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Artificial intelligence and neuropsychological measures: The case of Alzheimer's disease

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ABSTRACT

One of the current challenges in the field of Alzheimer's disease (AD) is to identify patients with mild cognitive impairment (MCI) that will convert to AD. Artificial intelligence, in particular machine learning (ML), has established as one of more powerful approach to extract reliable predictors and to automatically classify different AD phenotypes. It is time to accelerate the translation of this knowledge in clinical practice, mainly by using low-cost features originating from the neuropsychological assessment.

We performed a meta-analysis to assess the contribution of ML and neuropsychological measures for the automated classification of MCI patients and the prediction of their conversion to AD. The pooled sensitivity and specificity of patients' classifications was obtained by means of a quantitative bivariate random-effect meta-analytic approach. Although a high heterogeneity was observed, the results of meta-analysis show that ML applied to neuropsychological measures can lead to a successful automatic classification, being more specific as screening rather than prognosis tool. Relevant categories of neuropsychological tests can be extracted by ML that maximize the classification accuracy.

1. Introduction

It was estimated that in 2015 there would have been more than 47 million people worldwide affected by dementia; these estimates were confirmed and the projections for 2050 are even more worrying with 131 million people living with dementia (Prince et al., 2013). This high prevalence has led to significant health and social problems and is expected to rise due to the increase in life expectancy and under- or mis-diagnosis.

Several forms of dementia have been described in the literature with Alzheimer's disease (AD) being considered the primary cause of neurodegenerative dementia (Querfurth and LaFerla, 2010). Pathologically, this neurodegenerative disease has been linked by protein misfolding in the brain, with specific abnormal protein and pattern of deposition, which can occur years or even decades before clinical manifestation. However, currently, the only definitive diagnosis can be performed in *post-mortem* examination by detecting the presence of senile plaques and neurofibrillary tangles associated with amyloid angiopathy in the brain tissues (Beach et al., 2012).

In living human brain, the criteria for the diagnosis of AD are those proposed by the National Institute of Neurological Disorders and Stroke–Alzheimer Diseases and Related Disorders working group (McKhann et al., 1984). Since their publication, thanks to biological advances and neuroimaging studies on AD, several other international

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criteria have been proposed (Albert et al., 2011; Dubois et al., 2007, 2014; McKhann et al., 2011; Sperling et al., 2011). The National Institute on Aging and the Alzheimer's Association define different stages of AD progression (Jack et al., 2011), starting from the asymptomatic pre-clinical and the symptomatic prodromal stages. The stage of AD identified by merely subjective cognitive impairment (SCI) which cannot be detected by objective measures (Lautenschlager et al., 2005) can emerge several years before the onset of the prodromal stage (Solfrizzi et al., 2004). The subsequent stage (prodromal) displaying clear symptoms is referred to as Mild Cognitive Impairment (MCI), which is characterized by symptoms that are not severe enough to meet currently accepted diagnostic criteria for AD (Petersen, 2004). Indeed, the term MCI is applied to subjects with a deficit of at least one cognitive domain, without significant effects on their daily activities (Albert et al., 2011). Finally, when cognitive and behavioural symptoms interfere with daily functional abilities, a diagnosis of AD can be made, with a label of probable or possible according to various clinical conditions (McKhann et al., 2011).

However, at the state of the art it is still difficult to predict patients at risks of AD (MCI) and whether and when individuals at risk (with MCI) will progress to AD-type dementia and how much time will lapse for progression. Thus, the current challenge is to identify markers that capture MCI and discriminate between patients with MCI who will convert (MCI converters, MCIc) and who will not convert (MCI not-converters, MCInc) to AD-type dementia.

In the last ten years, the international neuroimaging community has made considerable efforts to identify surrogate biomarkers of AD pathophysiology to be used for early (pre-clinical/prodromal stages) diagnosis. According to Alzheimer's disease Neuroimaging Initiative (Mueller et al., 2005), an ideal AD biomarker should be simple to perform, reliable, minimally invasive/expensive and able to detect features of the pathophysiologic processes active in AD before symptom onset. The vast majority of these biomarkers have been carried out in neurobiology realm by means of very sophisticated technologies. Tau- or amyloid- aggregation within the brain, cortical hypo-metabolism, and hippocampal atrophy can be obtained, *in vivo,* by Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) (Frisoni et al., 2010; Bateman et al., 2012; Jack and Holtzman, 2013). However, the availability of these technologies only in some expert centres and financial constraints limit their adoption into routine clinical use. More importantly, despite they are reliable biomarkers of disease, they have relatively limited ability in the prediction of AD at the individual level (Arbabshirani et al., 2017; Petersen et al., 2001).

In the last few years, artificial intelligence has proven to be a new effective way in designing prognostic/diagnostic tools for improving the clinical practice of AD. In particular, machine learning (ML) methods, which are intelligent systems capable of *learning* complex relationships or patterns from empirical data and extracting predictive data models, have found fertile ground in the study of AD with promising results for biomarkers also at an early-stage (Bishop, 2006; Orru et al., 2012; Salvatore et al., 2016). ML methods have been applied on several features with ability in the prediction of which subjects with MCI will progress to AD. These include biological, neuroimaging data and neuropsychological testing. Neuroimaging is the most important realm where ML methods have widely been applied (Weiner et al., 2017). By combining, in a multivariate way, information hidden in the brain images of patients and invisible to a naked eye, ML methods can automatically classify an individual subject on the basis of image differences or similarities with images of known classes of subjects (Noirhomme et al., 2014; Bryan, 2016). From the first seminal paper by Klöppel et al. (2008), in the last 10 years, a plethora of ML studies on neuroimaging have been published with the aim to reach the best accuracy level in the automated clinical diagnosis of AD. Whilst classification accuracy in discriminating AD from healthy controls (HC) range between 80–95% (Mateos-Pérez et al., 2018) the real challenge is to automatically classify between prodromal forms of disease. A recent review of more than 30 papers showed that the ML automatic classification of MCIc vs MCInc, based on neuroimaging data, can achieve a median accuracy, specificity and sensitivity of 70 %, 66 % and 75 %, respectively (Salvatore et al., 2016).

ML has also been applied to biological data of AD and MCI patients. By combining different biological markers in a multivariate way, this approach has been used to identify a biological signature of AD. For example, it was shown that the cerebrospinal fluid calbindin combined with cerebrospinal fluid Aβ42 can automatically discriminate between mildly and very mildly demented subjects from HC with a sensitivity and specificity > 80 % (Craig-Schapiro et al., 2011). However, in the classification of MCIc vs MCInc, this combination of measures led to a good sensitivity (80 %) but a very low specificity (44 %), with a balanced accuracy of 62 % (Yang et al., 2012).

At a cognitive and behavioural level, international Working Group guidelines have proposed a list of neuropsychological tests for the diagnosis of AD (Dubois et al., 2014). However, there is still no clear consensus on the specific composite measures to be used for the early diagnosis of AD, since the discussion is still open as to what the most sensitive/specific tests are for early-stage AD. Some authors have argued that stringent cut-off should be fixed in order to identify whether performance is impaired for MCI subjects (Gainotti et al., 2014). To date, studies on the application of ML to neuropsychological tests are increasingly emerging, since some evidence show that ML systems can support the clinical classification of AD patients when trained on neuropsychological measures (Weiner et al., 2017).

In such a changing and stimulating scenario, we aim at performing, for the first time, a meta-analytic evaluation of the contribution of ML and neuropsychological measures for the automated classification of AD and MCI patients and the prediction of MCIs' conversion to AD-type dementia. Specifically, our purpose is to establish, from the results reported by independent studies, whether ML algorithms, trained on a set of neuropsychological measures, could be used for the automatic diagnosis of MCI and to automatically predict conversion to AD-type dementia. We also discuss the advantages associated with the adoption of intelligent tools in the field of neuropsychological assessments for clinical and experimental neuropsychologists by underlying a number of methodological issues that should be taken under consideration for translating these powerful approaches into reliable clinical studies.

2. Material and methods

2.1. Search strategy and selection criteria

This systematic review was conducted on papers published on the use of ML applied to neuropsychological assessment for the automatic classification of AD, MCI and prediction of conversion of MCI to Alzheimer's type dementia. The protocol was not registered, but it was structured in accordance with the PRISMA statement (Moher et al., 2009), so that the PICOS approach was used to identify the studies to be included in the review and meta-analyses. Criteria for including or excluding papers were determined a priori. Papers were considered for inclusion only if: (a) they were written in full-text English language in a peer-reviewed journal, (b) they were published from 2010 to the end of search July 15, 2018, (c) they included subjects with a primary diagnosis of AD according to McKhann's criteria (McKhann et al., 1984), or subsequent versions, or subjects with a primary diagnosis of MCI according to Petersen's criteria (Petersen et al., 1999) and subsequent modifications (Petersen, 2004; Petersen and Negash, 2008), or who had available the global score of the Clinical Dementia Rating (CDR, total score 0.5); and (d) they included at least the neuropsychological measures for the classification. Articles were excluded if: (a) they did not include neuropsychological measures in the classification process, (b) they did not perform a classification of subjects, (c) they did not provide any classification performance, and (d) they did consider subjects with a history of other neurological or psychiatric disorders such as

Parkinson's disease, and stroke. The two authors screened the publications on their relevance for the review. The final resulting papers were considered eligible for the review. Major details about information sources, search strategies and study selection process can be found in Supplementary Material.

2.2. Data extraction strategy

The data collected from each article were categorized as: information on the first author and year of publication, the size of cohorts, the modalities of measures used for the classification, the classification algorithm, the method used to validate the classification, and the classification performance in terms of study-specific accuracy, study-specific specificity, study-specific sensitivity, and study-specific AUC. The final papers were set into four categories, according to the following groups of subjects used for the automatic classification: 1) MCI vs HC, 2) MCIc vs MCInc, 3) AD vs HC, and 4) other comparisons (comparisons not already included in the first three categories).

Neuropsychological tests included in the automatic classification. For all comparisons, we assessed the neuropsychological tests whose scores were most frequently used as input for the classification and whose overall accuracy and/or AUC was higher than 0.7, since, according to the literature (Belleville et al., 2017) an accuracy score higher than 0.7 is considered to be good. The resulting subset of neuropsychological tests was referred to as *optimal predictors*.

