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# Staging the cognitive continuum in prodromal Alzheimer's disease with episodic memory

Alexis Moscoso [a], Jesús Silva-Rodríguez [a], Jose Manuel Aldrey [b], Julia Cortés [a], Anxo Fernández-Ferreiro [c], Noemí Gómez-Lado [a], Álvaro Ruibal [a,d,e], Pablo Aguiar [a,d,*], for the Alzheimer's Disease Neuroimaging Initiative[†]

[a] Nuclear Medicine Department and Molecular Imaging Group, University Hospital CHUS-IDIS, Santiago de Compostela, Spain
[b] Neurology Department, University Hospital CHUS-IDIS, Santiago de Compostela, Spain
[c] Pharmacy Department and Pharmacology group, University Hospital CHUS-IDIS, Santiago de Compostela, Spain
[d] Department of Radiology, Molecular Imaging Group, Faculty of Medicine, University of Santiago de Compostela (USC), Campus Vida, Santiago de Compostela, Spain
[e] Fundación Tejerina, Madrid, Spain

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ABSTRACT

It is unclear whether episodic memory is an appropriate descriptor of the cognitive continuum in mild cognitive impairment (MCI). Here, we investigated the ability of episodic memory to track cognitive changes in patients with MCI with biomarker evidence of Alzheimer's disease (AD). We examined 387 MCI amyloid-positive subjects, cognitively staged as "early" or "late" on the basis of episodic memory impairment. Cross-sectional and longitudinal comparisons between these 2 groups were performed for each amyloid, tau, and neurodegeneration (AT(N)) profile. Cross-sectional analyses indicate that "early" MCI represents a transitional phase between normal cognition and "late" MCI in the AD biomarker pathway. After adjusting by confounders and levels of A, T, and (N), "late" MCI progressed significantly faster than "early" MCI only in profiles with both abnormal amyloid and tau markers (A+T+(N)− $p < 0.05$, A+T+(N)+ $p < 0.001$). Episodic memory staging is useful for describing symptoms in prodromal AD and complements the AT(N) profiles. Our findings might have implications for the Numeric Clinical staging scheme of the National Institute on Aging and Alzheimer's Association research framework.



## 1. Introduction

Recent research efforts shifted toward a biological description of Alzheimer's disease (AD) in terms of in vivo biomarkers of brain amyloidosis (A), tauopathy (T), and neurodegeneration (N), all of them integrated in the purported AT(N) scheme (Jack et al., 2016). This system plays a central role in the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework (Jack et al., 2018), in which the definition of AD relies only on the presence of abnormal levels of both A and T (A+T+), whereas (N) biomarkers and cognitive symptoms, both nonspecific for AD, provide complementary staging information (Jack et al., 2018).

Apart from the 3 classical syndromal cognitive stages, that is, cognitively unimpaired (CU), mild cognitive impairment (MCI), and dementia, the NIA-AA research framework proposed a new 6-stage numeric clinical (NC) staging scheme for patients in the Alzheimer's continuum (patients with A+). Although this staging scheme is designed to monitor subtle changes in cognition in CU individuals, only a single stage (stage 3) is used to describe the entire cognitive continuum of MCI.

In an attempt to stage cognitive symptoms in MCI, the Alzheimer's Disease Neuroimaging Initiative (ADNI) and other studies defined the "early" and "late" stages of MCI on the basis of episodic memory performance (Aisen et al., 2010; Jessen et al., 2014; Petersen et al., 2010). Many studies demonstrated differences between these 2 groups, namely, slower progression rates to AD dementia (Aisen et al., 2010; Jessen et al., 2014), different prevalence

* Corresponding author at: Choupana s/n, Santiago de Compostela, 15706, Spain. Tel.: 981 950 000; fax: 981 950 900.
*E-mail address:* pablo.aguiar.fernandez@gmail.com (P. Aguiar).

† Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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in the community in comparison with the clinic (Jessen et al., 2014; Petersen et al., 2010), and different neuropathologic features (Cai et al., 2015; Lee et al., 2016, 2017; Risacher et al., 2013; Wolfsgruber et al., 2013; Wu et al., 2012; Ye et al., 2014), supporting the idea of a sequential evolution between these 2 groups. However, recent evidence has suggested that the observed differences might be caused by the high number of false positive MCI diagnoses in the early MCI group (Edmonds et al., 2014, 2015, 2019; Thomas et al., 2019), casting doubt on the effectiveness of this staging scheme to track the cognitive continuum in AD. Moreover, no previous study has investigated whether episodic memory provides independent information about severity and progression when applying the NIA-AA research framework criteria to define AD.

