Received: 6 December 2021 | Accepted: 4 April 2022

DOI: 10.1002/gps.5718

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Establishing an individualized model of conversion from normal cognition to Alzheimer's disease after 4 years, based on cognitive, brain morphology and neuropsychiatric characteristics

Lucas Ronat[1,2] | Van-Tien Hoang[1] | Alexandru Hanganu[1,3]

[1]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada

[2]Faculté de Médecine, Département de Médecine, Université de Montréal, Montréal, Québec, Canada

[3]Faculté des Arts et des Sciences, Département de Psychologie, Université de Montréal, Montréal, Québec, Canada

Correspondence

Lucas Ronat and Alexandru Hanganu, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, M6828, 4545 ch. Queen Mary, Montréal H3W 1W6, Québec, Canada.
Email: lucas.ronat@umontreal.ca and alexandru.hanganu@umontreal.ca

Funding information

IUGM Foundation; Fonds de Recherche du Québec - Santé; Parkinson Canada; Parkinson Quebec; Faculty of Medicine University of Montreal; Lemaire Foundation

Abstract

Objectives: The impact of neuropsychiatric symptoms (NPS) on cognitive performance has been reported, and this impact was better defined in the aging population. Yet the potential of using the impact of NPS on brain and cognitive performance in a longitudinal setting, as prediction of conversion – have remained questionable. This study proposes to establish a predictive model of conversion to Alzheimer's disease (AD) and mild cognitive impairment (MCI) based on current cognitive performance, NPS and their associations with brain morphology.

Methods: 156 participants with MCI from the *Alzheimer's Disease Neuroimaging Initiative* database cognitively stable after a 4-year follow-up were compared to 119 MCI participants who converted to AD. Each participant underwent a neuropsychological assessment evaluating verbal memory, language, executive and visuospatial functions, a neuropsychiatric inventory evaluation and a 3 Tesla MRI. The statistical analyses consisted of 1) baseline comparison between the groups; 2) analysis of covariance model (controlling demographic parameters including functional abilities) to specify the variables that distinguish the two subgroups and; 3) used the significant ANCOVA variables to construct a binary logistic regression model that generates a probability equation to convert to a lower cognitive performance state.

Results: Results showed that MCI who converted to AD in comparison to stable MCI, exhibited a higher NPS prevalence, a lower cognitive performance and a higher number of involved brain structures. Functional abilities, memory performance and the sizes of inferior temporal, hippocampal and amygdala sizes were significant predictors of MCI to AD conversion. We also report two models of conversion that can be implemented on an individual basis for calculating the percentage risk of conversion after 4 years.

Conclusion: These analytical methods might be a good way to anticipate cognitive and brain declines.

ADNI group is Alzheimer's disease Neuroimaging Initiative.

KEYWORDS
Alzheimer's disease, cognitive decline, cognitive performance, MRI, neuropsychiatry

Key points

- Low functional abilities are a significant factor of MCI to AD conversion
- Smaller volumes of inferior temporal region, hippocampus and amygdala are characteristic of MCI to AD conversion
- Neuropsychiatric symptoms seem to play a diminished role in predicting the conversion from MCI to AD

1 | INTRODUCTION

1.1 | Clinical states of age-related cognitive decline

Current clinical evaluations of cognitive decline include only two stages: (a) the mild cognitive impairment (MCI) and (b) dementia (or major cognitive impairment). These stages are based on cognitive markers[1–3] that are evaluated with comprehensive neuropsychological assessments. One of the leading clinical presentations of dementia is the Alzheimer's disease (AD) type.[4] An MCI level that would lead to AD has been characterized by either subjective concern about a change in cognition, or a lower performance in one or more cognitive domains in comparison to those expected for the patient's age and educational background, without significant impairment in social or occupational functioning.[1]

On the other hand, in the demented state, cognitive deficits are sufficiently extensive that the individual is no longer able to carry out his or her daily life tasks alone or without supervision. These cognitive stages are frequently accompanied by psychological suffering for participants, relatives and caregivers[5,6] as well as psychological and behavioral disturbances called neuropsychiatric symptoms (NPS).[7]

1.2 | Neuropsychiatric symptoms in cognitive decline

Most of NPS are clearly observed in dementia,[7] but they also occur in the MCI stage[8] and can be present in cognitively healthy individuals.[9] NPS presence was shown to increase the risk of AD in MCI.[10] Indeed, these NPS are found in the cognitively healthy (CH) population,[9,11,12] and their prevalence increases with the advancement of clinical stages: it is higher in the MCI population and even higher in the AD population.[11] Also, they may increase the likelihood of MCI progressing into AD[10] and thus increase the likelihood of developing dementia.[8] These include depression,[13,14] apathy[15] and anxiety,[16–18] but the latter is more controversial.[19,20] However, the impact of depression on cognitive decline is greater in MCI than in AD.[21]

In addition, several studies have looked at longitudinal follow-ups of participants and participants with NPS. For example, the study by Moon et al. (2017) confirms a greater progression from MCI to AD in participants with depressive symptoms according to the amyloid status of MCI participants: the study is based on the analysis of longitudinal ADNI data and shows, in MCI participants with amyloid-positive amyloid and depression, a higher rate of AD conversion than participants without depression.[22] In addition, cognitive decline is accelerated over the 2-year follow-up period. Also based on the ADNI database, Zahodne et al. (2013) studied the atrophy pathways of MCI subjects with and without depression and apathy on a longitudinal level. Their results show that depression is associated with greater baseline entorhinal atrophy and accelerated anterior cingulate atrophy.[23] To our knowledge, fewer studies have looked at the factors of conversion from normal cognition to MCI and the course of cognitive decline in healthy individuals. However, these studies were able to highlight that healthy individuals with mild behavioral impairment exhibited greater attentional and working memory decline after 1 year of follow-up.[24] Also, the presence of NPS, including depression, apathy, and anxiety, is also associated with faster global and domain-specific decline.[25,26] In addition, MRI data were also exploited as predictors of conversion from MCI to AD. Thus, it has been shown that MCI that convert to AD have reduced volumes in the medial temporal lobe (hippocampus, amygdala, and entorhinal cortex), the insular, posterior cingulate, precuneus and orbitofrontal cortex.[27–29] However, these data do not appear to have been addressed in the conversion from CH to MCI. This shows the importance of screening for NPS and to more investigate MRI in CH subjects.