2.3. Risk of bias in individual studies

Following the Cochrane guidelines, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (Whiting et al., 2011) was used to assess the methodological quality and the risk of bias of each study. This quality assessment allowed classifying studies as a having low, high or unknown risk of bias. We used a high-quality report subgroup for meta-analyses.

2.4. Meta-analysis

The data stored in the "predetermined grid" described at point 1.4 (namely sample sizes, study-specific sensitivity, study-specific specificity and study-specific accuracy) were used to compute, for each single study, the number of true positive, true negative, false positives and false negatives cases. These were used as raw data for the meta-analysis.

The statistical analyses were carried out in R-Studio (version 13.1) using the MADA package (Doebler and Holling, 2015). In particular, we first explored the neuropsychological data by producing forest plots. By using the "madad" function we obtained univariate measures of heterogeneity for the meta-analytic sensitivity and specificity ($Sensitivity_m$, $Specificity_m$) and we computed the heterogeneity I^2 index as follows:

$$I^2 = [(\chi^2 - df)/ \chi^2]*100.$$

Furthermore, by adopting the "reitsma" function, we computed a bivariate empty model (i.e. with the intercept only) to obtain the meta-analytic AUC (AUC_m) parameter for each summary ROC curve (with 95 % contour ellipsoid). Here we report an example of the syntax of the bivariate reitsma model:

$$AUC_{NPS\_AD} = AUC(reitsma(NPS\_AD, formula = cbind(tsens, tfpr) \sim 1))$$

Finally, to explore the effect of covariates, that could explain the level of between-studies heterogeneity, we run a bivariate random effect model for logit-transformed pairs of sensitivity and specificity. In this latter case, we entered as predictor the factor "comparison" (namely, "AD vs HC", "MCI vs HC" and "MCIc VS MCInc) in the "reitsma" function.

3. Results

3.1. Study selection

The literature search yielded 203 papers related to the established timeframe (January 1, 2010 - July 15, 2018) from electronic databases. Two authors included further six papers from the reference list of previously retrieved articles. A total of 209 papers were identified. Based on the abstract and title, the two authors selected potentially relevant articles. Six hits were excluded because they were not referenced journal articles, 19 were excluded because they were reviews, books and book chapters not reporting original results, which left 184 records. Another 46 papers were further excluded because: a) they focused on a different topic; b) automatic classification was not performed; c) different populations were investigated. At this point in the screening, there were 138 papers left. These papers were checked by studying the full-text to exclude papers that did not meet inclusion criteria when this was not directly apparent from the title and the abstract. At this step, 6 papers were excluded due to the lack of information about sensitivity, specificity and accuracy; 46 papers were excluded because they did not perform a classification; 18 papers were excluded because they did not include neuropsychological tests, 9 papers were excluded because a comparison was made with other neurodegenerative disorders (e.g. Parkinson's disease). Finally, 59 papers were selected as eligible, which were therefore included in this review (see Fig. 1).

3.2. Study characteristics

Grouping papers according to the classes used in the automatic classification generated 4 tables. Table 1 shows papers on the classification of MCI vs HC, Table 2 on MCIc vs MCInc, Table 3 on AD vs HC, (for a total of 45 papers). Papers on the other classification (specifically, MCI vs AD, AD vs MCI vs HC, MCIc vs MCIreverting (MCIr), naMCI vs aMCI vs SCI, for a total of 24 studies) are shown in Table S1 (see Supplementary Materials), because not included in the meta-analysis due to the high heterogeneity of comparisons (only 4 studies compared MCI vs AD and some papers performed more than one comparison, so they could have been reported in more than one table).

Each table reports also the sample size and the follow-up duration (in terms of years) adopted to assess the conversion to Alzheimer's type dementia or to ensure a stable diagnosis (when available).

Concerning MCI vs HC (Table 1), 20 papers were retrieved from the search. Cohort characteristics were very different among the considered studies. The median (range) of the cohort size was 60 (8–763) for MCI patients and 63 (8–5883) for HC. Six studies used subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (marked with * in the table). In these papers, measures included in the classification were extracted from neuropsychological, linguistic, demographical, anamnestic, and neuroimaging. The most frequently used ML algorithms were Support Vector Machine (SVM) and regression. The most common validation method was cross-validation.

Concerning MCIc vs MCInc (Table 2), 24 papers were included, 17 of which used subjects from the ADNI dataset. The median (range) of the cohort size was 86 (14–257) for MCIc and 100 (20–462) for MCInc. The mean of the follow up was 3 years. Measures included in the classification were neuropsychological, demographical, medical, socio-anamnestic, neuroimaging and biological data. Regression was the most frequently used ML classifier and cross-validation was the most frequently employed validation method.

Concerning AD vs HC (Table 3), 19 papers were included, 9 of which used subjects from ADNI dataset. The median value (range) of the cohort size was 59 (9–257) for AD patients and 125 (9–346) for HC. Also, for this comparison, measures included in the classification were obtained from neuropsychological, linguistic, demographical, anamnestic, neuroimaging and biological data. The most frequently used

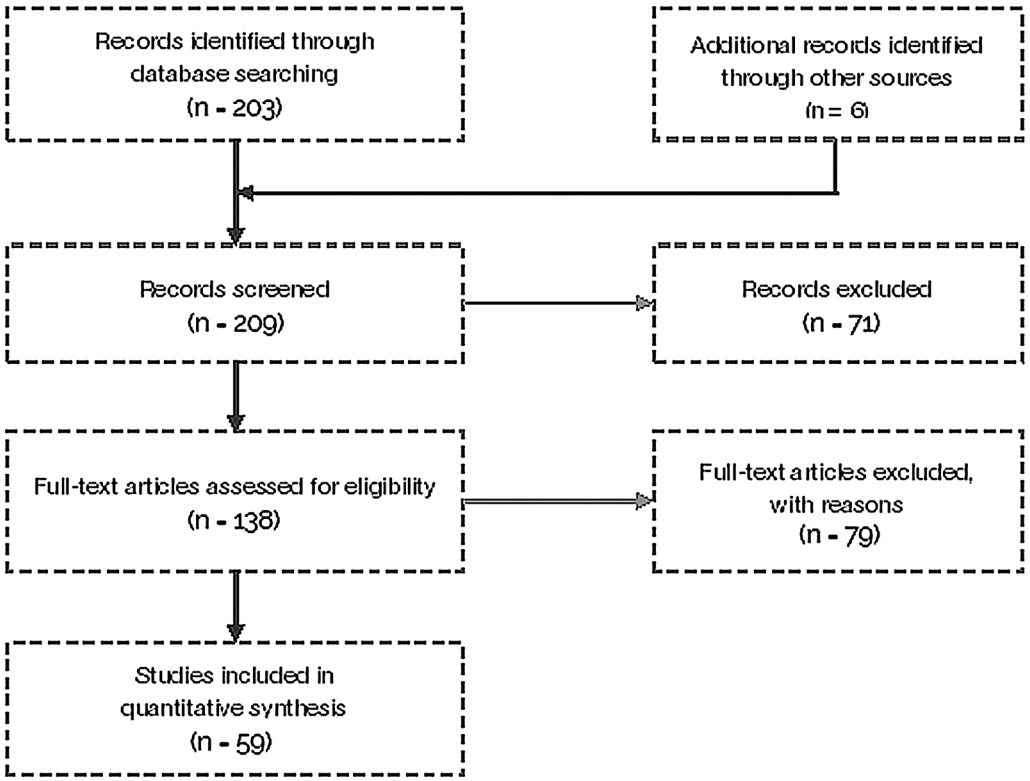

Fig. 1. PRISMA flow diagram depicting the different phases of the review selection process.

algorithm and validation methods were SVM and cross-validation, respectively.

3.3. Risk of bias within studies

The risk of bias associated with the studies as well as the comments of the authors concerning the seven domains of the QUADAS tool has been assessed. Figs. 2 and 3 show QUADAS-2 charts of the studies included in the review. Most of the studies (70 %, 41/59) achieved a low *risk of bias* (Fig. 2) and low *concerns regarding applicability* (Fig. 3). The other papers showed a high risk of bias about the *appropriateness of reference standard* and *patient selection*.

The risk of bias tools highlighted some frequent limitations:

- only a small set of studies included sufficient details about the selection process (i.e., Cui et al., 2012, Quintana et al., 2012, Schmid et al., 2013, Beltrachini et al., 2015, Tabaton et al., 2010, Runtti et al., 2014);
- some studies relied on data samples of small size (i.e., less than 40 subjects overall, according to Belleville et al. (2017), or less than 20 subjects per diagnostic class for binary comparisons in order to perform proper training of ML algorithms); among the works included in this meta-analysis, the papers by König et al. (2015), Fasano et al. (2018), and Jarrold et al. (2014) fall in this category;
- most studies included in this meta-analysis did not ensure or did not provide information about the strict independence between measures used as input to the ML algorithm and measures used to assign a gold-standard diagnostic label to patients. This issue is of particular importance for studies that use neuropsychological tests. As a consequence, ML algorithms may be trained on data that are not independent of the gold-standard label to be predicted. This leads to an over-estimate of the classification performance due to circularity or double-dipping. In order to highlight this problem, some papers clearly declared that the neuropsychological tests used in their gold standard diagnosis of patients were not used as a part of the experimental procedure (e.g. Casanova et al., 2013; Chapman et al., 2011; Goryawala et al., 2015; König et al., 2015; Lv et al., 2010; Quintana et al., 2012; Weakley et al., 2015; Battista et al., 2017a);
- some studies did not have a follow up or did not specify this information in the manuscript (Lv et al., 2010; Ewers et al., 2012; García et al., 2012; Zhou et al., 2014; Goryawala et al., 2015, König et al., 2015, Orimaye et al., 2015; Weakley et al., 2015; Guerrero et al., 2016; Beheshti et al., 2017; Asgari et al., 2017; Fasano et al., 2018; Hernández-Domínguez et al., 2018; Tunvirachaisakul et al., 2018);
- only one study reported, for a subsample of their patients, the post-mortem analyses and confirmation of the diagnosis (Fraser et al., 2016).