In this study, we investigated whether episodic memory staging describes the sequential evolution of cognitive symptoms in patients with MCI with biomarker evidence of AD, as defined by the NIA-AA research framework, and whether it provides complementary prognostic information to the AT(N) profiles.

## 2. Methods

### 2.1. Study design

Data used in the preparation of this article were obtained from the ADNI database http://adni.loni.usc.edu. The ADNI was launched in 2003 as a public-private partnership, led by the Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Data were downloaded from the LONI website in November 2018.

### 2.2. Participants

We examined all the patients in the ADNI1/GO/2 study with available clinical, MRI and cerebrospinal fluid (CSF) data at the baseline. The diagnostic categories included, as defined in the ADNI study, were cognitively normal (CN), subjective memory complaints (SMC), early MCI (EMCI), late MCI (LMCI), and AD dementia. CN and SMC subjects had Mini–Mental State Examination (MMSE) scores of 24–30, a Global Clinical Dementia Rating (CDR) and Memory Box Score of 0, scores in the Logical Memory II Delayed Recall test from the Weschler Memory Scale-Revised (Weschler, 2008) not below 1.5 standard deviations from normative scores, and absence of significant impairment in cognitive functions or activities of daily living. CN and SMC differed only in the presence of subjective memory concerns. EMCI and LMCI had the same MMSE range as CN and SMC, a Global CDR of 0.5, a Memory Box Score of at least 0.5, and functional performance sufficiently preserved to not being considered demented. The inclusion criteria for EMCI and LMCI differed only in the score obtained in the Logical Memory II Delayed Recall test from the Weschler Memory Scale-Revised (Weschler, 2008), with LMCI patients scoring below 1.5 standard deviations from normative data and EMCI scoring between 1 and 1.5 standard deviations below the standard. Finally, AD dementia patients had MMSE scores of 20–26, a Global CDR of 0.5 or 1, and met the NINCDS/ADRDA criteria for probable AD. Although patients with MCI were the main focus of our case, the remaining cohorts were also included in a cross-sectional analysis to determine whether EMCI represents a transitional stage between SMC and LMCI in terms of biomarker abnormalities. Further details can be found at http://adni.loni.usc.edu/methods/documents/. Only patients with MCI with clinically suspected MCI due to AD at the baseline, as reported by the ADNI investigators, were included. A total of 1147 patients, including 267 CN, 88 SMC, 252 EMCI, 324 LMCI, and 216 AD dementia had all available clinical, imaging, and CSF examinations.

### 2.3. Cerebrospinal fluid

CSF measurements of Aβ42, phosphorylated tau181 (p-tau), and total tau (t-tau) were performed by the Center of Neurodegenerative Disease Research, University of Pennsylvania, for ADNI. We downloaded the measurements from the Roche Elecsys electrochemiluminescence immunoassay batch. Recent evidence indicates that this fully automated assay provides transferable cut-points between independent studies (Hansson et al., 2018) which might result in a higher applicability of the findings of this study. A detailed description of the procedures used for CSF analysis can be found at http://adni.loni.usc.edu/methods/.

### 2.4. Magnetic resonance imaging

All the examined patients had a T1-weighted MRI (1.5T or 3T) scan at the baseline. A detailed MRI acquisition protocol of the different parts of the ADNI project can be found at http://adni.loni.usc.edu/methods/documents/. T1 scans were segmented with Freesurfer v5.1 (Fischl, 2012). The ADNI collaborators at the Center for Imaging of Neurodegenerative Diseases at University of California, San Francisco, performed a thorough quality control of their own Freesurfer segmentations. We only included those patients with segmentations of the hippocampus that passed the ADNI quality control. Only nonaccelerated MPRAGE or IR-SPGR sequences were used. We estimated total intracranial volume (TIV) with SPM12 (Malone et al., 2015; Penny et al., 2007) because this measure demonstrated to be more accurate than the Freesurfer TIV (Malone et al., 2015) and because the Freesurfer TIV is biased by brain volume (Klasson et al., 2018). Given that the variability associated to different field strengths is small and comparable with within-scanner variability (Jack et al., 2015; Jovicich et al., 2009), we combined 1.5T and 3T volumetric measures and included a term to account for field strength in our linear analyses (see Implementation of the AT(N) framework and Supplementary Material for more details).