For this study, we hypothesized that (1) participants who convert to a lower cognitive performance state would exhibit increased variation in NPS; (2) these variations would be associated with brain morphology and cognitive performance; and (3) these correlations can be used to predict the conversion.

The purpose of this work is to propose probabilistic models for predicting conversion to Alzheimer's disease in participants with MCI, and conversion to MCI in CH participants. From a clinical perspective, the construction of models with good psychometric characteristics would allow to estimate, for an individual evaluated in a clinical context, an objective probability of conversion.

2 | MATERIALS AND METHODS

2.1 | Participants

275 participants with MCI and 185 cognitively healthy participants (CH) from the ADNI database were extracted. Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI, launched in 2003 and led by Principal Investigator Michael W. Weiner, MD, has for main objective to understand the progression of MCI and early AD by combining imaging, biological and neuropsychological data[30,31] (http://www.adni-info.org/). Entry criteria for participants with amnestic MCI include a Mini-Mental State Examination score of 24–30 and a Memory Box score of at least 0.5, whereas other details on the ADNI cohort can be found online. All participants with AD met National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD with a Mini-Mental State Examination score between 20 and 26, a global Clinical Dementia Rating of 0.5 or 1, a sum-of-boxes Clinical Dementia Rating of 1.0–9.0, and, therefore, are only mildly impaired. Exclusion criteria at baseline and follow-up included any serious neurological disease or neurodegenerative disease other than possible AD, any history of brain lesions or head trauma, or psychoactive medication use (including antidepressants, neuroleptics, chronic anxiolytics, or sedative hypnotics).

Sample size is dependent on participants completing a neuropsychiatric examination, a comprehensive neuropsychological assessment, a 3 Tesla MRI and having a change in diagnosis available (MCI to AD or CH to MCI). Participants whose change in diagnosis was remittent (e.g., MCI to CH, AD to CH) were not included nor were CH participants converting to AD because of their too low prevalence.

The clinical status was available until 4-year follow-up for all participants. Based on the clinical stage at follow-up, four groups were created in order to distinguish participants who converted to a worse cognitive performance compared to those that maintained their previous cognitive level. Our groups consisted of: 156 MCI remained MCI at follow-up (MCI-non-converted), 119 MCI participants that converted to AD (MCI-converted), 170 CH both at baseline and at follow-up (CH-non-converted) and 15 CH that converted to MCI (CH-converted) (Table 1). As mentioned above, others neurological diagnosis or conversions were not considered.

TABLE 1 Demographic, neuropsychiatric and neuropsychological characteristics for MCI and CH groups (non-converted and converted)

	MCI				CH			
	Non-converted	Converted	T/Chi^2	P	Non-converted	Converted	T/Chi^2	p
N	156	119			170	15		
Demographic (mean/sd)								
Age	75.07/7.75	74.54/7.52	0.572	0.568	75.41/4.92	74.00/5.28	1.06	0.291
Education	15.55/3.07	15.93/2.81	−1.060	0.290	16.15/2.81	16.07/2.84	0.114	0.909
Sex (% women)	39.1	35.3	0.418	0.518	48.8	40	0.430	0.512
MMSE	27.51/1.73	26.87/1.67	**3.125**	**0.002**	29.12/1.00	28.67/1.50	1.598	0.112
FAQ	2.72/3.83	5.75/5.22	**−5.329**	**0.000**	0.06/0.33	0.73/1.71	−1.512	0.153
NPS (%)								
Delusion	0	0.8	1.316	0.251	0	0	-	-
Hallucination	0	0.8	1.316	0.251	0.6	0	0.089	0.766
Agitation	12.8	26.9	**8.716**	**0.003**	3.5	0	0.547	0.459
Depression	14.7	21.8	2.327	0.127	4.7	0	0.738	0.390
Anxiety	16.0	21.0	1.127	0.288	3.5	6.7	0.373	0.542
Euphoria	3.2	3.4	0.005	0.942	0	0	-	-
Apathy	10.9	15.1	1.087	0.297	1.8	0	0.269	0.604
Disinhibition	5.1	9.2	1.778	0.182	0.6	0	0.089	0.766
Irritability	27.6	30.3	0.238	0.625	7.1	6.7	0.003	0.955
AMB	4.5	4.2	0.013	0.909	0.6	0	0.089	0.766
Nighttime behavior	12.2	13.4	0.097	0.755	9.4	20	1.677	0.195
Appetite changes	7.7	15.1	**3.838**	**0.050**	0.6	0	0.089	0.766

(Continues)

TABLE 1 (Continued)