3.4. Results of the systematic review

The results of our review were obtained from the first three groups of papers (Tables 1, 2 and 3), since, as previously reported, the last category (Table 1S) included a high heterogeneity of comparisons making statistical analysis not possible. Moreover, the violin plots in Fig. 4 graphically show the results regarding the performance by Accuracy, Sensitivity and Specificity of the three comparisons (MCI vs HC; MCIc vs MCInc; AD vs HC). The most-frequently-used neuropsychological tests with good overall accuracy are shown in the Heatmap displayed in Fig. 5. Tests are divided according to the neuropsychological domain they belong to and are ranked according to their frequency within each domain. Further, the most frequent (≥ 25 % frequency) optimal predictors of the three comparisons are graphically summarized in the radar plot reported in Fig. 6.

- *MCI vs HC*

Considering the set of studies that compared MCI vs HC using ML on neuropsychological data, the accuracy of classification (%) ranged from 60 to 98 (sensitivity 45–97, specificity 67–100, AUC 63–99).

Table 1
Characteristics of studies targeted MCI vs HC. The table reports the first author, year of publication and information about the use (or not) of data obtained from the ADNI public repository (marked as * if ADNI was used); the sample size; the follow up (in terms of years) adopted to assess the conversion to Alzheimer's type dementia or to ensure a stable diagnosis (when available); the modality (or modalities) of data used for the classification; the classification algorithm; the method used to validate and test the classifier; the performance of classification in terms of accuracy, specificity, sensitivity, and AUC (the best performance was reported when different classifiers were used).

Author	Sample size	Follow up (y)	Modalities of data	Classification algorithm	Validation-and-testing method	Performance [acc / sen / spe / AUC]			
						NPS	NPS + IMG	NPS + BIO	NPS + IMG + BIO
Lv et al., 2010	42 MCI; 45 HC	–	Neuropsychological; Demographical	SVM	Train-and-test	.85/.85/.86/.92			
Hinrichs et al., 2011*	119 MCI; 66 HC	2	Neuropsychological; Neuroimaging; Biological	SVM (Multi Kernel Learning)	Cross Validation	-/-/-/.74			-/-/-/.77
Cui et al., 2012*	33 MCI; 153 HC	2	Neuropsychological; Neuroimaging	SVM	Cross Validation	.64/.46/.68/.63	.79/.73/.80/.84		
García et al., 2012	18 MCI; 39 HC (this dataset was extended using an over-sampling strategy)	–	Neuropsychological; Demographical	Neural Networks	Train-and-test	.91/.87/.94/-			
Quintana et al., 2012	79 MCI; 346 HC	0.5 (at least)	Neuropsychological; Demographical	Neural Networks	Train-and-test	.98/-/-/-			
Casanova et al., 2013*	153 MCIc; 182 MCInc; 188 HC	3	Neuropsychological; Neuroimaging	Logistic Regression	Nested Cross Validation	–			
Schmid et al., 2013	29 MCIc; 29 HC	~8	Neuropsychological; Anamnestic	Regression	Cross Validation	.60/-/-/-			
Zhou et al., 2014	67 aMCI; 56 naMCI; 127 HC	–	Neuropsychological; Neuroimaging	SVM	Cross Validation		.75/.61/.83/-.74/.55/.82/-		
Beltrachini et al., 2015	29 MCI; 21 HC	Yes, but not specified	Neuropsychological; Neuroimaging	Linear Discriminant Analysis Quadratic Discriminant Analysis	Cross Validation	.93/.93/.94/.95 .89/.88/.91/.92	.96/.96/.95/.95 .94/.92/.97/.94		
Goryawala et al., 2015*	114 early-MCI; 91 late-MCI; 125 HC	–	Neuropsychological; Demographical; Neuroimaging	Linear Discriminant Analysis	Cross Validation	.85/-/-/- .89/-/-/-	.86/.96/.74/- .91/.97/.84/-		
König et al., 2015	23 MCI; 15 HC	–	Neuropsychological; Linguistic	SVM	Cross Validation	.79/.79/.79/-			
Orimaye et al., 2015	Cohort I: 19 MCI; 19 HC; Cohort II: 8 MCI; 8 HC	–	Linguistic	SVM	Cross Validation	-/-/.97/.99			
Salvatore et al., 2015*	76 MCIc; 162 HC	1.5	Neuropsychological; Neuroimaging	SVM	Nested Cross Validation		.78/-/-/-		
Weakley et al., 2015	97 MCI; 161 HC	–	Neuropsychological; Demographical	Naive Bayes	Train-and-test	.92/.98/.81/-			
Asgari et al., 2017	14 MCI; 27 HC	–	Linguistic and phonetic metrics	SVM	Cross Validation	.83/.81/.76/.80			
Battista et al., 2017a*	143 MCI; 126 HC	1.5−3	Neuropsychological	SVM	Nested Cross Validation	.86/.84/.89/-			
Lin et al., 2018	763 aMCI; 253 naMCI; 127 Dementia; 5883 HC	4	Neuropsychological	SVM	Cross Validation	.71/.71/.71/.77 .75/.57/.75/.73			
Fasano et al., 2018	11 aMCI; 11 HC	–	Neuropsychological; Neuroimaging	SVM	Nested Cross Validation	.91/.85/1/-	1/1/1/-		
Tunvirachaisakul et al., 2018	60 MCI; 63 HC	–	Neuropsychological	SVM	Cross Validation	.77/-/-/-			

Table 2
Characteristics of studies targeted MCIc vs MCInc. The table reports the first author, year of publication and information about the use (or not) of data obtained from the ADNI public repository (marked as * if ADNI was used); the sample size; the follow up (in terms of years) adopted to assess the conversion to Alzheimer's type dementia or to ensure a stable diagnosis (when available); the modality (or modalities) of data used for the classification; the classification algorithm; the method used to validate and test the classifier; the performance of classification in terms of accuracy, specificity, sensitivity, and AUC (the best performance was reported when different classifiers were used).

Author	Sample size	Follow up (y)	Modalities of data	Classification algorithm	Validation-and-testing method	Performance [acc / sen / spe / AUC]			
						NPS	NPS + IMG	NPS + BIO	NPS + IMG + BIO
Tabaton et al., 2010	37 MCIc; 43 MCInc	2	Neuropsychological; Demographical; Biological	Neural Networks	Cross Validation			.80/.77/.83/-	
Chapman et al., 2011	Cohort I: 29 MCInc; 14 MCIc; Cohort II: 55 AD; 78 HC; 35 MCI; 5 AAMI	1.7	Neuropsychological	Discriminant Analysis	Cross Validation	.79/.79/.79/-			
Cui et al., 2011*	56 MCIc; 87 MCInc (training on 96 AD and 111 HC)	2 (at least)	Neuropsychological; Neuroimaging; Biological	SVM	Train-and-test	.65/.91/.48/.76	.62/.93/.43/.78	.65/.95/.46/.78	.67/.96/.48/.80
Hinrichs et al., 2011*	119 MCI, including MCIc, MCInc, and reverting MCI (training on 48 AD and 66 HC)	2 − 3	Neuropsychological; Neuroimaging; Biological	SVM (Multi Kernel Learning)	Train-and-test	-/-/-/.74			-/-/-/.77
Ye et al., 2012*	142 MCIc; 177 MCInc	4	Neuropsychological; Neuroimaging; Biological	Logistic Regression	Leave One Out	-/-/-/.77		-/-/-/.81	-/-/-/.86
Ewers et al., 2012*	58 MCIc; 72 MCInc	1.9	Neuropsychological; Demographical; Neuroimaging; Biological	Logistic Regression	Cross Validation	.65/.50/.76/-	.72/.78/.68/-	.68/.82/.57/-	.76/.88/.68/-
Koikkalainen et al., 2012*	156 MCIc; 222 MCInc	3	Neuropsychological; Demographical; Neuroimaging; Biological	Linear Regression	Cross Validation	.69/-/-/-			
Toussaint et al., 2012*	40 MCIc; 40 MCInc	2	Neuropsychological; Neuroimaging; Biological	SVM	Leave One Out	.62/.55/.70/-	.82/.85/.80/-	.68/.65/.70/-	.80/.75/.85/-
Casanova et al., 2013*	153 MCIc; 182 MCInc	3	Neuropsychological; Neuroimaging	Logistic Regression	Nested Cross Validation	.65/.58/.70/-			
Silva et al., 2013*	162 MCIc; 88 MCInc	5 (at least)	Neuropsychological	Linear Discriminant Analysis	Cross Validation	.79/.79/.80/-			
Clark et al., 2014*	44 MCIc; 36 MCInc	Up to 2 (at least 1)	Neuropsychological	Random Forest	Cross Validation	.84/.84/.83/.91			
Peters et al., 2014	18 MCIc; 22 MCInc	2	Neuropsychological; Neuroimaging	Logistic Regression	Leave One Out	.83/.72/.91/.93	.88/.83/.91/.98		
Runtti et al., 2014*	140 MCIc; 149 MCInc	2 (at least)	Neuropsychological; Neuroimaging; Biological	Linear Regression	Nested Cross Validation	.75/.74/.76/.80			.77/.82/.73/.82
Segovia et al., 2014*	26 MCIc; 20 MCInc	3	Neuropsychological; Demographical; Neuroimaging	SVM	Leave One Out	.85/.85/.85/.85	.89/.92/.85/.87		
Dukart et al., 2015*	177 MCIc; 265 MCInc (training on 144 AD and 112 HC)	2 (at least)	Neuropsychological; Neuroimaging; Biological	Naive Bayes	Train-and-test	.69/.85/.52/.72	.74/.74/.74/.77 .74/.81/.68/.80 .69/.78/.61/.72	.69/.87/.52/.72	.74/.74/.73/.77 .74/.81/.67/.79 .68/.76/.61/.72
Eskildsen et al., 2015*	161 MCIc; 227 MCInc (training on 194 AD and 226 HC)	3	Neuropsychological; Demographical; Neuroimaging	Linear Discriminant Analysis	Leave One Out	.61/.76/.51/.67			
Moradi et al., 2015*	164 MCIc; 100 MCInc	3 (up to 8)	Demographical (age); Neuropsychological; Neuroimaging	Low Density Separation / Random Forest	Nested Cross Validation	-/-/-/.88	.82/.87/.74/.90		
Ritter et al., 2015*	86 MCIc; 151 MCInc	3 (at least)	Demographical; Neuropsychological; Medical-Clinical; Neuroimaging; Biological	SVM	Nested Cross Validation	.72/-/-/-			.73/-/-/-
Salvatore et al., 2015*	76 MCIc; 134 MCInc	1.5	Neuropsychological; Neuroimaging	SVM	Nested Cross Validation		.60/-/-/-		
Arco et al., 2016*	73 MCIc; 61 MCInc	0.5 − 1	Neuropsychological; Neuroimaging	Linear Discriminant Analysis	Leave One Out		.74/.74/.74/.79		