### 2.5. Neuropsychology

Cognition measures, as assessed by MMSE and the Clinical Dementia Rating—Sum of Boxes (CDR-SB) (O'Bryant et al., 2008), were obtained at the baseline and in subsequent follow-up visits for all the participants, although we restricted the analysis to patients with MCI given that the goal of this study is to investigate the prognostic added value of the proposed NC substages.

### 2.6. Implementation of the AT(N) framework

We implemented the AT(N) framework using CSF Aβ42 and p-tau as markers of A and T, respectively, whereas hippocampal atrophy measured with MRI was used as a biomarker of (N). These measures are standard markers of A, T, and (N) in the NIA-AA research framework (Jack et al., 2018), and represent an accessible AT(N) implementation for most of the hospitals and memory clinics. CSF t-tau was not used here as (N) biomarker because of its tight correlation with p-tau in AD (Blennow et al., 1995) and because recent evidence suggests that CSF neurofilament light chain might be the most suitable CSF-based (N) marker (Kern et al., 2018).

Following recent recommendations, no adjustment for age was performed in CSF biomarkers (Herukka et al., 2017). To obtain an

index for (N), we used the average between left and right hippocampal volumes normalized by TIV, and adjusted by age and field strength using linear regression in the subsample of CN with A−, as defined in the following. By including the field strength term (categorical), we account for the small bias introduced by the different field strengths (Jovicich et al., 2009). A detailed description of this approach can be found in the Supplementary Material. This index is referred to as adjusted hippocampal volume (aHV) and increases with atrophy severity.

The AT(N) framework requires the definition of cut-points that establish the separation between normal (negative) and abnormal (positive) levels of biomarkers. For our A marker, we established an externally derived cut-point of 1100 pg/cc based on agreement with amyloid PET imaging (Hansson et al., 2018; Schindler et al., 2018; Shaw et al., 2018). For T and (N), however, no externally derived cut-points that directly reflect tauopathy or neurodegeneration have been established for the Roche Elecsys assay and MRI under the ADNI protocol. To derive independent cut-points to be applied in our CN and MCI cohorts, we established cut-points using the 10th percentile (90% sensitivity) of the biomarker distribution among AD dementia patients with A+, as defined by the aforementioned A cut-point. We used this approach because it provided similar imaging cut-points to those obtained by maximizing the discrimination between cognitively impaired patients versus young controls (Jack et al., 2017), which arguably represents the most reliable alternative when no direct neuropathology measures are available.

### 2.7. NC staging

Following the definition of the NC staging in the NIA-AA research framework (Jack et al., 2018), ADNI CN subjects with A+ can be regarded as stage 1, SMC with A+ as stage 2, and EMCI and LMCI with A+ as stage 3. To keep a similar nomenclature, we defined a subdivision of stage 3 patients into early and late substages (early stage 3 and late stage 3) following the same neuropsychological criteria used to define EMCI and LMCI (Aisen et al., 2010). A+ AD dementia patients are mildly demented and thus can be regarded as stage 4.

### 2.8. Statistical analysis

We used Kruskal-Wallis tests to evaluate differences in demographic continuous variables among the different NC stages. The Tukey-Kramer method was applied for pairwise comparisons. Discrete demographic variables were compared using the $\chi^2$ test.

We used a one-tailed exact binomial test to assess the hypothesis that stage 1 and stage 2 patients progressed first to early stage 3.

Cross-sectional proportions of each biomarker profile across the NC stages were compared using a logistic regression for each AT(N) profile with profile status (absent or present) as the dependent variable and NC stage as the independent variable. The model was adjusted for age, sex, education years, number of APOE ε4 alleles, and baseline MMSE score.

Annual rates of change of MMSE and CDR-SB across the NC substages were compared by fitting a linear mixed effects model for each AT(N) profile. The model included a random intercept per subject, and fixed effect terms for NC substage, the interaction between NC substage and time, time, covariates, and the interaction between each covariate and time. The covariates included age, sex, education years, number of APOE ε4 alleles, baseline cognitive score under consideration (MMSE or CDR-SB), and, as a sensitivity analysis, levels of CSF Aβ42, p-tau, t-tau, and age- and TIV-adjusted hippocampal volume. The adjusted mean rate of change, using late stage 3 as reference, was obtained from the coefficient of the interaction between NC substage and time.

We assessed the time of progression to AD dementia computing Kaplan Meier survival curves and fitting a cox proportional hazards model for each profile. The model was adjusted by the same covariates, including both baseline MMSE and CDR-SB, described previously.

