzikos C, Fan Y, Wu X, Shen D, Resnick SM. Detection of prodromal Alzheimer’s
516 disease via pattern classification of magnetic resonance imaging. *Neurobiol Aging*. 2008;
- 517 13. Klöppel S, Chu C, Tan GC, Draganski B, Johnson H, Paulsen JS, et al. Automatic
518 detection of preclinical neurodegeneration: Presymptomatic Huntington disease.

- 519 Neurology. 2009;
- 520 14. Lao Z, Shen D, Xue Z, Karacali B, Resnick SM, Davatzikos C. Morphological
521 classification of brains via high-dimensional shape transformations and machine learning
522 methods. Neuroimage. 2004;
- 523 15. Arbabshirani MR, Plis S, Sui J, Calhoun VD. Single subject prediction of brain disorders
524 in neuroimaging: Promises and pitfalls. Neuroimage. 2017 Jan;145(Pt B):137–65.
- 525 16. Jo T, Nho K, Saykin AJ. Deep Learning in Alzheimer’s Disease: Diagnostic Classification
526 and Prognostic Prediction Using Neuroimaging Data. Front Aging Neurosci. 2019
527 Aug;11.
- 528 17. Sarica A, Cerasa A, Quattrone A. Random forest algorithm for the classification of
529 neuroimaging data in Alzheimer’s disease: A systematic review. Front Aging Neurosci.
530 2017;9(OCT):1–12.
- 531 18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic
532 reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;
- 533 19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, John PA. The PRISMA
534 statement for reporting systematic reviews and meta-analyses of studies that evaluate
535 healthcare interventions: explanation and elaboration. 2009;
- 536 20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical
537 diagnosis of alzheimer’s disease: Report of the NINCDS-ADRDA work group* under the
538 auspices of department of health and human services task force on alzheimer’s disease.
539 Neurology. 1984;34(7):939–44.
- 540 21. Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al.
541 Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS-ADRDA
542 criteria. Lancet Neurol. 2007 Aug;6(8):734–46.
- 543 22. Higgins JPT GS (editors). Cochrane Handbook for Systematic Reviews of Interventions
544 Version 5.1.0 . The Cochrane Collaboration . 2011.
- 545 23. Kohoutová L, Heo J, Cha S, Lee S, Moon T, Wager TD, et al. Toward a unified
546 framework for interpreting machine-learning models in neuroimaging. Nat Protoc.

547 2020;15(4):1399–435.

- 548 24. Capecci E, Doborjeh ZG, Mammone N, La Foresta F, Morabito FC, Kasabov N.
549 Longitudinal study of Alzheimer’s disease degeneration through EEG data analysis with a
550 NeuCube spiking neural network model. In: Proceedings of the International Joint
551 Conference on Neural Networks. 2016.
- 552 25. Plant C, Teipel SJ, Oswald A, Böhm C, Meindl T, Mourao-Miranda J, et al. Automated
553 detection of brain atrophy patterns based on MRI for the prediction of Alzheimer’s
554 disease. *Neuroimage*. 2010 Mar;50(1):162–74.
- 555 26. Chincarini A, Bosco P, Calvini P, Gemme G, Esposito M, Olivieri C, et al. Local MRI
556 analysis approach in the diagnosis of early and prodromal Alzheimer’s disease.
557 *Neuroimage*. 2011 Sep;58(2):469–80.
- 558 27. Costafreda SG, Dinov ID, Tu Z, Shi Y, Liu CY, Kloszewska I, et al. Automated
559 hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment.
560 *Neuroimage*. 2011 May;56(1):212–9.
- 561 28. Filipovych R, Davatzikos C. Semi-supervised pattern classification of medical images:
562 Application to mild cognitive impairment (MCI). *Neuroimage*. 2011 Apr;55(3):1109–19.
- 563 29. Westman E, Simmons A, Zhang Y, Muehlboeck JS, Tunnard C, Liu Y, et al. Multivariate
564 analysis of MRI data for Alzheimer’s disease, mild cognitive impairment and healthy
565 controls. *Neuroimage*. 2011 Jan;54(2):1178–87.
- 566 30. Wolz R, Julkunen V, Koikkalainen J, Niskanen E, Zhang DP, Rueckert D, et al. Multi-
567 method analysis of MRI images in early diagnostics of Alzheimer’s disease. *PLoS One*.
568 2011 Oct;6(10).
- 569 31. Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Multimodal classification of Alzheimer’s
570 disease and mild cognitive impairment. *Neuroimage*. 2011;
- 571 32. Batmanghelich NK, Taskar B, Davatzikos C. Generative-discriminative basis learning for
572 medical imaging. *IEEE Trans Med Imaging*. 2012 Jan;31(1):51–69.
- 573 33. Cheng B, Zhang D, Shen D. Domain transfer learning for MCI conversion prediction. In:
574 Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial

- Intelligence and Lecture Notes in Bioinformatics). Springer Verlag; 2012. p. 82–90.
34. Cho Y, Seong JK, Jeong Y, Shin SY. Individual subject classification for Alzheimer's disease based on incremental learning using a spatial frequency representation of cortical thickness data. *Neuroimage*. 2012 Feb;59(3):2217–30.
35. Gray KR, Wolz R, Heckemann RA, Aljabar P, Hammers A, Rueckert D. Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer's disease. *Neuroimage*. 2012 Mar;60(1):221–9.
36. Li Y, Wang Y, Wu G, Shi F, Zhou L, Lin W, et al. Discriminant analysis of longitudinal cortical thickness changes in Alzheimer's disease using dynamic and network features. *Neurobiol Aging*. 2012;33(2):427.e15-427.e30.
37. Toussaint PJ, Perlberg V, Bellec P, Desarnaud S, Lacomblez L, Doyon J, et al. Resting state FDG-PET functional connectivity as an early biomarker of Alzheimer's disease using conjoint univariate and independent component analyses. *Neuroimage*. 2012 Nov;63(2):936–46.
38. Wee CY, Yap PT, Zhang D, Denny K, Browndyke JN, Potter GG, et al. Identification of MCI individuals using structural and functional connectivity networks. *Neuroimage*. 2012 Feb;59(3):2045–56.
39. Ye J, Farnum M, Yang E, Verbeeck R, Lobanov V, Raghavan N, et al. Sparse learning and stability selection for predicting MCI to AD conversion using baseline ADNI data. *BMC Neurol*. 2012 Jun;12.
40. Adaszewski S, Dukart J, Kherif F, Frackowiak R, Draganski B. How early can we predict Alzheimer's disease using computational anatomy? *Neurobiol Aging*. 2013 Dec;34(12):2815–26.
41. Aguilar C, Westman E, Muehlboeck JS, Mecocci P, Vellas B, Tsolaki M, et al. Different multivariate techniques for automated classification of MRI data in Alzheimer's disease and mild cognitive impairment. *Psychiatry Res - Neuroimaging*. 2013 May;212(2):89–98.
42. Babu GS, Suresh S, Mahanand BS. Meta-cognitive q-Gaussian RBF network for binary classification: Application to mild cognitive impairment (MCI). In: *Proceedings of the*

- 603 International Joint Conference on Neural Networks. 2013.
- 604 43. Casanova R, Hsu FC, Sink KM, Rapp SR, Williamson JD, Resnick SM, et al. Alzheimer's
605 disease risk assessment using large-scale machine learning methods. PLoS One. 2013
606 Nov;8(11).
- 607 44. Cheng B, Zhang D, Jie B, Shen D. Sparse multimodal manifold-regularized transfer
608 learning for MCI conversion prediction. In: Lecture Notes in Computer Science (including
609 subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics).
610 Springer Verlag; 2013. p. 251–9.
- 611 45. Liu M, Suk H Il, Shen D. Multi-task sparse classifier for diagnosis of MCI conversion to
612 AD with longitudinal MR images. In: Lecture Notes in Computer Science (including
613 subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics).
614 Springer Verlag; 2013. p. 243–50.
- 615 46. Liu X, Tosun D, Weiner MW, Schuff N. Locally linear embedding (LLE) for MRI based
616 Alzheimer's disease classification. Neuroimage. 2013 Dec;83:148–57.
- 617 47. Wee CY, Yap PT, Shen D. Prediction of Alzheimer's disease and mild cognitive
618 impairment using cortical morphological patterns. Hum Brain Mapp. 2013
619 Dec;34(12):3411–25.
- 620 48. Young J, Modat M, Cardoso MJ, Mendelson A, Cash D, Ourselin S. Accurate multimodal
621 probabilistic prediction of conversion to Alzheimer's disease in patients with mild
622 cognitive impairment. NeuroImage Clin. 2013;
- 623 49. Apostolova LG, Hwang KS, Kohannim O, Avila D, Elashoff D, Jack CR, et al. ApoE4
624 effects on automated diagnostic classifiers for mild cognitive impairment and Alzheimer's
625 disease. NeuroImage Clin. 2014;4:461–72.
- 626 50. Guerrero R, Wolz R, Rao AW, Rueckert D. Manifold population modeling as a neuro-
627 imaging biomarker: Application to ADNI and ADNI-GO. Neuroimage. 2014 Jul;94:275–
628 86.
- 629 51. Lebedev A V., Westman E, Van Westen GJP, Kramberger MG, Lundervold A, Aarsland
630 D, et al. Random Forest ensembles for detection and prediction of Alzheimer's disease