	MCI				CH			
	Non-converted	Converted	T/Chi^2	P	Non-converted	Converted	T/Chi^2	p
Cognitive assess. (Mean/sd)								
Clock drawing	4.43/0.76	4.13/1.05	**2.781**	**0.008**	4.71/0.59	4.60/0.74	0.650	0.516
Clock copy	4.76/0.49	4.61/0.69	1.924	0.056	4.89/0.35	4.67/0.82	1.043	0.314
RAVLT 1	4.62/1.64	3.76/1.26	**4.902**	**0.000**	5.18/1.61	4.73/1.03	1.047	0.296
RAVLT 2	6.10/2.06	5.00/1.48	**5.173**	**0.000**	7.72/1.97	6.60/1.18	**2.162**	**0.032**
RAVLT 3	7.24/2.32	5.90/1.53	**5.781**	**0.000**	9.44/2.32	8.53/2.59	1.429	0.155
RAVLT 4	7.77/2.54	6.27/1.54	**6.052**	**0.000**	10.54/2.38	9.33/2.61	1.860	0.065
RAVLT 5	8.47/2.67	6.64/2.00	**6.514**	**0.000**	11.18/2.24	10.53/2.62	1.061	0.290
RAVLT 6	4.79/3.58	2.55/2.08	**6.511**	**0.000**	8.39/3.44	7.07/2.63	1.456	0.147
RAVLT B	3.96/1.59	3.40/1.32	**3.103**	**0.002**	5.05/1.68	4.87/2.80	0.386	0.700
DS forward	8.34/2.06	8.32/1.99	0.083	0.934	8.88/2.02	8.13/1.96	1.378	0.170
DS backward	6.41/2.14	6.10/1.82	1.296	0.196	7.25/2.17	6.27/1.22	1.721	0.087
Animals	16.52/4.68	15.70/4.86	1.419	0.157	20.16/5.56	18.73/5.84	0.948	0.344
Vegetables	11.64/3.38	10.04/3.31	**3.922**	**0.000**	14.91/3.70	12.80/3.86	**2.114**	**0.036**
TMTA	40.72/17.02	48.76/26.19	**−2.912**	**0.004**	35.91/12.97	37.20/12.23	−0.370	0.712
TMTB	110.31/59.47	143.44/78.24	**−3.848**	**0.000**	86.12/43.96	91.20/26.92	−0.440	0.661
Symbol digit	39.75/11.00	35.15/10.72	**3.473**	**0.001**	46.20/10.34	43.47/6.96	1.003	0.317
BNT	26.17/3.55	25.50/3.90	1.487	0.138	27.88/2.31	27.80/2.18	0.133	0.894
RAVLT Del.	3.90/3.70	1.55/2.30	**6.470**	**0.000**	7.73/3.62	6.07/3.67	1.703	0.090
RAVLT tot	10.63/3.32	8.58/3.83	**4.736**	**0.000**	12.98/2.44	12.40/2.10	0.886	0.377

Note: **Bold values** = significant results.

Abbreviations: BNT, Boston Naming Test; DS, Digit Span; FAQ, Functional Abilities Questionnaire; MMSE, MiniMental State Examination; NPS, Neuropsychiatric Symptoms; RAVLT, Rey Auditory Verbal Learning Test (free recall 1–6, list B and delayed); sd, standard deviation; TMT, Trail Making Test.

2.2 | Data acquisition and processing

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012).

The neuropsychiatric changes were evaluated using the Neuropsychiatric Inventory.[7] The inventory consists of the evaluation of the presence, severity and frequency of 12 neuropsychiatric symptoms (NPS): delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behaviors and appetite changes. We included the evaluations performed by the participants' relatives and only the prevalence of each NPS is considered.

Neuropsychological assessment was based on the tests assessing: (1) anterograde verbal memory (Rey Auditory Verbal Learning Test - RAVLT), (2) focused attention (Trail Making Test A - TMTA), (2) processing speed (Wechsler Adult Intelligence Scale Code subtest), (3) mental flexibility (Trail Making Test B - TMTB), (4) visuoconstructive planning (clock test), (5) working memory (digit span), (6) semantic lexical evocation (animal and vegetable fluency) and (7) oral naming (Boston Naming Test - BNT). Moreover, the Mini-Mental State Examination score was used as a demographic factor of global cognitive efficiency.

MRI structural images were processed with FreeSurfer 7.1.1 software, on Linux Centos 7 on ComputeCanada environment, cluster Cedar and managed with our in-house pipeline (github.com/alexhanganu/nimb) that allowed automated exclusion of post-processed data with errors as well as extraction of statistical data, diminishing potential human error. Cortical thickness parameter was extracted based on the Destrieux et al. Atlas (2010) while subcortical volumes were extracted for all regions as well as sub-regional based on the corresponding atlases[32]; for the thalamus,[33] amygdala,[34] and hippocampus.[35] The volumes of subcortical structures were corrected with the estimated Total Intracranial Volume (eTIV).[36]

Also, in order to consider and control the risk of neuropsychiatric symptoms due to difficulties in performing daily activities, the Functional Abilities Questionnaire (FAQ) score was compared between groups and included as a covariate in case of significant difference between groups.

2.3 | Statistical analysis

The statistical analyses are based on the methodology of Orso et al. (2020).[37] For this study, the data were analyzed using SPSS version 26.0 software. Descriptive analyses verified the similarity of the groups (MCI-converted vs. MCI-non-converted; CH-converted vs. CH-non-converted) in terms of age, years of education, MMSE score, FAQ and sex distribution (respectively mean comparisons by Student test and contingency Chi^2 analysis). Statistical analysis consisted of three steps. (I) First, the groups were compared based on (i) means of cognitive performances (Two sample *t*-tests), (ii) prevalence of NPS (Chi^2 tests) and (iii) means of neuroimaging structure sizes (Student *t*-tests of cortical thickness and subcortical volumes). (II) Features that were shown to be significant in the first three comparisons, were included in the Analysis of Covariance Model with age, sex, years of education, FAQ and MMSE scores as covariates. (III) Finally, features that were deemed significant in the ANCOVA model were imputed in a two binary logistic regression model to generate probability equations for AD and MCI conversion based on neuropsychiatric, cognitive and neuroimaging data.

3 | RESULTS

3.1 | Demographical, neuropsychiatric and neuropsychological differences

At baseline, in comparison to MCI-non-converted, the MCI-converted group had a lower MMSE and higher FAQ scores, worse performance on some cognitive tests (clock test, RAVLT immediate recall A and B, RAVLT delayed recall, semantic lexical evocation for "vegetables", TMT A and B, WAIS code) and a significantly higher prevalence of agitation and appetite changes (Table 1 near here).

On the other hand, the CH-converted and CH-non-converted groups showed similar results regarding age, years of education, sex distribution, MMSE and FAQ scores as well as distributions of neuropsychiatric symptoms. Several significant differences were depicted in the cognitive performance at baseline, with the CH-converted group having a worse performance in comparison to CH-non-converted on RAVLT second recall, digit span backward and semantic lexical evocation of "vegetables".

3.2 | Brain morphology differences

Considering the large number of structures compared between the converted versus non-converted groups, the results for MCI and CH are summarized in Tables S1 and S2 respectively. Briefly, the MCI-converted group showed multiple significant difference in comparison to the MCI-non-converted one. Significant changes were depicted in all brain lobes both on the cortical level in gyri and sulci as well as regarding the volumes of subcortical structures, notably the volumes of hippocampus, amygdala and thalamus subregions (Table S1).