F tests were used to assess the significance of model coefficients. Post hoc contrasts were conducted for pairwise comparisons. The significance level was set $\alpha = 0.05$. The Bonferroni correction was applied to correct for multiple inferences. We reported two-tailed $p$ values, except for the binomial exact test. The Statistics and Machine Learning Toolbox from MATLAB (R2017a) (https://es.mathworks.com/help/pdf_doc/stats/stats.pdf) was used for all statistics.

## 3. Results

### 3.1. Cohort characteristics

The proportion of patients with A+ increased with symptomatology: 113 (42%) CN had A+, 32 (36%) in SMC, 132 (52%) in EMCI, 255 (79%) in LMCI, and 200 (93%) in AD dementia. Demographic information for A− participants is presented in Supplementary Table 1. Table 1 shows the characteristics of the A+ participants examined in this study, stratified by NC stages and the proposed substaging.

Each stage had small differences in age, sex, and education. Cognitive measures worsened with increasing stage, with early stage 3 representing a trade-off between stage 2 and late stage 3. APOE genotype followed the expected trend. Pairwise comparisons between early and late stage 3 only showed that early stage 3 had significantly higher baseline MMSE score (median difference 1, 95% CI: 1 to 2; $p < 0.001$). Post hoc analyses can be found in the Supplementary Material. Biomarker levels also had a higher rate of abnormality in the progression of NC stages (Fig. 1). Again, early stage 3 levels demonstrated to imbricate between stage 2 and late stage 3, specially for T and (N) markers. Late stage 3 displayed significantly more abnormal biomarker levels than early stage 3 ($p < 0.05$ for all the biomarkers). Biomarker levels for A− participants are presented in Supplementary Fig. 1.

### 3.2. AT(N) profiles across NC stages

The 90% sensitivity approach used to derive biomarker cut-points yielded the following results: p-tau cut-point = 19.39 pg/

**Table 1**
Demographic information for A+ (abnormal CSF Aβ42 levels) participants

| NC stage | Stage 1 | Stage 2 | E. Stage 3 | L. Stage 3 | Stage 4 | $p$ value |
|---|---|---|---|---|---|---|
| N | 113 | 32 | 132 | 255 | 200 | |
| Demographics | | | | | | |
| Age (y) | 75 ± 6 | 73 ± 5 | 73 ± 7 | 74 ± 7 | 74 ± 8 | 0.14 |
| Female (%) | 50 | 69 | 38 | 37 | 42 | 0.021 |
| Education (y) | 16 ± 3 | 17 ± 2 | 16 ± 3 | 16 ± 3 | 15 ± 3 | 0.032 |
| MMSE | 29 ± 1 | 29 ± 1 | 28 ± 2 | 27 ± 2 | 23 ± 2 | <0.001 |
| CDR-SB | 0 ± 0 | 0 ± 0 | 1 ± 1 | 2 ± 1 | 4 ± 2 | <0.001 |
| Follow-up (y) | 5 ± 3 | 3 ± 2 | 4 ± 2 | 4 ± 2 | N/A | <0.001 |
| APOE ε4 carriers (%) | 40 | 59 | 58 | 63 | 74 | <0.001 |

Continuous variables are reported as means ±standard deviation. $p$ values were calculated using a Kruskal-Wallis test (continuous variables) or a $\chi^2$ test (categorical variables).
Key: NC, numeric clinical; E. stage 3, early stage 3; L. stage 3, late stage 3; MMSE, Mini–Mental State Examination score; CDR-SB, Clinical Dementia Rating—Sum of Boxes; APOE, apolipoprotein E; N/A, not assessed.

