Predictive models for mild cognitive impairment to Alzheimer's disease conversion

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Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease as well as the most common form of dementia. It usually affects the older population, but early onset AD is still possible (Ritchie et al., 2015). Recent studies propose that AD is a middle-life disease (Ritchie et al., 2015). Regardless the onset of the disease, it is important to note that it takes years for the symptoms to manifest. Specifically, it is believed that AD begins 20 years before the onset of symptoms. AD broadly includes three stages: preclinical AD, mild cognitive impairment (MCI) and dementia (Grassi et al., 2019). Researchers find it challenging to classify the MCI stage. This is partly because although MCI patients appear to have neurological deficits, their symptoms are not advanced enough to meet the AD criteria. MCI is also known as the stage between normal cognitive ageing and dementia and is often thought of as the prodromal stage of AD (Grassi et al., 2019). MCI patients can either remain stable at this stage of the disease or convert to AD. Approximately 20–40% of MCI patients convert to AD (MCI converters-MCIc; Grassi et al., 2019). Like any other disease, early diagnosis is important. Therefore, identifying subtle brain changes that occur during the MCI-to-AD conversion as early as possible could be the key to the development of more effective treatment plans.

The majority of current approaches aim to help patients manage behavioral symptoms and impede others such as memory loss and cognitive decline. Because of the complexity of the disease, one specific drug or treatment intervention appears unlikely to successfully treat the disease. Predicting the exact point when patients convert from the prodromal stage of the disease (MCI) to AD would be extremely beneficial in identifying novel mechanisms of disease prevention.

In the era of big data, analysis of large volumes of data requires progressive approaches. Advances in neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans enable scientists to search for AD patterns in the entire brain. Because of AD complexity, image analysis in combination with pre-existing *in vivo* biomarkers (amyloid-β (Aβ), tau, etc.) is a more reliable diagnostic tool (Westman et al., 2011). Machine learning methodologies are often utilized for the examination of said high dimensional data (Cuingnet et al., 2011). Models based on machine learning provide a promising opportunity for developing tools that can detect disease progression. A variety of methodologies have been suggested for patient classification (AD and/or MCI; Cuingnet et al., 2011). The majority of methods work by reducing the dimensionality of the feature space. This approach relies on the extraction of different features types, clustering and/or selection methods (Cuingnet et al., 2011).

Machine learning techniques have been used for classification of MCI patients who convert to AD (MCIc) and MCI patients who remain stable at this stage (MCInc; **Additional Table 1**).

Our previous work was set to create predictive models in order to identify any emerging patterns of conversion from MCI to AD (Skolariki et al., 2020). For the establishment of such models, we relied on machine learning for analysis of multivariate data. The supervised machine learning algorithms that were utilized for classification tasks include: i) support vector machine (SVM) for which a linear C-SVM algorithm was applied, ii) decision trees, for which a Java open source implementation of the C4.5 algorithm (the J48 algorithm) was used and iii) the Naive Bayes (NB) classifier, which even though is considered a fairly simple approach oftentimes outperforms more complex classification methods. The aforementioned filters are available in the WEKA 3.9.2 software.

Features based on cortical thickness (CTH) and hippocampal volumes (HCV) extracted from brain scans were used to train the learning algorithms. CTH was utilized as a classification feature seeing as literature shows that cortical thickness characterizes atrophy manifestation, making it a potential AD diagnostic biomarker (Thompson et al., 2001). HCV was chosen as a feature because the hippocampus is a region of the brain found to be associated with early stages of AD making it an early AD marker (Schuff et al., 2008).

All data used to develop the models was obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www. adni-info.org). Participants consisted of AD patients, subjects in several stages of MCI, and healthy controls (55–90 years old). For this study, subjects were divided into healthy controls, MCI converters (MCIc), MCI non-converters (MCInc) and AD.

Using the WEKA filter for random data division, a "train" file was produced that included data from the three diagnostic groups (AD, healthy control and MCIc) and a "test" file that included data from MCIc (**Figure 1**). Utilization of the "train" file resulted in the six predictive models for MCIc identification (**Additional Table 2**). The test set was used for the training of the algorithms and model development.

As a result, six models were created CTH-SVM, CTH-J48, CTH-NB, HCV-SVM, HCV-J48 and HCV-NB (**Additional Table 2**). The best model, which is SVM trained by CTH-based features (CTH-SVM), accurately identified 99% of MCI patients that converted to AD (**Additional Table 2**). Additionally, the CTH-based models consistently outperformed the HCV-based models (**Additional Table 2**). Based on the study, evidence suggests that multivariate methods (SVM, J48 and NB) are highly promising for group differentiation (MCI *vs*. AD) that take into consideration the synchronized involvement of the input features.

The aforementioned predictive models could prove effective in the identification of MCI-to-AD inhibitory mechanisms, leading, thus, to a prolonged MCI stage allowing patients to live an increasingly moderate life at the prodromal stage of the disease.