631 with a good between-cohort robustness. *NeuroImage Clin.* 2014;6:115–25.

632 52. Liu M, Zhang D, Shen D. Identifying informative imaging biomarkers via tree structured
633 sparse learning for AD diagnosis. *Neuroinformatics.* 2014;12(3):381–94.

634 53. Liu F, Wee CY, Chen H, Shen D. Inter-modality relationship constrained multi-modality
635 multi-task feature selection for Alzheimer’s Disease and mild cognitive impairment
636 identification. *Neuroimage.* 2014 Jan;84:466–75.

637 54. Min R, Wu G, Cheng J, Wang Q, Shen D. Multi-atlas based representations for
638 Alzheimer’s disease diagnosis. 2014;35(10):5052–70.

639 55. Suk H Il, Lee SW, Shen D. Hierarchical feature representation and multimodal fusion
640 with deep learning for AD/MCI diagnosis. *Neuroimage.* 2014 Nov;101:569–82.

641 56. Tong T, Wolz R, Gao Q, Guerrero R, Hajnal J V., Rueckert D. Multiple instance learning
642 for classification of dementia in brain MRI. *Med Image Anal.* 2014;18(5):808–18.

643 57. Cabral C, Morgado PM, Campos Costa D, Silveira M. Predicting conversion from MCI to
644 AD with FDG-PET brain images at different prodromal stages. *Comput Biol Med.* 2015
645 Mar;58:101–9.

646 58. Cheng B, Liu M, Suk H Il, Shen D, Zhang D. Multimodal manifold-regularized transfer
647 learning for MCI conversion prediction. *Brain Imaging Behav.* 2015 Dec;9(4):913–26.

648 59. Cheng B, Liu M, Zhang D, Munsell BC, Shen D. Domain Transfer Learning for MCI
649 Conversion Prediction. *IEEE Trans Biomed Eng.* 2015 Jul;62(7):1805–17.

650 60. Moradi E, Pepe A, Gaser C, Huttunen H, Tohka J. Machine learning framework for early
651 MRI-based Alzheimer’s conversion prediction in MCI subjects. *Neuroimage.* 2015
652 Jan;104:398–412.

653 61. Raamana PR, Weiner MW, Wang L, Beg MF. Thickness network features for prognostic
654 applications in dementia. *Neurobiol Aging.* 2015 Jan;36(S1):S91–102.

655 62. Ritter K, Schumacher J, Weygandt M, Buchert R, Allefeld C, Haynes JD. Multimodal
656 prediction of conversion to Alzheimer’s disease based on incomplete biomarkers.
657 *Alzheimer’s Dement Diagnosis, Assess Dis Monit.* 2015;1(2):206–15.