By contrast, the CH-converted group exhibited smaller frontal inferior orbital gyrus and suborbital sulcus, cingulate ventral posterior gyrus, temporal pole and temporal middle gyrus thicknesses and some hippocampal, amygdala and thalamic subregions volumes than CH-non-converted group (Table S2).

3.3 | ANCOVA model

After control for age, sex, years of education, FAQ and MMSE scores as covariates, ANCOVA showed a significant lower performance in MCI-converted for every score of the RAVLT than in MCI-non-converted. Conversion interacted with agitation on the recall of the B-list of the RAVLT (non-converted with agitation perform better than those without while the opposite trend is present in converted) (Table S3). By contrast, the CH-converted group exhibited significative lower performance on the second recall of the RAVLT and in semantic lexical evocation of "vegetables" than CH-non-converted (Table S4).

Regarding brain structures, most of the structures (all lobes [except insula], hippocampi and amygdala) were smaller in MCI-converted than in MCI-non-converted. Presence of agitation was featured by greater cortical thicknesses (frontal, parietal, occipital, temporal) and subcortical volumes (hippocampus and amygdala) whereas appetite changes were featured by precentral and lingual thinning and larger hippocampus and amygdala volumes (Table S3). An interaction effect between conversion and agitation showed a greater thickness in the MCI-converted with agitation than in those without agitation, while the opposite difference is found in the non-converted, at the inferior occipital, intraparietal, left parieto-occipital, right middle temporal and bilateral precentral levels. The opposite effect was found in the left subcallosal gyrus. Another interaction effect between conversion and appetite changes showed thinning in MCI-converts with appetite changes compared to those without, whereas the opposite pattern was found in non-converted, at the bilateral superior parietal, precuneus, subparietal, left intraparietal, right lingual and parieto-occipital structures (Table S3). In CH-converted, the previous structures (Table S2) remained significantly smaller than in CH-non-converted, except for the central lateral and paratenial thalamic nuclei (Table S4).

3.4 | Prediction of AD from MCI and MCI from CH based on logistic regression

Binary logistic regression models (Tables 2 and 3 near here) based on the significant results of the ANCOVA models provided probabilistic prediction equations for conversion of MCI participants to AD and CH participants to MCI.

The probability equation for an MCI participant to convert to AD is sustained by age, the FAQ score, the RAVLT first immediate recall score, the RAVLT fifth immediate recall score, the right inferior temporal gyrus thickness, the right molecular layer of the right

TABLE 2 Binary Logistic Regression for the conversion from MCI to AD after 4 years

Variables	B	Sig.	Exp(B)	95% Confidence interval	
Age	−0.071	0.001	0.932	0.892	0.973
FAQ	0.084	0.012	1088	1019	1162
Free recall 1 of RAVLT	−0.300	0.012	0.741	0.587	0.936
Free recall 5 of RAVLT	−0.199	0.007	0.820	0.709	0.948
Temporal inferior gyrus right	−2800	0.001	0.061	0.011	0.340
Hippocampus tail right	−23,741,592	0.009	0.000	0.000	0.000
Amygdala accessory basal nucleus right	−19,389,102	0.006	0.000	0.000	0.000
Constante	20,115	0.000	5,44E+8		

Abbreviations: ***β***, Coefficient from each significative variable; FAQ, Functional Abilities Questionnaire; Sig., Significancy.

TABLE 3 Psychometric characteristics for regression model of the conversion from MCI to AD

		Prediction		
		MCI	**To AD**	**Correct prediction**
Observed	MCI	130	26	83.3(Spe.)
	To AD	32	87	73.1(Sens.)
Accuracy				78.9
Positive predictive value				76.99
Negative predictive value				80.25
Yule Q coefficient				0.86

Abbreviations: Spe., Specificity; Sens., Sensitivity.

hippocampus body volume, and the left amygdala accessory basal nucleus volume. The model had a sensitivity of 73.1%, specificity of 83.3% (Table 3) and Yule Q coefficient indicating a very strong link between the diagnosis and the clinical characteristics.

Then, the probability equation for a CH participant to convert to MCI is sustained by age, the semantic lexical evocation for "vegetables" performance, the right subiculum body volume, and the left medial pulvinar thalamic nucleus volume. The models were characterized by a sensitivity and specificity of 6.7% and 99.4% a (Table 5) and Yule Q coefficient was 0.85 indicating a very strong link between the diagnosis and the clinical characteristics (Tables 4 and 5 near here).

4 | DISCUSSION

Our results show that (1) participants with MCI and CH who maintain their cognitive performance at the 4 years follow-up, tend to exhibited (i) a lower NPS prevalence (for MCI), (ii) a higher cognitive performance and (iii) a lower number of involved brain structures; (2) none of the NPS have potential of predicting MCI participants who might convert in AD over 4 years when considering functional abilities score; (3) from all cognitive performance tests, only poorer mnesic performances seems to predict MCI who convert to AD over 4 years, and only language performance might predict CH who convert to MCI over 4 years; (4) brain regions that seem to have the highest relevance in predicting conversion over 4 years, seem to be the hippocampus, amygdala, and temporal inferior in the case of MCI participants, and hippocampus and thalamus in the case of CH participants.

It was expected that agitation and appetite changes would be involved in predicting MCI to AD conversion. Indeed, agitation along with appetite changes first appeared to have a significant higher prevalence in the MCI-converted group. Previous studies also outlined this potential trend by reporting agitation a precursor to future AD development[8,10,38,39] and a sign in MCI participants that would correspond to an early AD diagnosis.[40] Yet no specific link was reported regarding appetite changes. However, these implications were not significant when functional abilities were considered. This suggests that in this sample of MCI participants, the SNPs are at least partly explained by the reduction in functional abilities. Furthermore, the involvement of other NPS has been reported: depression, anxiety, apathy, irritability, psychotic symptoms. Though in our model these NPS did not survive the significant threshold for the prevalence, nor did they appear in the prediction model, they did show a non-significant up to double increase in prevalence. Whereas several studies have been able to describe that the presence of NPS in CH increased the risk of conversion to MCI 9.13–16, our results did not show any difference between the CH-converted group in comparison to CH-non-converted.