(*continued on next page*)

Table 2 (*continued*)

Author	Sample size	Follow up (y)	Modalities of data	Classification algorithm	Validation-and-testing method	Performance [acc / sen / spe / AUC]			
						NPS	NPS + IMG	NPS + BIO	NPS + IMG + BIO
Moradi et al., 2017*	164 MCIc; 100 MCInc (additional sample for training: 186 [180] AD; 226 HC; 130 [129] unknown MCI)	3 (up to 8)	Neuropsychological; Neuroimaging	Gaussian classifier	Cross Validation	.71/-/-/-	.75/-/-/-		
Pereira et al., 2017	257 MCIc; 462 MCInc	3.3 ± 2.8	Demographical; Clinical; Neuropsychological	Naive Bayes	Nested Cross Validation Train-and-test	-/.88/.71/.88 -/.56/.70/.76			
Grassi et al., 2018	30 MCIc; 93 MCInc	3 (at least)	Socio-demographical; Clinical; Neuropsychological; Neuroimaging (MRI)	SVM	Cross Validation		.87/.87/.88/.91		

Fig. 5 reports the neuropsychological tests most frequently used as input for the classification and with good overall accuracy (see Appendix A for a full list of abbreviations of tests). Tests are divided according to the neuropsychological domain they belong to and are ranked according to their frequency within each domain. The most frequent (≥ 25 % frequency) *optimal predictors* include: AVLT (43 %), LM (29 %), and Prose Memory Test (29 %) for auditory episodic memory; MMSE (43 %) for global cognitive efficiency; Category Fluency Test (36 %) and BNT (29 %) for language; Digit Span Test Forward and Backward Test (36 %) for sustained attention and working memory; Letter Fluency Test (29 %) for executive functions (Fig. 6). In the Supplementary Material we reported individual tests with very good overall accuracy and/or AUC (≥ 0.7) for this diagnostic comparison (Table S3).

- *MCIc vs MCInc*

Considering the set of studies that classified MCIc vs MCInc using ML on neuropsychological tests the accuracy of classification (%) ranged from 61 to 85 (sensitivity 50–91, specificity 48–91, AUC 67–93).

Similarly, to previous results, the neuropsychological tests most frequently used as input for the classifications and with good overall accuracy are shown in Fig. 5. The most frequent (≥ 25 % frequency) *optimal predictors* include: AVLT (73 %) and LM (33 %) for auditory episodic memory; MMSE (40 %) for global cognitive efficiency; TMT-B (40 %) and TMT-A (33 %) for executive functions; ADAS-cog battery (33 %); Digit-Span Forward and Backward test (27 %) for sustained attention and working memory; Category-Fluency Test (27 %) for language; FAQ (33 %) for activities in daily living; GDS (27 %) for depression (Fig. 6). Regarding the neuropsychological tests adopted in these papers, it is interesting to note that some papers reported the total score extracted from the ADAS-cog battery (Arco et al., 2016; Casanova et al., 2013; Dukart et al., 2015; Moradi et al., 2015; Ritter et al., 2015; Runtti et al., 2014; Ye et al., 2012), while others also reported subscores of the same test, such as the Q11 sub-score (measure of word finding) (Moradi et al., 2015; Ritter et al., 2015). Behavioral and functional abilities scales were also selected in the classification (Cui et al., 2011; Dukart et al., 2015; Moradi et al., 2015; Ritter et al., 2015; Ye et al., 2012). No studies included measures of the different linguistic levels (phonological, semantic, morpho-syntactic and pragmatic) in the classification. In the Supplementary Material we reported individual tests with very good overall accuracy and/or AUC (≥ 0.7) for this comparison (Table S4).

- *AD vs HC*

Considering the studies that classified AD vs HC using ML on neuropsychological data, the accuracy of classification (%) ranged from 72 to 100 (sensitivity 73–100, specificity 77–100, AUC 79–98).

The most-frequently-used neuropsychological tests with good overall accuracy are shown in Fig. 5. The most frequent (≥ 25 % frequency) *optimal predictors* include: MMSE (25 %) for global cognitive efficiency; AVLT (31 %) for auditory episodic memory; and Category-Fluency test (38 %) for language (see Appendix A for a full list of abbreviations of tests).

Regarding neuropsychological data, measures of verbal episodic memory were most frequently included in the final subset of neuropsychological predictors (Fig. 6). Overall, measures of linguistic abilities achieved a high level of accuracy (ranging from 0.84 to 0.93), and in particular those extracted from the picture description task (e.g., Jarrold et al., 2014; König et al., 2015). In the Supplementary Material we reported individual tests with very good overall accuracy and/or AUC (≥ 0.7) for this diagnostic comparison (Table S2).

Table 3
Characteristics of studies targeted AD vs HC. The table reports the first author, year of publication and information about the use (or not) of data obtained from the ADNI public repository (marked as * if ADNI was used); the sample size; the follow up (in terms of years) adopted to assess the conversion to Alzheimer's type dementia or to ensure a stable diagnosis (when available); the modality (or modalities) of data used for the classification; the classification algorithm; the method used to validate and test the classifier; the performance of classification in terms of accuracy, specificity, sensitivity, and AUC (the best performance was reported when different classifiers were used).

Author	Sample size	Follow up (y)	Modalities of data	Classification algorithm	Validation-and-testing method	Performance [acc / sen / spe / AUC]			
						NPS	NPS + IMG	NPS + BIO	NPS + IMG + BIO
Hinrichs et al., 2011*	48 AD; 66 HC	2	Neuropsychological; Neuroimaging; Biological	SVM (Multi Kernel Learning)	Cross Validation	.91/.89/.93/.98			.92/.87/.97/.98
Ewers et al., 2012*	81 AD; 101 HC	–	Neuropsychological; Demographical; Neuroimaging; Biological	Logistic Regression	Cross Validation	.91/.90/.91/-		.95/.92/.98/-	
Koikkalainen et al., 2012*	191 AD; 217 HC	3	Neuropsychological; Demographical; Neuroimaging; Biological	Linear Regression	Cross Validation	1/-/-/-			
Quintana et al., 2012	97 AD; 346 HC	0.5 (at least)	Neuropsychological; Demographical	Neural Networks	Train-and-test	1/-/-/-			
Toussaint et al. 2012*	40 AD; 40 HC	2	Neuropsychological; Neuroimaging; Biological	SVM	Leave One Out	1/1/1/-		1/1/1/-	1/1/1/-
Casanova et al., 2013*	171 AD; 188 HC	3	Neuropsychological; Neuroimaging	Logistic Regression	Nested Cross Validation	–			
Clark et al., 2014*	41 AD; 44 HC	Up to 2	Neuropsychological	Random Forest	Cross Validation	.94/.93/.95/.97			
Jarrold et al., 2014	9 AD; 9 HC	–	Linguistic	Neural Networks	Cross Validation	.88/.83/.90/-			
Reverberi et al., 2014	75 AD; 307 HC	1 (at least)	Neuropsychological	SVM	Leave One Out	.72/-/-/-			
Zhou et al., 2014	59 AD; 127 HC	–	Neuropsychological; Neuroimaging	SVM	Cross Validation		.92/.84/.96/-		
Fraser et al., 2016	167 AD (240 samples); 97 HC (233 samples)	4 to 9 (in some cases, post-mortem)	Linguistic	Logistic Regression	Cross Validation	.82/-/-/-			
Goryawala et al., 2015*	55 AD; 125 HC	–	Neuropsychological; Demographical; Neuroimaging	Linear Discriminant Analysis	Cross Validation	.92/-/-/-	.94/.96/.90/-		
König et al., 2015	26 AD; 15 HC	–	Neuropsychological; Linguistic	SVM	Cross Validation	.87/.87/.87/-			
Salvatore et al., 2015*	137 AD; 162 HC	1.5	Neuropsychological; Neuroimaging	SVM	Nested Cross Validation		.99/-/-/-		
Weakley et al., 2015	52 AD; 161 HC	–	Neuropsychological; Demographical	Naive Bayes	Training-and-testing	.99/1/.96/-			
Guerrero et al., 2016	39 AD; 42 HC	–	Neuropsychological	Bayesian Network	Leave One Out	.91/.87/.94/.96			
Battista et al., 2017a*	55 AD; 126 HC	1.5 – 3	Neuropsychological	SVM	Nested Cross Validation	.96/.95/.97/-			
Beheshti et al., 2017*	102 AD; 99 HC	–	Neuropsychological; Neuroimaging	SVM	Cross Validation	.85/.73/.98/.87 (FAQ)	.97/.96/.98/.97		
Hernández-Domínguez et al., 2018	257 AD; 217 HC	–	Linguistic and phonetic metrics	SVM	Cross Validation	.79/.81/.77/.79			

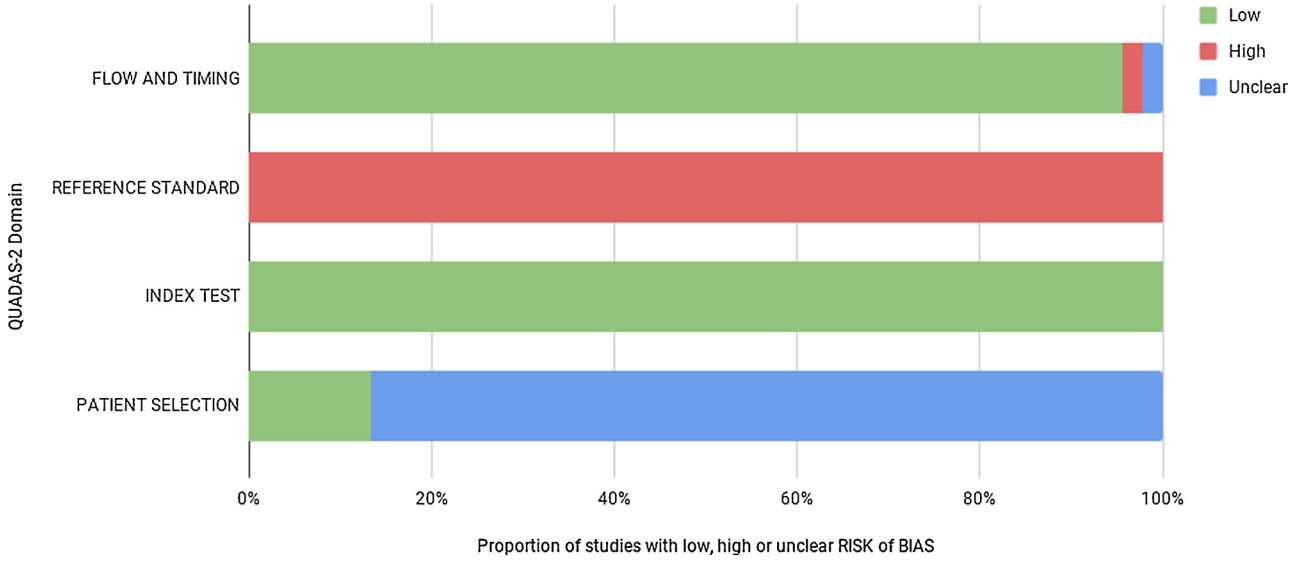

Fig. 2. Proportion of studies included with low, high or unclear risk of bias.