- 658 63. Salvatore C, Cerasa A, Battista P, Gilardi MC, Quattrone A, Castiglioni I. Magnetic
659 resonance imaging biomarkers for the early diagnosis of Alzheimer's disease: A machine
660 learning approach. *Front Neurosci.* 2015;9(SEP).
- 661 64. Xu L, Wu X, Chen K, Yao L. Multi-modality sparse representation-based classification
662 for Alzheimer's disease and mild cognitive impairment. *Comput Methods Programs*
663 *Biomed.* 2015 Nov;122(2):182–90.
- 664 65. Ardekani BA, Bermudez E, Mubeen AM, Bachman AH. Prediction of incipient
665 Alzheimer's disease dementia in patients with mild cognitive impairment. *J Alzheimer's*
666 *Dis.* 2016;55(1):269–81.
- 667 66. Collij LE, Heeman F, Kuijter JPA, Ossenkoppele R, Benedictus MR, Möller C, et al.
668 Application of machine learning to arterial spin labeling in mild cognitive impairment and
669 Alzheimer disease. *Radiology.* 2016 Dec;281(3):865–75.
- 670 67. Li Y, Wang X, Li Y, Sun Y, Sheng C, Li H, et al. Abnormal Resting-State Functional
671 Connectivity Strength in Mild Cognitive Impairment and Its Conversion to Alzheimer's
672 Disease. *Neural Plast.* 2016;
- 673 68. Liu M, Zhang D, Shen D. Relationship Induced Multi-Template Learning for Diagnosis of
674 Alzheimer's Disease and Mild Cognitive Impairment. *IEEE Trans Med Imaging.* 2016
675 Jun;35(6):1463–74.
- 676 69. López ME, Turrero A, Cuesta P, López-Sanz D, Bruña R, Marcos A, et al. Searching for
677 Primary Predictors of Conversion from Mild Cognitive Impairment to Alzheimer's
678 Disease: A Multivariate Follow-Up Study. *J Alzheimer's Dis.* 2016 Apr;52(1):133–43.
- 679 70. Suk H II, Lee SW, Shen D. Deep sparse multi-task learning for feature selection in
680 Alzheimer's disease diagnosis. *Brain Struct Funct.* 2016 Jun;221(5):2569–87.
- 681 71. Thung KH, Wee CY, Yap PT, Shen D. Identification of progressive mild cognitive
682 impairment patients using incomplete longitudinal MRI scans. *Brain Struct Funct.* 2016
683 Nov;221(8):3979–95.
- 684 72. Vasta R, Augimeri A, Cerasa A, Nigro S, Gramigna V, Nonnis M, et al. Hippocampal
685 Subfield Atrophies in Converted and Not-Converted Mild Cognitive Impairments Patients

- 686 by a Markov Random Fields Algorithm. *Curr Alzheimer Res.* 2016 Jan;13(5):566–74.
- 687 73. Zhang J, Shi J, Stonnington C, Li Q, Gutman BA, Chen K, et al. Hyperbolic space sparse
688 coding with its application on prediction of Alzheimer’s disease in mild cognitive
689 impairment. In: *Lecture Notes in Computer Science (including subseries Lecture Notes in*
690 *Artificial Intelligence and Lecture Notes in Bioinformatics)*. Springer Verlag; 2016. p.
691 326–34.
- 692 74. Zhang J, Stonnington C, Li Q, Shi J, Bauer RJ, Gutman BA, et al. Applying sparse coding
693 to surface multivariate tensor-based morphometry to predict future cognitive decline. In:
694 *Proceedings - International Symposium on Biomedical Imaging*. IEEE Computer Society;
695 2016. p. 646–50.
- 696 75. Çitak-Er F, Goularas D, Ormeci B. A novel convolutional neural network model based on
697 voxel-based morphometry of imaging data in predicting the prognosis of patients with
698 mild cognitive impairment. *J Neurol Sci.* 2017;34(1):52–69.
- 699 76. Hojjati SH, Ebrahimzadeh A, Khazaei A, Babajani-Feremi A. Predicting conversion from
700 MCI to AD using resting-state fMRI, graph theoretical approach and SVM. *J Neurosci*
701 *Methods.* 2017 Apr;282:69–80.
- 702 77. Long X, Chen L, Jiang C, Zhang L. Prediction and classification of Alzheimer disease
703 based on quantification of MRI deformation. *PLoS One.* 2017 Mar;12(3).
- 704 78. Mathotaarachchi S, Pascoal TA, Shin M, Benedet AL, Kang MS, Beaudry T, et al.
705 Identifying incipient dementia individuals using machine learning and amyloid imaging.
706 *Neurobiol Aging.* 2017 Nov;59:80–90.
- 707 79. Suk H II, Lee SW, Shen D. Deep ensemble learning of sparse regression models for brain
708 disease diagnosis. *Med Image Anal.* 2017 Apr;37:101–13.
- 709 80. Tong T, Gao Q, Guerrero R, Ledig C, Chen L, Rueckert D. A novel grading biomarker for
710 the prediction of conversion from mild cognitive impairment to Alzheimer’s disease.
711 *IEEE Trans Biomed Eng.* 2017 Jan;64(1):155–65.
- 712 81. Choi H, Jin KH. Predicting cognitive decline with deep learning of brain metabolism and
713 amyloid imaging. *Behav Brain Res.* 2018 May;344:103–9.