Cognitively, our results show lower verbal mnesic performance and semantic lexical evocation in MCI-converted versus MCI-non-converted. Interestingly, we do not find executive weaknesses in MCI-converted although these deficits are frequent in MCI in relation to NPS (Rosenberg et al. 2011) as well as in AD.[41] In addition, mnesic difficulties occur much earlier than the diagnosis of AD in comparison to executive difficulties.[41] The CH-converted versus CH-non-converted showed worse verbal mnesic, working

TABLE 4 Variables significantly involved in predicting conversion from CH to MCI after 4 years

Variables	B	Sig.	Exp(B)	95% Confidence interval	
Age	−0.153	0.027	0.858	0.750	0.982
Semantic lexical evocation « vegetables »	−0.194	0.036	0.824	0.687	0.988
Hippocampus, subiculum body, right	−50,786,249	0.011	0.000	0.000	0.000
Thalamus, pulvinar medial, left	−18,793,242	0.001	0.000	0.000	0.000
Constante	30,892	0.000	2.608 E+13		

Abbreviations: ***β***, Coefficient from each significative variable; Sig., Significancy.

TABLE 5 Psychometric characteristics for regression model of the conversion from CH to MCI

		Prediction		
		CH	To MCI	Correct prediction
Observed	CH	169	1	99.4(Spe.)
	To MCI	14	1	6.7(Sens.)
Accuracy				91.9
Positive predictive value				50%
Negative predictive value				92.35
Yule Q coefficient				0.85

Abbreviations: Spe., Specificity; Sens., Sensitivity.

memory and semantic lexical evocation performance. These performances remains within the populational norms but they can probably be cognitive fragilities and signs of a beginning of cognitive decline, potentially in line with subjective cognitive complaints, not objectified by the neuropsychological tests.[42–44] As such, only verbal memory performance remained significantly involved in predicting conversion to AD and to MCI in our logistic regression models.

Regarding this significant role of memory performance, this is in line with the results of Baerresen et al. (2015).[45] The use of this type of model, with predictive purposes, is more frequent in recent years and could be applied in individuals with non-amnestic MCI,[21] MCI due to Parkinson's disease[46] or even multiple sclerosis.[47] Unfortunately, these studies do not systematically mention the reliability criteria of their models.

Concerning brain difference between MCI-converted and MCI-non-converted, brain characteristics were broader and involve cortical structures of all lobes and subcortical regions of the hippocampus and amygdala. This suggests that diffuse cerebral frailties may already be present at the MCI stage, prior to the diagnosis of AD. However, only right temporal inferior, right hippocampus and right amygdala remained significantly predictive of conversion in the logistic regression model. Other studies have also shown cortical thinning of several lobes in MCI participants and even more so in AD, with a more important involvement of the left hemisphere.[48,49] The opposite asymmetry was found in our data.

When analyzing specific brain changes from the perspective of involved NPS (agitation and appetite changes) and their potential to influence the brain in MCI-converted participants, previous studies showed that agitation was characterized by insular, superior frontal, middle, orbital, parieto-occipital, hippocampal, and amygdala atrophies in MCI.[50–52] Furthermore, these atrophies were broadly similar between MCI and AD participants. Our data comparing the effect of agitation in converters and non-converters instead showed occipital, cingulate, precentral, intraparietal, and temporal features. Note that the impact of agitation in non-converters was characterized mainly by reductions in structure size, and by increases in size in converters. This might suggest that the underlying physiological processes are not the same (e.g., atrophy vs. compensation or inflammation). According to Bateman et al. (2020), pro-inflammatory versus anti-inflammatory processes have respectively a positive and negative correlation with agitation in AD. Since the increase in brain structures here is only observed in our converted group, we should look at the age of the agitation.[53] It could be assumed that in the converted group, agitation is older and could have allowed the development of inflammatory processes.

Interestingly, appetite changes seem more prevalent in MCI converted in AD than in non-converted but them were also not retained by regression models as significant factor who predict the conversion. Frequently, these behavioral changes are mainly associated with posterior structures. Particularly, them have been described in participants with posterior cortical atrophy but associated with posterior structures also in typical AD,[54] indicating that posterior brain damage is not specific to these disorders. Overall, these are understudied disorders and often dependent on other NPS such as anxiety or depression.[55,56] This makes these disorders more complicated to study, especially on a neuroanatomical level.

In the CH to MCI conversion, the poorer performance in memory suggested that the brain structures involved in memory would be reduced in people who convert to MCI. However, the cortical and subcortical structures involved appear to be broader and involved in emotional (cingular, amygdala, frontal orbital), memory (temporal, hippocampus) and multimodal functions (thalamus). According to regression model, smaller volumes in the right hippocampus and the left thalamus predicted better the conversion to MCI. Previous studies that have looked at brain differences have focused on comparisons between CH individuals and individuals with MCI. These

studies showed reductions in hippocampal, entorhinal and parahippocampal cortex volumes[57,58] and were supported by other studies showing cortical thinning in healthy participants with subjective cognitive impairment compared to participants without, in hippocampal, parahippocampal, amygdala, entorhinal, fusiform, posterior cingulate, and inferior parietal regions.[59–61] These reductions may have been associated with poorer performance in verbal memory.[59]

To our knowledge, most studies have focused on regions of interest known to be involved in AD, whereas our study looked at the entire cortex and subcortical structures. Furthermore, our results may suggest brain changes that precede medial temporal damage, which is usually considered as an anatomical precursor of cognitive decline due to AD.