3.5. Results of the metanalysis

Fig. 7 shows the forest plots of sensitivities and specificities of the classifiers as reported in the three groups of papers (contrasts) included in the meta-analysis. Average sensitivities ranged from 73 %, in the contrast MCIc vs MCInc, to 83 % in the contrast MCI vs HC, up to 92 % in the contrast AD vs HC, while mean specificities ranged from 69 % in the contrast MCIc vs MCInc to, to 83 % in the contrast MCI vs HC, up to 86 % in the contrast AD vs HC.

Table 4 shows the I^2 values for the sensitivity$_m$ and specificity$_m$, and AUC$_m$. Consistently with the forest plots, AUC$_m$ values were higher for AD vs HC and MCI vs HC (> 89 %). However, AUC$_m$ was good also for the MCIc vs MCInc contrast (> 0.75). It should be noted that a high level of heterogeneity in sensitivity$_m$ and specificity$_m$ was found.

Fig. 8 completes these investigations by showing study-specific confidence regions in the ROC space and ROC curves in the contrasts of interest. The highest range of specificity was found in the contrasts AD vs HC and MCI vs HC.

Finally, we combined the data from all the neuropsychological studies to account for the effect of "comparison". The results of the random effects bivariate model are reported in Table 5. The meta-regression showed that the contrast AD vs HC has a higher sensitivity than the contrast MCI vs HC (Z = -2.12, p = 0 0.034), this gap was even larger when comparing AD vs HC with MCIc vs MCInc (-Z = 4.49, p < 0 .001). In this latter case, the contrast MCIc vs MCInc showed also a significant increment of the false positive rate (+Z = 4.91, p < 0 .001) when compared with the contrast AD vs HC.

4. Discussion

This is the first meta-analytic review aimed at demonstrating the reliability of ML approach trained on neuropsychological measures for performing automatic AD-related clinical screening and prognosis. Evaluating data from 59 published studies on this field of study, the majority (70 %) with low risks of bias, we provided two fundamental advancements:

1) neuropsychological measures alone can lead to a successful automatic classification of prodromal AD phenotypes regardless of the employment of different ML algorithms. The contrasts MCI vs HC,

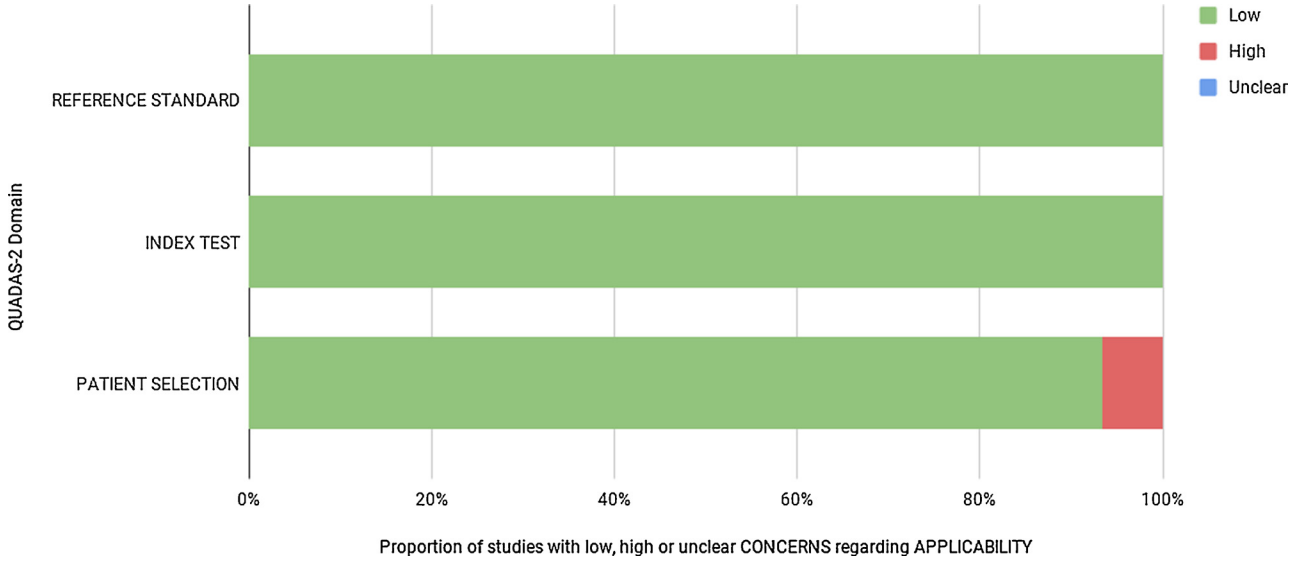

Fig. 3. Proportion of studies included with low, high or unclear concerns regarding applicability.

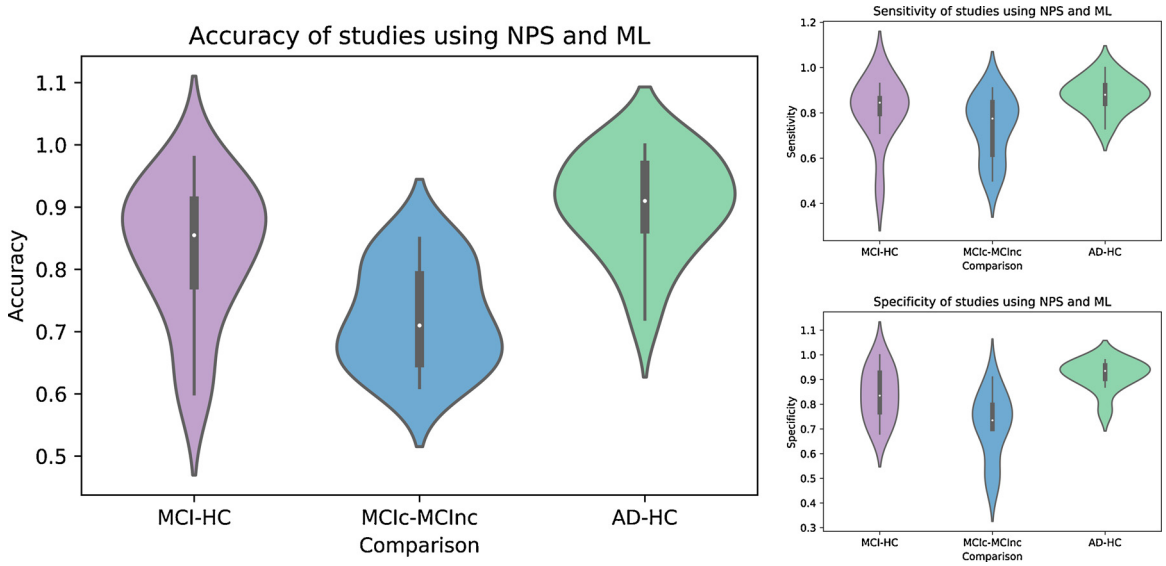

Fig. 4. Violin plots of model performance by Accuracy, Sensitivity and Specificity stratified by the different comparisons, MCI vs HC (violet), MCIc vs MCInc (blue), and AD vs HC (green).

MCIc vs MCInc and AD vs HC were automatically recognized with a pooled accuracy of 0.896, 0.759 and 0.914, respectively. However, the measure of heterogeneity demonstrates that the ability of ML with neuropsychological measures to predict if a patient with MCI will convert or not (the comparison between MCIc Vs MCInc) is affected by the lowest value of specificity, or in other words with a significant increment of false positive rate (Fig. 4).

2) ML algorithms are able to extract relevant categories of neuropsychological tests that maximize the classification accuracy. In particular: a) MMSE, for evaluating the global cognitive status; b) AVLT, for evaluating the long-term memory performance; c) Category Fluency Test, for evaluating the language ability; and d) Digit Span Forward and Backward, for evaluating verbal short-term memory, sustained attention (I.e., TMT) and working memory capacities (Fig. 6). These four neuropsychological tests showed the highest coefficient of discrimination in the ML automatic classification for all classes of interest.