- 714 82. Donnelly-Kehoe PA, Pascariello GO, Gómez JC. Looking for Alzheimer's Disease
715 morphometric signatures using machine learning techniques. *J Neurosci Methods*. 2018
716 May;302:24–34.
- 717 83. Gao N, Tao LX, Huang J, Zhang F, Li X, O'Sullivan F, et al. Contourlet-based
718 hippocampal magnetic resonance imaging texture features for multivariant classification
719 and prediction of Alzheimer's disease. *Metab Brain Dis*. 2018 Dec;33(6):1899–909.
- 720 84. Gómez-Sancho M, Tohka J, Gómez-Verdejo V. Comparison of feature representations in
721 MRI-based MCI-to-AD conversion prediction. *Magn Reson Imaging*. 2018 Jul;50:84–95.
- 722 85. Hojjati SH, Ebrahimzadeh A, Khazaei A, Babajani-Feremi A. Predicting conversion from
723 MCI to AD by integrating rs-fMRI and structural MRI. *Comput Biol Med*. 2018
724 Nov;102:30–9.
- 725 86. Khanna S, Domingo-Fernández D, Iyappan A, Emon MA, Hofmann-Apitius M, Fröhlich
726 H. Using Multi-Scale Genetic, Neuroimaging and Clinical Data for Predicting
727 Alzheimer's Disease and Reconstruction of Relevant Biological Mechanisms. *Sci Rep*.
728 2018 Dec;8(1).
- 729 87. Lin W, Tong T, Gao Q, Guo D, Du X, Yang Y, et al. Convolutional neural networks-
730 based MRI image analysis for the Alzheimer's disease prediction from mild cognitive
731 impairment. *Front Neurosci*. 2018 Nov;12(NOV).
- 732 88. Liu J, Li M, Lan W, Wu FX, Pan Y, Wang J. Classification of Alzheimer's Disease Using
733 Whole Brain Hierarchical Network. *IEEE/ACM Trans Comput Biol Bioinforma*. 2018
734 Mar;15(2):624–32.
- 735 89. Liu M, Gao Y, Yap PT, Shen D. Multi-Hypergraph Learning for Incomplete
736 Multimodality Data. *IEEE J Biomed Heal Informatics*. 2018 Jul;22(4):1197–208.
- 737 90. Lu D, Popuri K, Ding GW, Balachandar R, Beg MF, Weiner M, et al. Multimodal and
738 Multiscale Deep Neural Networks for the Early Diagnosis of Alzheimer's Disease using
739 structural MR and FDG-PET images. *Sci Rep*. 2018 Dec;8(1).
- 740 91. Minhas S, Khanum A, Riaz F, Khan SA, Alvi A. Predicting progression from mild
741 cognitive impairment to Alzheimer's disease using autoregressive modelling of

742 longitudinal and multimodal biomarkers. *IEEE J Biomed Heal Informatics*. 2018
743 May;22(3):818–25.

744 92. Popuri K, Balachandar R, Alpert K, Lu D, Bhalla M, Mackenzie IR, et al. Development
745 and validation of a novel dementia of Alzheimer’s type (DAT) score based on metabolism
746 FDG-PET imaging. *NeuroImage Clin*. 2018 Jan;18:802–13.

747 93. Sørensen L, Nielsen M. Ensemble support vector machine classification of dementia using
748 structural MRI and mini-mental state examination. *J Neurosci Methods*. 2018
749 May;302:66–74.

750 94. Sun Z, Qiao Y, Lelieveldt BPF, Staring M. Integrating spatial-anatomical regularization
751 and structure sparsity into SVM: Improving interpretation of Alzheimer’s disease
752 classification. *Neuroimage*. 2018 Sep;178:445–60.

753 95. Wu C, Guo S, Hong Y, Xiao B, Wu Y, Zhang Q. Discrimination and conversion
754 prediction of mild cognitive impairment using convolutional neural networks. *Quant*
755 *Imaging Med Surg*. 2018 Nov;8(10):992–1003.

756 96. Yan Y, Lee H, Somer E, Grau V. Generation of Amyloid PET Images via Conditional
757 Adversarial Training for Predicting Progression to Alzheimer’s Disease. In 2018. p. 26–
758 33.