Because the risk of developing MCI was dependent on certain demographic data, we chose to include them in the regression model, whereas these variables were controlled in the ANCOVA model to isolate differences related to cognitive performance and brain structure size. Other analyses, on other databases, should also consider the systematic presence of SMC in CH individuals, as well as the presence of symptoms related to awareness of changes and difficulties (anosognosia and/or anosodiaphoria). Alternatively, if our results do not show neuropsychiatric differences in CH-converted, this may suggest the existence of "subjective behavioral complaints" that would precede the objectification of a mild behavioral disorder, as described by Ismail et al. (2016, 2017), in analogy to the stages of cognitive decline model.

This study should be viewed in light of several limitations. First, in the AD conversion model, the duration of cognitive impairment was not available in the extracted data. Due to this limitation, it cannot be excluded that some MCI participants who converted to AD, had the longest duration of impairment. Another limitation of this study concerns the small proportion of CH individuals who convert to MCI,[63,64] correspondingly, this small sample cannot be representative of this population limiting our understanding regarding potential factors involved in conversion to MCI. Finally, our model did not consider the socioeconomic aspect that may influence NPS, such as marital status, residential patterns, accompanied housemate, unemployment, or family income, as suggested by previous studies.[62,65,66]

The generalizability of our results refers to the possibility of its implementation in a clinical setting and on an individual basis, in order to calculate the predictive value of the risk of cognitive decline after 4 years, especially in individuals with such complaints. After the corresponding parameters are being quantified, the probability of conversion can be calculated using the equation: $P(event) = 1/(1+e^{-[\beta 1*X1+\ \beta 2*X2+\ \beta 3*X3+\ldots+\ \beta n*Xn+constant]})$. The regression tables (Tables 2 and 4) provide the β coefficients of each significant variable in the model and the X values are the individual-specific values quantified using corresponding tests and MRI data. For example, the equation for conversion from MCI to AD after 4 years is $P(AD) = 1/(1+e^{-[-0.071*X1+0.084*X2-0.300*X3-0.199*X4-2\ \ 800*X5-23,741,592*X6-19,389,102*X7+20,115]})$ where e = 271,828 (the base of natural logarithm), X1 = Age, X2 = the FAQ score, X3 = the RAVLT first immediate recall score, X4 = the RAVLT fifth immediate recall score, X5 = the right inferior temporal gyrus thickness, X6 = the right hippocampal tail volume, X7 = the right amygdala accessory basal nucleus volume and 20,115 is the model's constant. A 70-year-old individual with MCI, a FAQ score of 10, RAVLT scores of 3 and 5, and structure values of 2.5, 0.0002, and 0.0001 would have a 60% probability of converting to AD after 4 years (Odds Ratio = 1.50). The data obtained from the calculation of each equation allows us to estimate, from the data of a given individual, the percentage risk of conversion of this individual.

5 | CONCLUSION

Research on the preclinical stages of AD is frequent and focuses on different diagnostic criteria and risk factors. As far as we know, our study is one of the first to apply these types of models with MCI and CH individuals using both neuropsychiatric, cognitive and neuromorphological data. We proposed to distinguish MCI and CH participants who convert to AD and MCI, respectively, after 4 years of follow-up from the ADNI database. We were able to establish two predictive models to distinguish participants evolving to a more severe clinical stage. The conversion from MCI to AD was characterized by the presence of agitation, lower memory performance and smaller volumes of inferior temporal, hippocampal and amygdala brain structures, whereas the conversion from CH to MCI was characterized by lower performance on semantic evocation and smaller volumes of hippocampal and thalamic brain structures. From a clinical perspective, the construction of models with good psychometric characteristics would allow to estimate, for an individual evaluated in a clinical context, an objective probability of conversion and to anticipate cognitive and brain declines thanks to cognitive, family or social care and support.

ACKNOWLEDGEMENTS

This work was supported by the doctoral research scholarship *Centre de Recherche de l'Institut Universitaire de Gériatrie Montréal (CRIUGM)*-Volet B in collaboration with NiEmoLab; a Faculty of Medicine of the Université de Montréal merit scholarship in collaboration with NiEmoLab; funding from the Parkinson Canada-Parkinson Quebec (2018-00,355); IUGM Foundation; *Fonds de Recherche du Québec Santé*; Lemaire Foundation. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE

Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research and Development, LLC.; Johnson and Johnson Pharmaceutical Research and Development LLC.; Lumosity; Lundbeck; Merck and Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

All data are available on the ADNI websites upon demand (http://adni.loni.usc.edu/data-samples/access-data/).