4.1. Automated classification obtained with machine learning applied on neuropsychological testing: the heterogeneity question

ML algorithms can accurately detect AD and its prodromal phase but to a different extent. In particular, the results of our meta-regression approach suggest that ML algorithms have a higher level of sensitivity

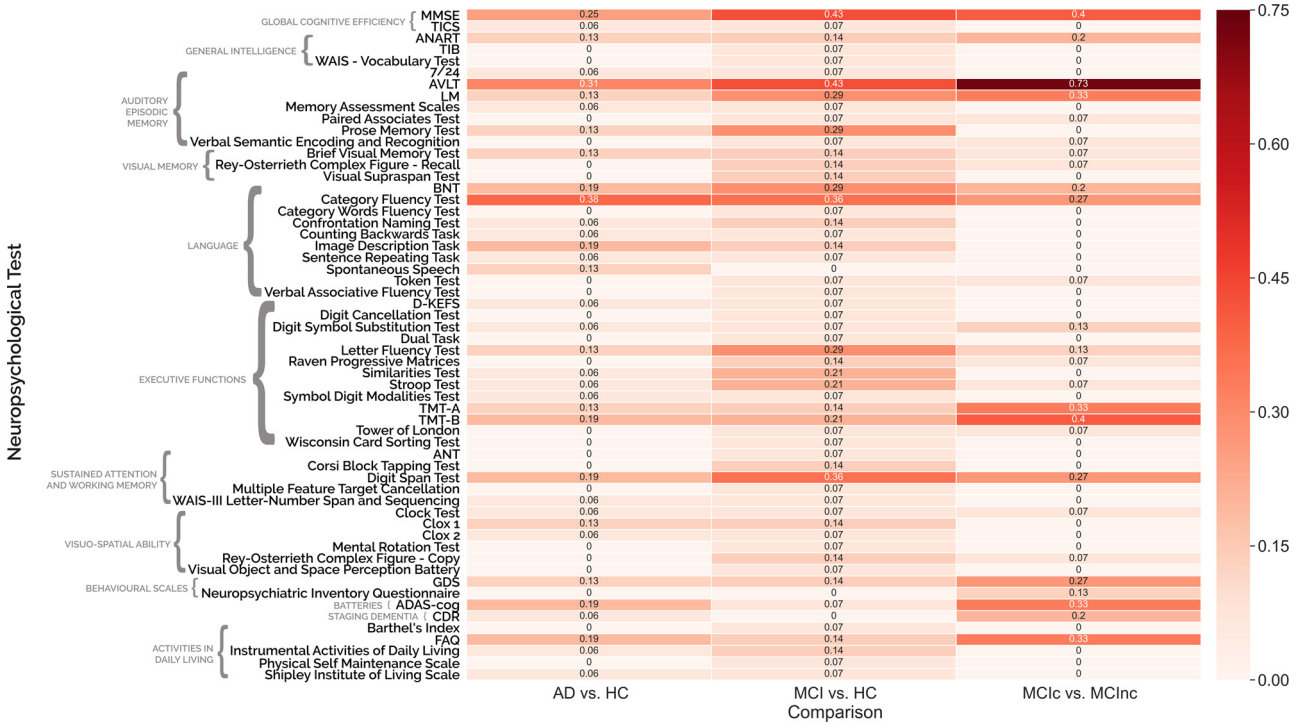

Fig. 5. Heatmap of the neuropsychological tests most frequently used as input for the classifications and with good overall accuracy and/or AUC. Tests are divided according to the neuropsychological domain they belong to and are ranked according to their frequency within each domain. The frequency of each neuropsychological test and for each binary comparison is reported in the heatmap.

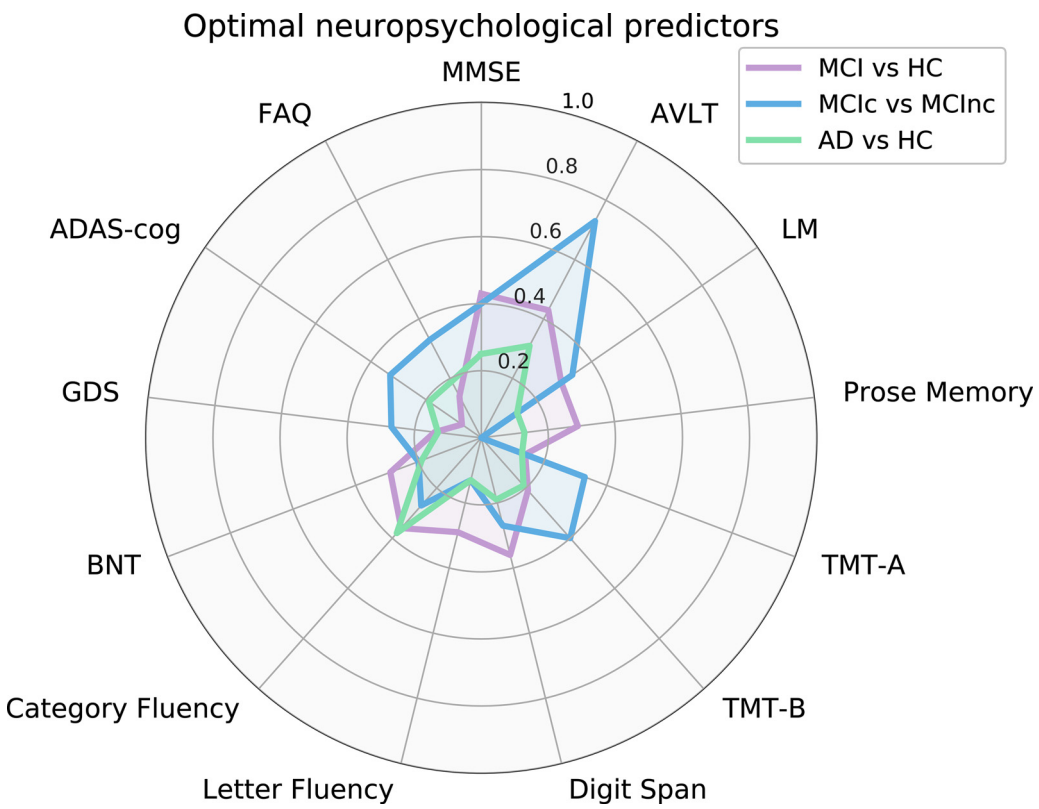

Fig. 6. Radar plot of the most frequent optimal predictors (≥ 25 % frequency), for the different comparisons, MCI vs HC (violet), MCIc vs MCInc (blue), and AD vs HC (green).

in classifying AD vs HC than in classifying either MCI vs HC, or MCIc vs MCInc. A different pattern of results emerged for the false positive rate parameter, indeed while the level of false positive rate was similar between AD vs HC and MCI vs HC, ML algorithms obtained a lower level of performance in classifying MCIc vs MCInc. This pattern of results suggests that ML algorithms could support the automatic screening phase with a sensitivity higher than the 70 % both with AD and MCI patients, but, at the state of the art they seem to have a relatively low prognostic power due to a relatively higher level of false positives in the contrast MCIc vs MCInc with respect to AD vs HC. However, every single paper included in the meta-analytic process has deeply been evaluated to identify the source of such heterogeneity. As expected, in most of the cases, the studies with higher variability in the estimates are those with relatively low sample sizes. For example, if one looks at the sensitivity measure for the contrast AD vs HC, the two studies with larger variability included 18 participants (Jarrold et al., 2014) and 41 participants (König et al., 2015), respectively. However, from Fig. 7 is clear that the overall level of sensitivity heterogeneity for the contrast AD vs HC is driven by the Hernandez-Rodriguez et al. (2017) study in which 257 AD patients were compared with 217 HC. As a matter of fact, if we exclude this latter study by our pooled analysis, the level of heterogeneity for sensitivity drops from 87.03 to 49.6, even though the overall AUC level does not change (from 0.91 to 0.95). On one hand, this should reassure the readers about the reliability of the results reported in this meta-analysis. On the other hand, this result actually contributes to delineating the specific route that this field of research has to follow. Indeed, our results do not suggest that smaller sample sizes are better, but that at the dawn of this field of research, relatively small sample sizes were enough to prove the concept (i.e., ML can be used also to classify patients on the basis of neuropsychological tests) and indeed, 6 out of the 11 selected papers that compared AD vs HC with a sample size smaller than 85 (with at most 41 patients) were all published between 2012 and 2016. On the contrary, studies published in the last two years adopted considerably higher sample sizes (more than 180 participants with at least 55 patients). This source of heterogeneity is intrinsic in the rapid growth of this field of research.

4.2. *The best neuropsychological measures to automatically distinguish AD-related conversion*

In most of the papers considered in our review, ML led to the identification of subsets of *optimal* classification features, resulting in a subset of *optimal* neuropsychological predictors that can be useful to characterize the different groups of patients (Figs. 5–6). Specifically, for the classification of MCI vs HC, measures of decline in verbal episodic memory appear to be the most frequently extracted, together with measures of global cognitive status, naming, letter fluency. Concerning the classification of MCIc vs MCInc, the most frequently selected measures were verbal episodic memory, global cognitive efficiency, attentional shifting/flexibility and verbal fluency. These results are in line with the current literature, that highlights the importance of including measures not only from episodic memory, but also from more fluid functions as predictors of conversion to Alzheimer's type of dementia (Gibbons et al., 2012; Litvan et al., 2012). Two neuropsychological measures appeared to be the most commonly extracted for the classification of AD patients: verbal episodic memory and the verbal fluency tasks, i.e. measures that, from the neuropsychological point of view, tackled the most impaired functions in AD (i.e., Weintraub et al., 2012).

Of note, this meta-analytic review highlights the influence that linguistic features may have on the automated classification of Alzheimer's type dementia. Several previous works used ML algorithms to automatically extract linguistic features from the connected speech task in order to enhance classification performance (Orimaye et al., 2015; Asgari et al., 2017; König et al., 2015; Jarrold et al., 2014; Fraser et al., 2016;Hernández-Domínguez et al., 2018). Picture description tasks seem to be able to discriminate between normal and pathological