759 97. Basaia S, Agosta F, Wagner L, Canu E, Magnani G, Santangelo R, et al. Automated
760 classification of Alzheimer’s disease and mild cognitive impairment using a single MRI
761 and deep neural networks. *NeuroImage Clin*. 2019 Jan;21.

762 98. Cheng B, Liu M, Zhang D, Shen D. Robust multi-label transfer feature learning for early
763 diagnosis of Alzheimer’s disease. *Brain Imaging Behav*. 2019 Feb;13(1):138–53.

764 99. Collazos-Huertas D, Cárdenas-Peña D, Castellanos-Dominguez G. Instance-Based
765 Representation Using Multiple Kernel Learning for Predicting Conversion to Alzheimer
766 Disease. In: *International Journal of Neural Systems*. World Scientific Publishing Co. Pte
767 Ltd; 2019.

768 100. Elahifasae F, Li F, Yang M. A Classification Algorithm by Combination of Feature
769 Decomposition and Kernel Discriminant Analysis (KDA) for Automatic MR Brain Image

770 Classification and AD Diagnosis. *Comput Math Methods Med.* 2019;2019.

771 101. Ezzati A, Zammit AR, Harvey DJ, Habeck C, Hall CB, Lipton RB. Optimizing Machine
772 Learning Methods to Improve Predictive Models of Alzheimer's Disease. *J Alzheimer's*
773 *Dis.* 2019;71(3):1027–36.

774 102. Gupta Y, Lama RK, Kwon G-R. Prediction and Classification of Alzheimer's Disease
775 Based on Combined Features From Apolipoprotein-E Genotype, Cerebrospinal Fluid,
776 MR, and FDG-PET Imaging Biomarkers. *Front Comput Neurosci.* 2019 Oct;13.

777 103. Lee G, Nho K, Kang B, Sohn KA, Kim D, Weiner MW, et al. Predicting Alzheimer's
778 disease progression using multi-modal deep learning approach. *Sci Rep.* 2019 Dec;9(1).

779 104. Lee E, Choi J-S, Kim M, Suk H-I. Toward an interpretable Alzheimer's disease diagnostic
780 model with regional abnormality representation via deep learning. *Neuroimage.* 2019
781 Nov;202:116113.

782 105. Lei B, Hou W, Zou W, Li X, Zhang C, Wang T. Longitudinal score prediction for
783 Alzheimer's disease based on ensemble correntropy and spatial–temporal constraint.
784 *Brain Imaging Behav.* 2019 Feb;13(1):126–37.

785 106. Li H, Habes M, Wolk DA, Fan Y. A deep learning model for early prediction of
786 Alzheimer's disease dementia based on hippocampal magnetic resonance imaging data.
787 *Alzheimer's Dement.* 2019 Aug;15(8):1059–70.

788 107. Li Y, Fang Y, Zhang H, Hu B. Self-Weighting Grading Biomarker Based on Graph-
789 Guided Information Propagation for the Prediction of Mild Cognitive Impairment
790 Conversion. *IEEE Access.* 2019;7:116632–42.

791 108. Oh K, Chung YC, Kim KW, Kim WS, Oh IS. Classification and Visualization of
792 Alzheimer's Disease using Volumetric Convolutional Neural Network and Transfer
793 Learning. *Sci Rep.* 2019 Dec;9(1).

794 109. Pan X, Adel M, Fossati C, Gaidon T, Guedj E. Multilevel Feature Representation of FDG-
795 PET Brain Images for Diagnosing Alzheimer's Disease. *IEEE J Biomed Heal Informatics.*
796 2019 Jul;23(4):1499–506.

797 110. Pusil S, Dimitriadis SI, López ME, Pereda E, Maestú F. Aberrant MEG multi-frequency

798 phase temporal synchronization predicts conversion from mild cognitive impairment-to-
799 Alzheimer's disease. *NeuroImage Clin.* 2019 Jan;24.

800 111. Spasov S, Passamonti L, Duggento A, Liò P, Toschi N. A parameter-efficient deep
801 learning approach to predict conversion from mild cognitive impairment to Alzheimer's
802 disease. *Neuroimage.* 2019 Apr;189:276–87.

803 112. Wang Y, Xu C, Park JH, Lee S, Stern Y, Yoo S, et al. Diagnosis and prognosis of
804 Alzheimer's disease using brain morphometry and white matter connectomes.
805 *NeuroImage Clin.* 2019 Jan;23.