REFERENCES

1. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279. https://doi.org/10.1016/j.jalz.2011.03.008
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed.
3. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatr*. 2009;17(5):368-375. https://doi.org/10.1097/JGP.0b013e31819431d5
4. Heidebrink JL. Is dementia with Lewy bodies the second most common cause of dementia? *J Geriatr Psychiatr Neurol*. 2002;15(4):182-187. https://doi.org/10.1177/089198870201500402
5. Bednarek A, Mojs E, Krawczyk-Wasielewska A, et al. *Correlation between depression and burden observed in informal caregivers of people suffering from dementia with time spent on caregiving and dementia severity*. 2016;20:59-63.
6. Schulz R, McGinnis KA, Zhang S, et al. Dementia patient suffering and caregiver depression. *Alzheimer Dis Assoc Disord*. 2008;22(2):170-176. https://doi.org/10.1097/WAD.0b013e31816653cc
7. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308. https://doi.org/10.1212/WNL.44.12.2308
8. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and alzheimer disease. *Am J Geriatr Psychiatr*. 2013;21(7):685-695. https://doi.org/10.1016/j.jagp.2013.01.006
9. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *Int Psychogeriatr*. 2018;30(2):221-232. https://doi.org/10.1017/S1041610217001909
10. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cognit Disord*. 2007;24(4):253-259. https://doi.org/10.1159/000107100
11. Geda YE, Smith GE, Knopman DS, et al. De novo genesis of neuropsychiatric symptoms in Mild Cognitive Impairment (MCI). *Int Psychogeriatr*. 2004;16(1):51-60. https://doi.org/10.1017/S1041610204000067
12. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatr*. 2008;65(10):1193-1198. https://doi.org/10.1001/archpsyc.65.10.1193
13. Lee GJ, Lu PH, Hua X, et al. Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatr*. 2012;71(9):814-821. https://doi.org/10.1016/j.biopsych.2011.12.024
14. Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A. Late-life depression as a risk factor for mild cognitive impairment or Alzheimer's disease in 30 US Alzheimer's disease centers. *J Alzheimers Dis*. 2012;31(2):265-275. https://doi.org/10.3233/JAD-2012-111922
15. vanDalen JW, vanWanrooij LL, MollvanCharante EP, Brayne C, vanGool WA, Richard E. Association of apathy with risk of incident dementia: a systematic review and meta-analysis. *JAMA Psychiatr*. 2018;75(10):1012-1021. https://doi.org/10.1001/jamapsychiatry.2018.1877
16. Gallagher D, Coen R, Kilroy D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int J Geriatr Psychiatr*. 2011;26(2):166-172. https://doi.org/10.1002/gps.2509
17. Ma L. Depression, anxiety, and apathy in mild cognitive impairment: current perspectives. *Front Aging Neurosci*. 2020;12:9. https://doi.org/10.3389/fnagi.2020.00009
18. Rozzini L, Chilovi BV, Peli M, et al. Anxiety symptoms in mild cognitive impairment. *Int J Geriatr Psychiatr*. 2009;24(3):300-305. https://doi.org/10.1002/gps.2106
19. Devier DJ, Pelton GH, Tabert MH, et al. The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *Int J Geriatr Psychiatr*. 2009;24(12):1335-1342. https://doi.org/10.1002/gps.2263
20. Robert PH, Berr C, Volteau M, et al. Importance of lack of interest in patients with mild cognitive impairment. *Am J Geriatr Psychiatr*. 2008;16(9):770-776. https://doi.org/10.1097/JGP.0b013e31817e73db
21. Lee JS, Cho SK, Kim HJ, et al. Prediction models of cognitive trajectories in patients with nonamnestic mild cognitive impairment. *Sci Rep*. 2018;8(1):10468. https://doi.org/10.1038/s41598-018-28881-1
22. Moon B, Kim S, Park YH, et al. Depressive symptoms are associated with progression to dementia in patients with amyloid-positive mild cognitive impairment. *J Alzheimers Dis*. 2017;58(4):1255-1264. https://doi.org/10.3233/JAD-170225
23. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G. Are apathy and depression independently associated with longitudinal trajectories of cortical atrophy in mild cognitive impairment? *Am J Geriatr Psychiatr*. 2013;21(11):1098-1106. https://doi.org/10.1016/j.jagp.2013.01.043
24. Creese B, Brooker H, Ismail Z, et al. Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. *Am J Geriatr Psychiatr*. 2019;27(8):823-834. https://doi.org/10.1016/j.jagp.2019.01.215
25. Burhanullah MH, Tschanz JT, Peters ME, et al. Neuropsychiatric symptoms as risk factors for cognitive decline in clinically normal older adults: the cache county study. *Am J Geriatr Psychiatr*. 2020;28(1):64-71. https://doi.org/10.1016/j.jagp.2019.03.023