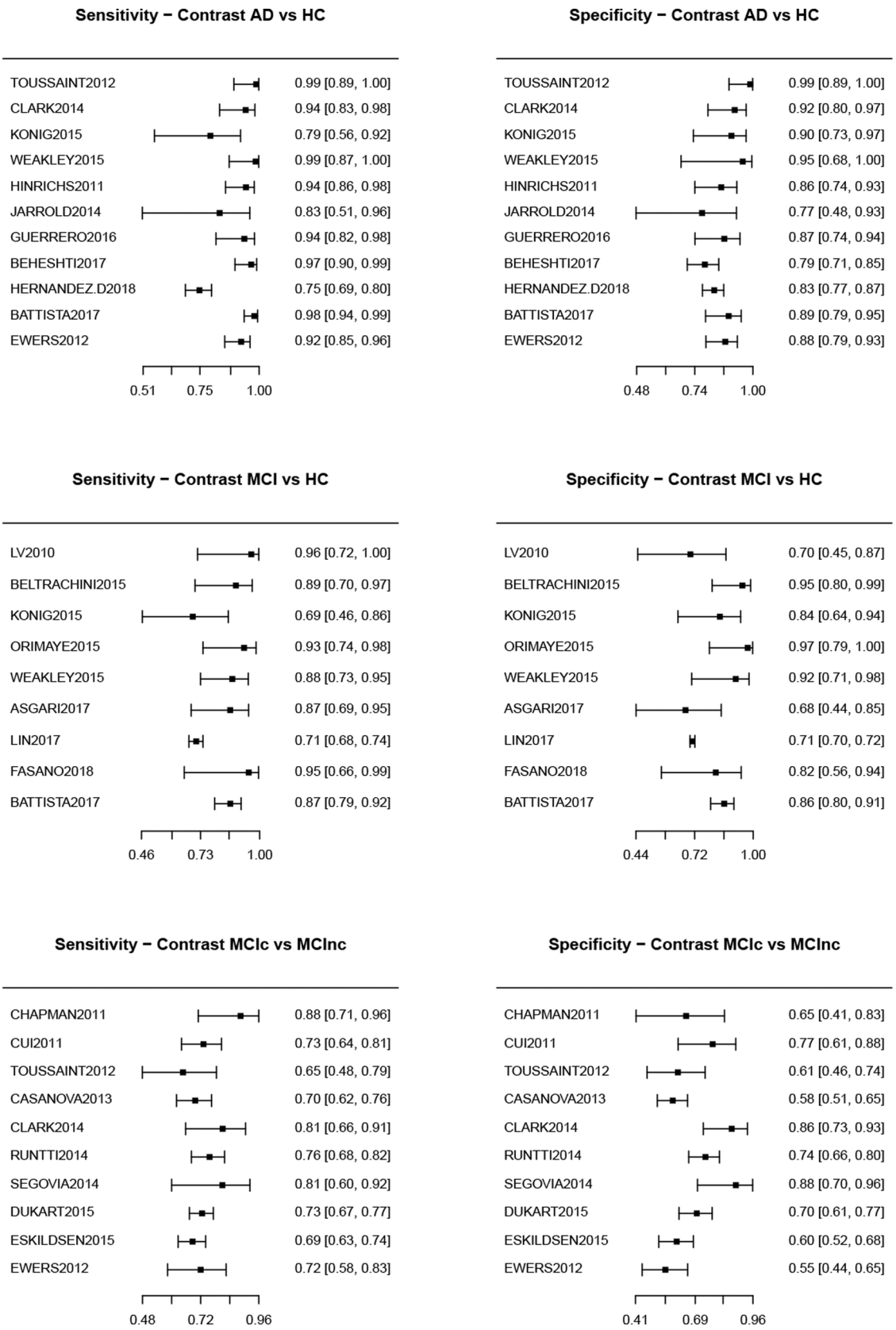

Fig. 7. Sensitivity and Specificity Forrest Plots for the three contrasts of interest (MCI vs HC, MCIc vs MCInc, and AD vs HC).

cognitive status. In addition, these measures are often analysed for neurodegeneration involving impairment in language ability as the first symptom (i.e., Primary Progressive Aphasia, PPA). Although PPA patients are out of the scope of this review, a considerable number of studies is focusing on the linguistic analysis of picture description tasks for the classification of different variants of PPA (Wilson et al., 2009;

Table 4
Measures of heterogeneity and AUC values for each single contrast.

Comparison	I^2 sensitivity$_m$	I^2 specificity$_m$	AUC$_m$
AD vs HC	87.03*	40.04	0.914
MCI vs HC	74.87*	78.11*	0.896
MCIc vs MCInc	9.84	71.07*	0.759

* χ^2 p-value < .05.

Fraser et al., 2015 ; Garrard et al., 2014). In brief, the results have shown that the mean length of sentences, the number of produced words and verbs, the frequency and the familiarity of words are consistent markers of PPA compared to HC. Recently, the need for a short evaluation of progressive aphasia, lead to the development of standardised language battery (Battista et al., 2017). ML algorithms could become a useful approach to identify the combinations of language measures that most reliably and accurately classify patients based on neuropsychological/linguistic features.

Unfortunately, the evaluation of the contribution of imaging and

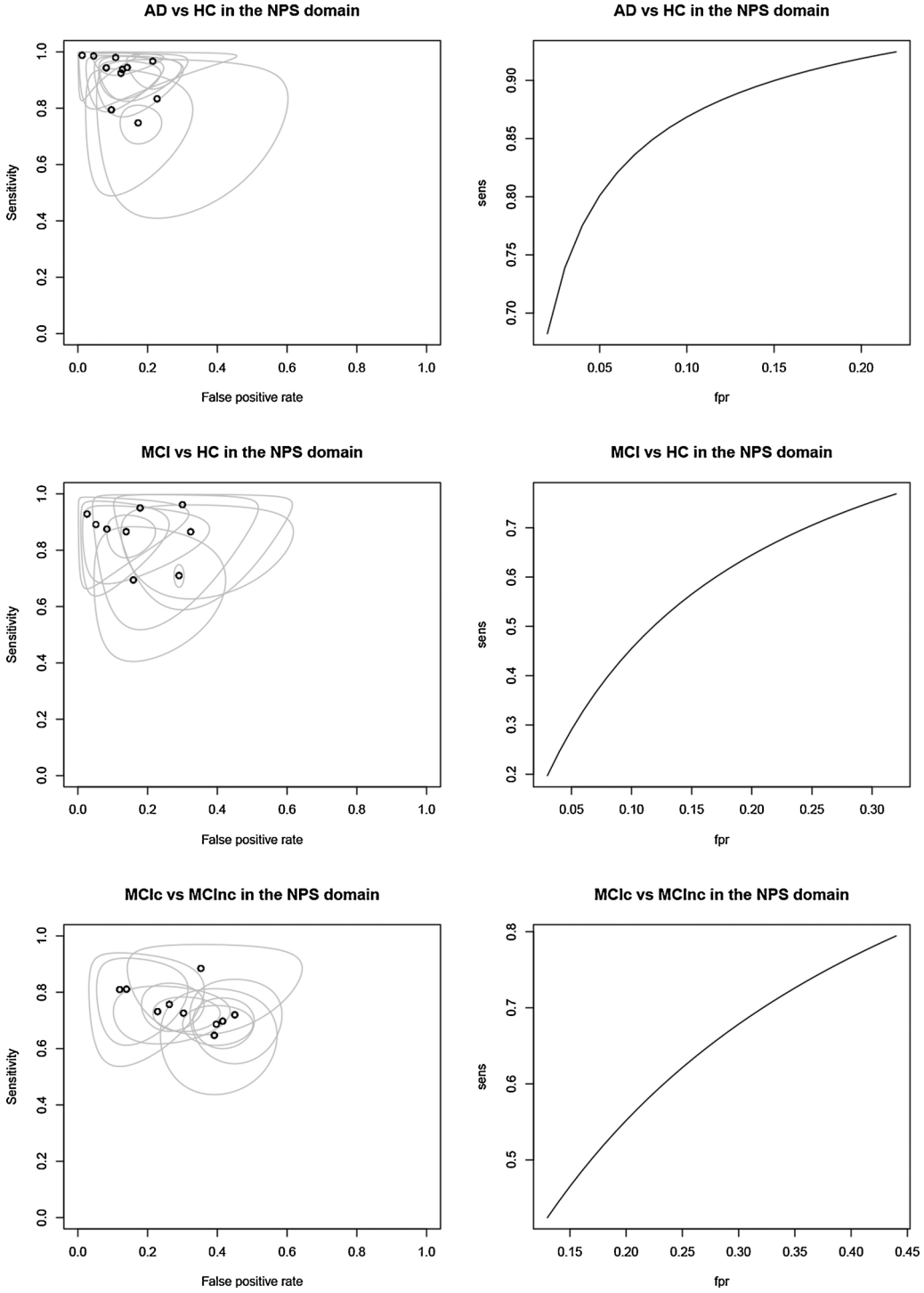

Fig. 8. Study-specific confidence regions in the ROC space and ROC curves in the contrasts of interest. The dots represent the study-specific estimates and the ellipses are obtained by plotting confidence intervals for the sensitivities and false positive rates.

Table 5
Meta-regression results. The table shows the estimates (together with their variability and 95 % confidence intervals) and the test statistics for the Reitsma's bivariate model.

	Estimate	Std. Error	95 %ci.lb	95 %ci.ub	z	Pr (> |z|)
tsens. (Intercept)	2.374	0.23	1.91	2.83	10.11	< .001
tsens. Comparison MCI vs HC	−0.72	0.33	−1.38	0.56	−2.12	0.034*
tsens. Comparison MCIc vs MCInc	−1.33	0.29	−1.91	−0.75	−4.49	< 0.001*
tfpr. (Intercept)	−1.87	0.17	−2.22	1.53	−10.65	< .001
tfpr. Comparison MCI vs HC	0.4	0.26	−0.12	0.92	1.51	0.13
tfpr. Comparison MCIc vs MCInc	0.13	0.23	0.67	1.58	4.91	< .001*

behavioural measures with respect to biological markers was not conducted due to the paucity of studies including these data. Although the use of multimodality markers is gaining more consensus in the literature, showing that combining measures from different modalities leads to higher discriminant accuracy compared to single modality results (e.g., Westman et al., 2012), we could not perform any quantitative analysis since the number of studies providing results on multimodal approaches was poor. This is not surprising, due to the limits of biological/genetic diagnostic tests, e.g., their less readily available to clinicians that can have instead easier access to neuropsychological and neuroimaging data. In particular, among the selected papers we found only 3 studies in the category AD-HC, 5 studies in the category MCI-C and 9 studies in the category MCIc-MCInc which included details about sensitivity and specificity. In the light of the relatively sparseness of the data, we decided not to consider these studies for a formal quantitative meta-analysis, but to adopt a purely descriptive approach. From Tables 1, 2 and 3 can be easily appreciated that the three studies that combined neuropsychological measures and imaging indexes obtained a good level of sensitivity (range .84–.98) and specificity (.90–.97), while there was a higher level of variability in the results of the studies that compared MCI vs HC [Sensitivity range = .55–.97; Specificity range = .74–.94] and MCIc vs MCInc [Sensitivity range = .74–.93; Specificity range = .43–.91]. These results suggest that the combination of neuropsychological and imaging feature is a promising approach that should be better explored by future empirical studies while taking into account the methodological issues discussed in this meta-analysis to obtain more reliable and less heterogeneous performance measures that could be formally meta-analyse.

4.3. Limitations

Although in our review several neuropsychological measures were identified as the most frequently optimized measures, there are some caveats that need highlighting.