806 113. Wee CY, Liu C, Lee A, Poh JS, Ji H, Qiu A. Cortical graph neural network for AD and
807 MCI diagnosis and transfer learning across populations. *NeuroImage Clin.* 2019 Jan;23.

808 114. Xu L, Yao Z, Li J, Lv C, Zhang H, Hu B. Sparse Feature Learning With Label
809 Information for Alzheimer's Disease Classification Based on Magnetic Resonance
810 Imaging. *IEEE Access.* 2019;7:26157–67.

811 115. Zhou T, Liu M, Thung KH, Shen D. Latent Representation Learning for Alzheimer's
812 Disease Diagnosis with Incomplete Multi-Modality Neuroimaging and Genetic Data.
813 *IEEE Trans Med Imaging.* 2019 Oct;38(10):2411–22.

814 116. Zhu X, Suk H Il, Shen D. Low-rank dimensionality reduction for multi-modality
815 neurodegenerative disease identification. *World Wide Web.* 2019 Mar;22(2):907–25.

816 117. Abrol A, Bhattarai M, Fedorov A, Du Y, Plis S, Calhoun V. Deep residual learning for
817 neuroimaging: An application to predict progression to Alzheimer's disease. *J Neurosci*
818 *Methods.* 2020;

819 118. Gao F, Yoon H, Xu Y, Goradia D, Luo J, Wu T, et al. AD-NET: Age-adjust neural
820 network for improved MCI to AD conversion prediction. *NeuroImage Clin.* 2020;

821 119. Giorgio J, Landau SM, Jagust WJ, Tino P, Kourtzi Z. Modelling prognostic trajectories of
822 cognitive decline due to Alzheimer's disease. *NeuroImage Clin.* 2020;

823 120. Khatri U, Kwon GR, Rostro-Gonzalez H. An Efficient Combination among sMRI, CSF,
824 Cognitive Score, and APOE ϵ 4 Biomarkers for Classification of AD and MCI Using
825 Extreme Learning Machine. *Comput Intell Neurosci.* 2020;2020.

- 826 121. Lin W, Gao Q, Yuan J, Chen Z, Feng C, Chen W, et al. Predicting Alzheimer's Disease
827 Conversion From Mild Cognitive Impairment Using an Extreme Learning Machine-Based
828 Grading Method With Multimodal Data. *Front Aging Neurosci.* 2020;
- 829 122. Lin Y, Huang K, Xu H, Qiao Z, Cai S, Wang Y, et al. Predicting the progression of mild
830 cognitive impairment to Alzheimer's disease by longitudinal magnetic resonance imaging-
831 based dictionary learning. *Clin Neurophysiol.* 2020 Oct;131(10):2429–39.
- 832 123. Pan D, Zeng A, Jia L, Huang Y, Frizzell T, Song X. Early Detection of Alzheimer's
833 Disease Using Magnetic Resonance Imaging: A Novel Approach Combining
834 Convolutional Neural Networks and Ensemble Learning. *Front Neurosci.* 2020;
- 835 124. Ramon-Julvez U, Hernandez M, Mayordomo E, Adni. Analysis of the Influence of
836 Diffeomorphic Normalization in the Prediction of Stable VS Progressive MCI Conversion
837 with Convolutional Neural Networks. In: *Proceedings - International Symposium on*
838 *Biomedical Imaging.* 2020.
- 839 125. Xiao R, Cui X, Qiao H, Zheng X, Zhang Y. Early diagnosis model of Alzheimer's
840 Disease based on sparse logistic regression. *Multimed Tools Appl.* 2020 Sep;1–12.
- 841 126. Xu M, Sanz DL, Garces P, Maestu F, Li Q, Pantazis D. A graph Gaussian embedding
842 method for predicting Alzheimer's disease progression with MEG brain networks. *arXiv.*
843 2020.
- 844 127. Yang Z, Liu Z. The risk prediction of Alzheimer's disease based on the deep learning
845 model of brain 18F-FDG positron emission tomography. *Saudi J Biol Sci.* 2020
846 Feb;27(2):659–65.
- 847 128. Yee E, Popuri K, Beg MF. Quantifying brain metabolism from FDG-PET images into a
848 probability of Alzheimer's dementia score. *Hum Brain Mapp.* 2020 Jan;41(1):5–16.
- 849 129. Zhou T, Thung KH, Liu M, Shi F, Zhang C, Shen D. Multi-modal latent space inducing
850 ensemble SVM classifier for early dementia diagnosis with neuroimaging data. *Med*
851 *Image Anal.* 2020 Feb;60.
- 852 130. Bae J, Stocks J, Heywood A, Jung Y, Jenkins L, Hill V, et al. Transfer learning for
853 predicting conversion from mild cognitive impairment to dementia of Alzheimer's type

854 based on a three-dimensional convolutional neural network. *Neurobiol Aging*. 2021
855 Mar;99:53–64.