26. Krell-Roesch J, Syrjanen JA, Machulda MM, et al. Neuropsychiatric symptoms and the outcome of cognitive trajectories in older adults free of dementia: the Mayo Clinic Study of Aging. *Int J Geriatr Psychiatr*. 2021;36(9):1362-1369. https://doi.org/10.1002/gps.5528
27. Davatzikos C, Bhatt P, Shaw LM, Batmanghelich KN, Trojanowski JQ. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. *Neurobiol Aging*. 2011;32(12):2322.e19-2322. https://doi.org/10.1016/j.neurobiolaging.2010.05.023
28. deToledo-Morrell L, Stoub TR, Bulgakova M, et al. MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. *Neurobiol Aging*. 2004;25(9):1197-1203. https://doi.org/10.1016/j.neurobiolaging.2003.12.007
29. Risacher SL, Saykin AJ, Wes JD, Shen L, Firpi HA, McDonald BC. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Curr Alzheimer Res*. 2009;6(4):347-361. https://doi.org/10.2174/156720509788929273
30. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's disease neuroimaging initiative (ADNI). *Alzheimers Dement*. 2005;1(1):55-66. https://doi.org/10.1016/j.jalz.2005.06.003
31. Shaw LM, Korecka M, Clark CM, Lee VMY, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov*. 2007;6(4):295-303. https://doi.org/10.1038/nrd2176
32. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage*. 2010;53(1):1-15. https://doi.org/10.1016/j.neuroimage.2010.06.010
33. Iglesias JE, Insausti R, Lerma-Usabiaga G, et al. A probabilistic atlas of the human thalamic nuclei combining ex vivo MRI and histology. *Neuroimage*. 2018;183:314-326. https://doi.org/10.1016/j.neuroimage.2018.08.012
34. Saygin ZM, Kliemann D, Iglesias JE, et al. High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *Neuroimage*. 2017;155:370-382. https://doi.org/10.1016/j.neuroimage.2017.04.046
35. Iglesias JE, Augustinack JC, Nguyen K, et al. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. *Neuroimage*. 2015;115:117-137. https://doi.org/10.1016/j.neuroimage.2015.04.042
36. Sanfilipo MP, Benedict RHB, Zivadinov R, Bakshi R. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. *Neuroimage*. 2004;22(4):1732-1743. https://doi.org/10.1016/j.neuroimage.2004.03.037
37. Orso B, Mattei C, Arnaldi D, et al. Clinical and MRI predictors of conversion from mild behavioural impairment to dementia. *Am J Geriatr Psychiatr*. 2020;28(7):755-763. https://doi.org/10.1016/j.jagp.2019.12.007
38. Gallagher D, Fischer CE, Iaboni A. Neuropsychiatric symptoms in mild cognitive impairment: an update on prevalence, mechanisms, and clinical significance. *Can J Psychiatr*. 2017;62(3):161-169. https://doi.org/10.1177/0706743716648296
39. Lü W, Duan J, Zhang W, Yang W, Yu W. Relationship between neuropsychiatric symptoms and cognitive functions in patients with cognitive impairment. *Psychogeriatrics*. 2021;21(5):773-782. https://doi.org/10.1111/psyg.12738
40. Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatr*. 2014;171(5):572-581. https://doi.org/10.1176/appi.ajp.2014.13060821
41. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J Int Neuropsychol Soc*. 2008;14(2):266-278. https://doi.org/10.1017/S1355617708080302
42. Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *J Int Neuropsychol Soc*. 2014;20(8):836-847. https://doi.org/10.1017/S135561771400068X
43. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):439-451. https://doi.org/10.1111/acps.12336
44. vanOijen M, deJong FJ, Hofman A, Koudstaal PJ, Breteler MMB. Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimers Dement*. 2007;3(2):92-97. https://doi.org/10.1016/j.jalz.2007.01.011
45. Baerresen KM, Miller KJ, Hanson ER, et al. Neuropsychological tests for predicting cognitive decline in older adults. *Neurodegener Dis Manag*. 2015;5(3):191-201. https://doi.org/10.2217/nmt.15.7
46. Chen PH, Cheng FY, Cheng SJ, Shaw JS. Predicting cognitive decline in Parkinson's disease with mild cognitive impairment: a one-year observational study. *Park Dis* 2020;2020:e8983960. https://doi.org/10.1155/2020/8983960
47. Eijlers AJC, vanGeest Q, Dekker I, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. *Brain*. 2018;141(9):2605-2618. https://doi.org/10.1093/brain/awy202
48. Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129(11):2885-2893. https://doi.org/10.1093/brain/awl256
49. Wang L, Goldstein FC, Veledar E, et al. Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. *Am J Neuroradiol*. 2009;30(5):893-899. https://doi.org/10.3174/ajnr.A1484
50. Hsu JL, Lee WJ, Liao YC, Lirng JF, Wang SJ, Fuh JL. Posterior atrophy and medial temporal atrophy scores are associated with different symptoms in patients with Alzheimer's disease and mild cognitive impairment. *PLOS ONE*. 2015;10(9):e0137121. https://doi.org/10.1371/journal.pone.0137121
51. Hu X, Meiberth D, Newport B, Jessen F, the Alzheimer ', s Disease Neuroimaging Initiative. Anatomical correlates of the neuropsychiatric symptoms in Alzheimer's disease. *Curr Alzheimer Res*. 2015;12(3):266-277.
52. Trzepacz PT, Yu P, Bhamidipati PK, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement*. 2013;9(5, Suppl):S95-S104. https://doi.org/10.1016/j.jalz.2012.10.005
53. Bateman DR, Gill S, Hu S, et al. Agitation and impulsivity in mid and late life as possible risk markers for incident dementia. *Alzheimers Dement Transl Res Clin Interv*. 2020;6(1):e12016. https://doi.org/10.1002/trc2.12016
54. Isella V, Villa G, Mapelli C, Ferri F, Appollonio IM, Ferrarese C. The neuropsychiatric profile of posterior cortical atrophy. *J Geriatr Psychiatr Neurol*. 2015;28(2):136-144. https://doi.org/10.1177/0891988714554713
55. Ismail Z, Herrmann N, Rothenburg LS, et al. A functional neuroimaging study of appetite loss in Alzheimer's disease. *J Neurol Sci*. 2008;271(1):97-103. https://doi.org/10.1016/j.jns.2008.03.023
56. Suma S, Watanabe Y, Hirano H, et al. Factors affecting the appetites of persons with Alzheimer's disease and mild cognitive impairment. *Geriatr Gerontol Int*. 2018;18(8):1236-1243. https://doi.org/10.1111/ggi.13455
57. Jessen F, Feyen L, Freymann K, et al. Volume reduction of the entorhinal cortex in subjective memory impairment. *Neurobiol Aging*. 2006;27(12):1751-1756. https://doi.org/10.1016/j.neurobiolaging.2005.10.010

58. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842. https://doi.org/10.1212/01.wnl.0000234032.77541.a2
59. Schultz SA, Oh JM, Koscik RL, et al. Subjective memory complaints, cortical thinning, and cognitive dysfunction in middle-age adults at risk of AD. *Alzheimers Dement Diagn Assess Dis Monit*. 2015;1(1):33-40. https://doi.org/10.1016/j.dadm.2014.11.010
60. Stewart R, Dufouil C, Godin O, et al. Neuroimaging correlates of subjective memory deficits in a community population. *Neurology*. 2008;70(18):1601-1607. https://doi.org/10.1212/01.wnl.0000310982.99438.54
61. Stewart R, Godin O, Crivello F, et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. *Br J Psychiatry*. 2011;198(3):199-205. https://doi.org/10.1192/bjp.bp.110.078683
62. Nagata T, Shinagawa S, Nakajima S, Mimura M, Shigeta M. Association between neuropsychiatric improvement and neurocognitive change in Alzheimer's disease: analysis of the CATIE-AD study. *J Alzheimers Dis*. 2018;66(1):139-148. https://doi.org/10.3233/JAD-180304
63. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement*. 2016;12(2):195-202. https://doi.org/10.1016/j.jalz.2015.05.017
64. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimers Dis*. 2017;56(3):929-938. https://doi.org/10.3233/JAD-160979
65. Nagata T, Nakajima S, Shinagawa S, et al. Psychosocial or clinico-demographic factors related to neuropsychiatric symptoms in patients with Alzheimer's disease needing interventional treatment: analysis of the CATIE-AD study. *Int J Geriatr Psychiatr*. 2017;32(12):1264-1271. https://doi.org/10.1002/gps.4607
66. Rouch I, Pongan E, Trombert B, et al. One-year evolution of behavioral and psychological symptoms of dementia in patients initially hospitalized in cognitive behavioral units: the EVITAL prospective cohort. *J Alzheimers Dis*. 2017;57:1-155. https://doi.org/10.3233/JAD-161023

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ronat L, Hoang V-T, Hanganu A. Establishing an individualized model of conversion from normal cognition to Alzheimer's disease after 4 years, based on cognitive, brain morphology and neuropsychiatric characteristics. *Int J Geriatr Psychiatry*. 2022;1-11. https://doi.org/10.1002/gps.5718