Overall, an important limitation is related to the reliability of the neuropsychological measures for the diagnosis of AD, especially in the early stages of the disease. Subjects diagnosed according to the criteria for MCI might not embody the earliest stage of AD. Our data suggest that neuropsychological tools, more sensitive than the traditional MMSE, should be taken into account to identify the earlier stages of the disease. Indeed, SCI also represents a prodromal period that could be more representative of earlier phases of the disease. Therefore, classification performance identified here should be extended further back in a phase preceding MCI in the natural history of the disease continuum.

Another relevant issue concerns the high heterogeneity among the papers selected, e.g. the neuropsychological tests used to measure the same cognitive function. For example, although the measures of the episodic memory were one of the most frequently optimized ones found in the profile of measures for AD, several tests have been reported by various authors for this measure (AVLT, HVLT, RAVLT, LM). One reason for this variety could be that there is still no consensus as to which test leads to the best discrimination of deficits in a cognitive domain. This, along with the different ML algorithms and validation procedures associated with the accuracy of different tests, may limit the generalization of our findings.

1) Based on the quality criteria used above (QUADAS tool), some studies showed a relatively low risk of bias, while others had some features that were found to be problematic.
2) The neuropsychological measures used for clinical diagnosis of patients (i.e., the measures used to *label* patients as belonging to AD or MCI classes) can generate bias (possible over-performance) in studies using ML classifiers if the same measures are also used in the training of such classifiers (Cui et al., 2011; Kriegeskorte et al., 2009). Therefore, also the subset of best measures of progression to AD found in our review needs further investigations.
3) The scarcity of prospective longitudinal studies available for this review also represents an important limitation in the identification of neuropsychological measures for the progression of the disease. The average follow-up of the studies included in this review was around three years, and it is plausible that there was insufficient time for some patients diagnosed with MCI to progress to the clinical stage of dementia. On the other hand, it should be highlighted that there is a lack of consensus regarding how early symptoms are detected. Therefore, a longer follow up would be desirable. Eckerström et al. (2015) conducted a study enrolling MCI subjects with a ten year follow up. They found that, when considering a longer period, attention deficit as measured by TMT-B was the best measure for predicting conversion to dementia, while hippocampal volume and TMT-B attention were the best multimodal measure for conversion.
4) None of the studies used post-mortem analyses to confirm the clinical diagnosis and to assign the gold-standard diagnostic label to the patients. This may lead to methodological problems related to the possible discrepancy between clinical and definite AD diagnosis. As highlighted above in this meta-analysis, only Fraser et al. (2015) used post mortem to limit this issue in a subset of the whole patients' sample.

Although the QUADAS tool allowed us recognizing and highlighting these limitations, it must be underlined that some of the items included in this tool are not appropriate to judge the quality of studies adopting ML approaches. This intrinsic issue is due to the fact that the QUADAS tool was originally conceived to assess the quality of diagnostic-accuracy tests included in systematic reviews (Whiting et al., 2011). In particular, patient-selection items seem to be unsuitable for this kind of studies. Patient selection in ML studies is usually made by selecting well-defined diagnostic groups (e.g. AD vs HC) that can be used to train a supervised classifier. This patient-selection process can be considered as a nested case-control design. The case-control design is penalized by the QUADAS tool, but it is almost necessary when analyzing data using ML techniques.

In order to overcome some of the issues described above, we identified 10 rules that could be taken into consideration by researchers in the ML domains when designing new studies using ML and neuropsychological measures for the automatic diagnosis and prognosis of AD phenotypes. These rules are reported in the Box 1 and could be useful as recommendations to design future studies.

Box 1
Recommendations to design machine learning studies for the neuropsychological assessment of Alzheimer's type dementia

1 Provide the risks of bias of your study, as this can help you to improve the study quality.
2 Focus your research on clinical questions of current interest. To date, the most critical ML classification task is the discrimination of MCIc vs MCInc.
3 Use post-mortem analysis as gold-standard diagnosis of classes (ML supervised labels) whenever possible. If not, use only currently accepted diagnostic criteria to assign a clinical diagnosis to classes. In this last case, prefer clinical follow-up periods that are as long as possible in order to effectively assess the conversion to Alzheimer's type dementia or to ensure as-stable-as-possible clinical diagnoses over time.
4 Provide appropriate and complete information about the patient-selection process, e.g. specifying if the sample enrollment was consecutive or random, if the study was observational or cross sectional.
5 Use large-enough samples of patients. The sample size should be of -at least- 20 subjects per class (i.e., 40 subjects for binary comparisons). Moreover, balance the number of subjects among the classes.
6 Ensure a complete independence among those neuropsychological measures used for the ML classification and those used to assign the gold-standard diagnosis to the patients.
7 Provide appropriate and complete information about the study design, including the approach used to validate and test the ML classifier.
8 Ensure a complete independence among the sub-samples used to train, validate and test the ML classifier, respectively. For this purpose, adopt a *nested cross-validation* approach, whenever possible. Also data pre-processing has to be performed independently for these sub-samples.
9 Always include accuracy, sensitivity, specificity and AUC (as performance-evaluation metrics for the ML classifier). Report also other evaluation metrics when specific features (e.g. geometric mean or dominance for imbalanced-domain problems) have been assessed in you study.
10 Fully report all cognitive measures with predictive roles, not only the more significant ones, as these could be useful, in the future, to address between-studies consistency through meta-analytic methods.

4.4. Future works

Cognitive deficits are the last events detected in the progression of the AD disease. Unfortunately, this inevitably delays clinical diagnosis. Only one study in our review reported data on the application of neuropsychological testing and ML on subjects at a pre-clinical stage of AD (Schmid et al., 2013). This study showed that pre-clinical neuropsychological measures of AD should consider subtle qualitative decays in verbal and visual memory, visuospatial processing, error control, and subjective neuropsychological complaints. This scarcity of studies is unexpected, since recent NIA-AA guidelines (Sperling et al., 2011; Jack et al., 2018) suggested that sensitive measures in several cognitive, functional and behavioural domains should be developed to detect early biological AD dysfunction even at a pre-clinical stage.

We would expect a focus of the more recent research on SCI, often spontaneously self-reported by the elderly, on using ML to assess the possibility that such information may represent a predictor for AD conversion even in the absence of objective deficit from the neuropsychological assessment. Since the actual predictive value for SCI remains unclear (Hohman et al., 2011; Mol et al., 2006) it would be interesting in the future to understand if using ML algorithms and longitudinal studies it might be possible to estimate this predictive value by extracting, at this very early stage, new unexpected sensitive and specific neuropsychological measures, or by increasing the specificity and sensitivity of already known neuropsychological tests by selecting a set of best predictors.

Moreover, we want to stress that future studies should also aim to evaluate whether other neuropsychological scores or sub-scores (i.e., speed, precision etc.) could be used for the classification. It must be considered that the performance might be confirmed or improved if other neuropsychological measures -not considered in the studies reported in this review- were included in the classification process. For instance, none of the studies analysed in this review evaluated the use of the Free and Cued Selective Reminding Test, developed by Dubois and colleagues (Dubois et al., 2010, 2014) for the early and differential diagnosis of AD.

Finally, very few studies compared the quality of classification and prediction based on neuropsychological tests as performed by a clinician or by an automatic classifier. Klöppel et al. (2008), showed that ML algorithms classify typical AD using MRI scans with an accuracy comparable to well-trained neuroradiologists. To the best of our knowledge, no study has been published comparing the classification of AD and MCI groups by ML with neuropsychologist/neurologist's classification accuracy, thereby further works are necessary to disentangle this issue.

5. Conclusion

This meta-analytic review demonstrates that ML applied on neuropsychological measures can be useful to automatically classify AD patients, even at an early stage of the disease, and to identify a combination of optimal neuropsychological predictors. In particular, it emerged that ML and neuropsychological assessment could be used for screening purpose. This brings several advantages, such as the development of more objective and efficient neuropsychological batteries for improving the neuropsychological contribution to the early diagnosis of Alzheimer's type of dementia. Future studies in this field should empirically test the combination of methodological features necessary to improve patients' classification also at the preclinical stages

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Appendix A

Glossary of the abbreviations of Neuropsychological Tests used by the included papers

Abbreviation	Full term
ADAS	Alzheimer Disease Assessment Scale
ADL	Activities of daily living
ANT	Attention Network Test

AVLT	Auditory verbal Learning Test
BCR	Buschke's Cued Recall
BDRS	Blessed Dementia Rating Scale
BLAD	Battery of Lisbon for the Assessment of Dementia
BNT	Boston Naming Test
BVMT-R	Brief Visuospatial Memory Test-Revised
BVRT	Benton Visual Retention Test
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CDR	Clinical Dementia Rating Scale
CDR-SOB	Clinical Dementia Rating Sum of Boxes
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CLOX	Clock drawing
CNT	Confrontation Naming Test
COWA	Controlled Oral Word Association Test
CTA	Computerized Test of Attention
CVLT	California Verbal Learning Test
DCT	Digit Cancellation Test
DLST	Digit Letter Substitution Test
DRS	Dementia Rating Scale
DS	Digit Span
DSCT	Digit Symbol-Coding Task
DSST	Digit Symbol Substitution Test
FAQ	Functional Assessment Questionnaire
FCI	Financial Capacity Instrument
GDS	Geriatric Depression Scale
GPT	Grooved Pegboard Test
HVLT	Hopkins Verbal Learning Test
IADL	Instrumental Activities of daily living
LM	Logical Memory
MMSE	Mini Language State Examination
MWT	Mehrfach-Wortwahl Test
NART	North American National Adult Reading Test
Neuropsychological Bat	Neuropsychological Battery
NPI	Neuropsychiatric Inventory Questionnaire score
PFT	Phonemic Fluency Test
RAVLT	Rey Auditory verbal Learning Test
ROCF	Rey-Osterreieth Complex Figure
SDMT	Symbol Digit Memory Test
SFT	Semantic Fluency Test
SILS	Shipley Institute of Living Scale
TICS	Telephone Interview for Cognitive Status
TMT	Trial Making Test
VAT	Visual Association Test
VFT	Verbal Fluency Tests
VPAL	Verbal Paired Associates Learning
WAIS	Wechsler Adult Intelligence Scale
WMS-III	Wechsler Memory Scale
WSUI	Washington State University Instrumental

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.04.026.

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