856 131. Mofrad SA, Lundervold AJ, Vik A, Lundervold AS. Cognitive and MRI trajectories for
857 prediction of Alzheimer's disease. *Sci Reports* |. 123AD;11:2122.

858 132. Mofrad SA, Lundervold A, Lundervold AS. A predictive framework based on brain
859 volume trajectories enabling early detection of Alzheimer's disease. *Comput Med*
860 *Imaging Graph*. 2021 Jun;90.

861 133. Pan X, Phan T Le, Adel M, Fossati C, Gaidon T, Wojak J, et al. Multi-View Separable
862 Pyramid Network for AD Prediction at MCI Stage by 18F-FDG Brain PET Imaging.
863 *IEEE Trans Med Imaging*. 2021 Jan;40(1):81–92.

864 134. Shen HT, Zhu X, Zhang Z, Wang SH, Chen Y, Xu X, et al. Heterogeneous data fusion for
865 predicting mild cognitive impairment conversion. *Inf Fusion*. 2021 Feb;66:54–63.

866 135. Syaifullah AH, Shiino A, Kitahara H, Ito R, Ishida M, Tanigaki K. Machine Learning for
867 Diagnosis of AD and Prediction of MCI Progression From Brain MRI Using Brain
868 Anatomical Analysis Using Diffeomorphic Deformation. *Front Neurol*. 2021 Feb;11.

869 136. Wen J, Samper-González J, Bottani S, Routier A, Burgos N, Jacquemont T, et al.
870 Reproducible Evaluation of Diffusion MRI Features for Automatic Classification of
871 Patients with Alzheimer's Disease. *Neuroinformatics*. 2021 Jan;19(1):57–78.

872 137. Zhang J, Zheng B, Gao A, Feng X, Liang D, Long X. A 3D densely connected
873 convolution neural network with connection-wise attention mechanism for Alzheimer's
874 disease classification. *Magn Reson Imaging*. 2021 May;78:119–26.

875 138. Zhu Y, Kim M, Zhu X, Kaufer D, Wu G. Long range early diagnosis of Alzheimer's
876 disease using longitudinal MR imaging data. *Med Image Anal*. 2021 Jan;67.

877 139. Steardo L, Carbone EA, Filippis R de, Pisanu C, Segura-Garcia C, Squassina A, et al.
878 Application of support vector machine on fmri data as biomarkers in schizophrenia
879 diagnosis: A systematic review. *Front Psychiatry*. 2020;

880 140. Metz CE. Receiver Operating Characteristic Analysis: A Tool for the Quantitative
881 Evaluation of Observer Performance and Imaging Systems. *J Am Coll Radiol*. 2006;

882 141. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating
883 characteristic (ROC) curve. Radiology. 1982;

884 142. Ebrahimighahnavieh MA, Luo S, Chiong R. Deep learning to detect Alzheimer's disease
885 from neuroimaging: A systematic literature review. Comput Methods Programs Biomed.
886 2020;

887 143. Chan D, Fox NC, Scahill RI, Crum WR, Whitwell JL, Leschziner G, et al. Patterns of
888 temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol. 2001;

889 144. Fan Y, Batmanghelich N, Clark CM, Davatzikos C. Spatial patterns of brain atrophy in
890 MCI patients, identified via high-dimensional pattern classification, predict subsequent
891 cognitive decline. Neuroimage. 2008;

892 145. Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rate of medial
893 temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology. 1998;

894 146. Lerch JP, Pruessner J, Zijdenbos AP, Collins DL, Teipel SJ, Hampel H, et al. Automated
895 cortical thickness measurements from MRI can accurately separate Alzheimer's patients
896 from normal elderly controls. Neurobiol Aging. 2008;

897 147. Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of
898 cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain. 2006;

899