Our current work includes validating the previous predictive models using a larger data set to establish their accuracy and performance as precisely as possible. This research will also allow us to determine whether our predictions are more dependent on the feature, the sample size or the models themselves. Next steps involve the inclusion of additional classification features in order to create an all-inclusive predictive model. These features should contain but not be limited to: apolipoprotein-E, cerebrospinal fluid protein levels (tau, Aβ), neurofilament light chain (NFL), plasma protein levels (tau, Aβ, NFL), electroencephalograph markers and volumetric differences in mapped hippocampal regions, MRI (used to analyze certain regions of interest), structural MRI (used to classify brain regions affected by AD at a voxel scale) and PET scans (Gupta et al., 2019). These features are established AD markers. Therefore, inclusion of a wider combination of AD indicators would increase model accuracy. Future research will utilize more sophisticated machine learning approaches, such as ensemble selection that

Figure 1 | Flow chart of subject inclusion.
AD: Alzheimer's disease; CTH: cortical thickness; HC: healthy control; HCV: hippocampal volume; MCI: mild cognitive impairment; MCIc: MCI converters; MCInc: MCI non-converters. Reprinted from Skolariki et al. (2020).

would allow for the combination of several different classifiers in order to accomplish higher decision boundaries (Aguilar et al, 2013).

Healthy control data were included in this study and the sample size for all three groups (healthy control, MCI and AD) was proportionate in order to represent the broader population. Future work should focus on exploring a similar research aim with the inclusion of additional features that would be obtained from the same subjects. The utilization of ADNI data encompasses a key restriction regarding sample subjects, seeing as it is still difficult to acquire data for all of the required features from the same participants. Therefore, the respective discriminative power of the different approaches could not be evaluated.

Based on the complexity and heterogeneity of AD, we conclude that an advanced machine learning predictive model that includes a panel of features would offer far greater insights into precise diagnostic and prognostic approaches in an unbiased manner. Thus, the overall aim of scientists is to develop therapeutic methods that incorporate all types of biological mechanisms (genetic, molecular, cellular, etc.) in order for AD to be prevented.

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Additional files:
Additional Table 1: Machine learning techniques used for MCIc and MCInc classification.
Additional Table 2: Predictions acquired using six different models.

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Additional Table 1 Machine learning techniques used for MCIc and MCInc classification

Feature	Methods	Number of subjects	Accuracy (SEN, SPE) %	Classifier	Database	Reference
Voxel-segmented probability maps	Direct	509	-(0,100)	Linear SVM	ADNI	Cuingnet et al. (2011)
	Direct VOI	509	- (0,100)	Linear SVM	ADNI	Cuingnet et al. (2011)
	STAND-score	509	- (0,100)	Linear SVM	ADNI	Cuingnet et al. (2011)
	Atlas	509	- (51,79)	Linear SVM	ADNI	Cuingnet et al. (2011)
	COMPARE	509	- (54,78)	Linear SVM	ADNI	Cuingnet et al. (2011)
Cortical Thickness	CTH-SVM*	504	75 (75,12)	Linear SVM	ADNI	
	CTH-J48*	504	70 (70,15)	J48	ADNI	
	CTH-NB*	504	71 (71,14)	Naive Bayes	ADNI	
	Direct	509	- (32,91)	Linear SVM	ADNI	Cuingnet et al. (2011)
	NTI	382	73 (75,68)	Trees	ADNI	Querbes et al. (2009)
	Atlas	509	- (27,85)	Linear SVM	ADNI	Cuingnet et al. (2011)
	ROI	509	- (24,82)	Logistic Regression	ADNI	Cuingnet et al. (2011)
	Feature Vector	203	71(63,76)	PCA	ADNI	Cho et al. (2012
Hippocampus	HCV-SVM*	299	56 (56,56)	Linear SVM	ADNI	
	HCV-J48*	299	56 (56,52)	J48	ADNI	
	HCV-NB*	299	55 (56,45)	Naive Bayes	ADNI	
	Volume- SPM5 Volume-FreeSurfer	509	- (62,69) - (70,61)	Parzen	ADNI	Cuingnet et al. (2011)
	Volume- SPM5	605	64 (60,65)	Incremental learning	ADNI	Chupin et al. (2009)
	Shape	509	0(0,100)	Linear SVM	ADNI	Cuingnet et al. (2011)

AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; CTH: cortical thickness; HCV: hippocampal volume; J48: the C4.5 algorithm; MCI: mild cognitive impairment; MCIc: MCI converters; MCInc: MCI non-converters; NB: Naive Bayes; NTI: normalized thickness index; PCA: principal component analysis; ROI: Region of interest; SEN: sensitivity; SPE: specificity; SPM5: Statistical Parametric Mapping; STAND: STructural Abnormality iNDex; SVM: support vector machine; VOI: volume of interest. The methods with the asterisk are the models from Skolariki et al. (2020).

Additional Table 2 Predictions acquired using six different models

	CTH-SVM		CTH-J48		CTH-NB		HCV-SVM		HCV-J48		HCV-NB	
	AD	**MCI**	**AD**	**MCI**	**AD**	**MCI**	**AD**	**MCI**	**AD**	**MCI**	**AD**	**MCI**
MCIc	99%	1%	99%	1%	99%	1%	0	100%	7%	93%	5%	95%
ACC	83%		84%		83%		6%		14%		9%	

The data are presented as the percentage of MCIc that were correctly classified as AD vs. misclassifications of MCIc as MCI (Skolariki et al., 2020). AD: Alzheimer's disease; ACC: accuracy; MCI: mild cognitive impairment; CTH: cortical thickness; J48: the C4.5 algorithm; MCIc: MCI converters; NB: Naive Bayes; SVM: support vector machine.