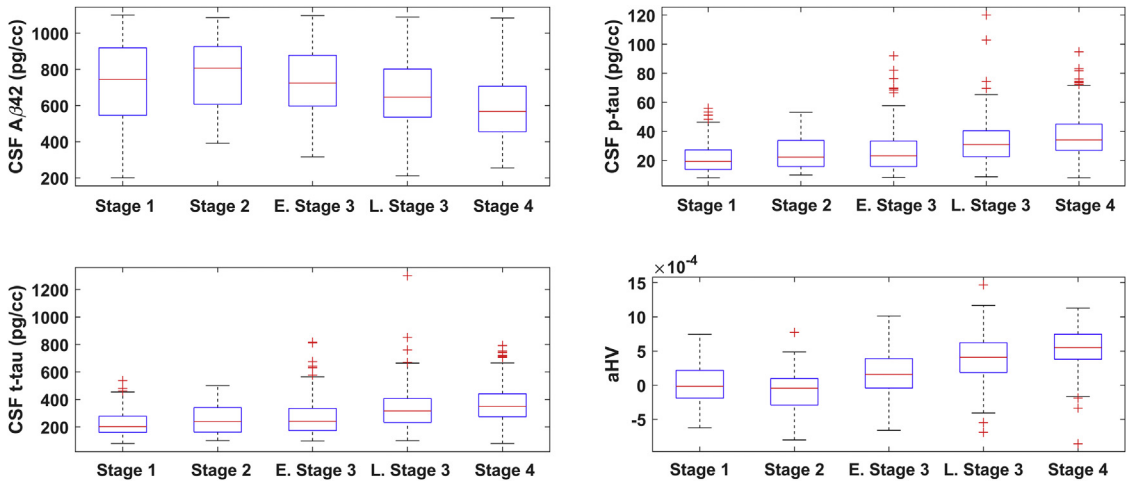


**Fig. 1.** Box plots showing biomarker levels across the different numeric clinical stages and substages. aHV stands for intracanial volume-, field strength-, and age-adjusted hippocampal volume, and is higher and positive for higher atrophies. Abbreviations: CSF, cerebrospinal fluid; E. stage 3, early stage 3; L. stage 3, late stage 3.

cc and aHV cut-point = $1.82 \times 10^{-4}$. Fig. 2 shows the prevalence of the AT(N) profiles for each stage. Demographic information for each profile in early and late stage 3 can be found in Supplementary Table 2. The proportion of A+T+(N)+ increased at every NC stage (stage 1 < early stage 3 < late stage 3, $p < 0.01$ for each comparison), whereas in A+T+(N)− and A+T−(N)− decreased (for A+T+(N)−, early stage 3 > late stage 3, $p < 0.05$; for A+T−(N)−, stage 1 > early stage 3 > late stage 3, $p < 0.01$ for each comparison). No significant differences in prevalence were observed for A+T−(N)+.

### 3.3. Longitudinal progression of stage 1 and 2 patients

During follow-up, 28 stage 1 and 7 stage 2 patients progressed to other stages on an average of 4.1 ± 2.6 and 2.6 ± 1.2 years, respectively. Nineteen stage 1 and 3 stage 2 progressed to early stage 3, whereas the rest progressed to late stage 3. No direct transitions to stages 4–6 were observed. We regarded early stage 3 as those who progressed to a clinical diagnosis of MCI but had neuropsychological scores above (more normal) the limits specified in the ADNI inclusion criteria. The proportion of stage 1 and 2 patients who transitioned to early stage 3 was higher than that of late stage 3 (65%, $p = 0.043$).

### 3.4. Cognitive decline

To ascertain whether the new NC stages provided prognostic information to the AT(N) profiles we conducted linear mixed effects models for longitudinal measures of MMSE and CDR-SB. Table 2 shows the mean difference in annual rates of change for early stage 3 compared with late stage 3 patients. Overall, early stage 3 patients showed a slower decline on both MMSE and CDR-SB than patients in late stage 3 (Fig. 3), with significant differences in A+T+(N)− and A+T+(N)+ profiles. Additional sensitivity analyses for varying p-tau and aHV cut-points (±15% around the values derived here) can be found in Supplementary Fig. 2, showing the stability of the results.

### 3.5. Progression to AD dementia

At follow-up, 41 early stage 3 and 147 late stage 3 progressed to AD dementia (see Supplementary Table 3 for details). Fig. 4 shows Kaplan Meier survival curves and hazard ratios for 3 of the 4 profiles (A+T−(N)− had only 6 progressions to AD dementia and was excluded from the analysis). Late stage 3 patients had higher risk of progression to AD dementia than early stage 3, this risk being significantly higher for A+T+(N)+ patients but not for those with A+T+(N)− (Fig. 4). Patients with an A+T−(N)+ profile showed a similar risk of progression to AD dementia. Sensitivity analyses for varying p-tau and aHV cut-points, presented in Supplementary Fig. 2, showed that these results were robust under slight variations in cut-points.

## 4. Discussion

In the study presented here, we investigated the effectiveness of episodic memory as a descriptor of the cognitive continuum in patients with MCI with biomarker evidence of AD. Although prior work had already drawn comparisons between the early and late stages of MCI in terms of progression and pathologic features (Aisen

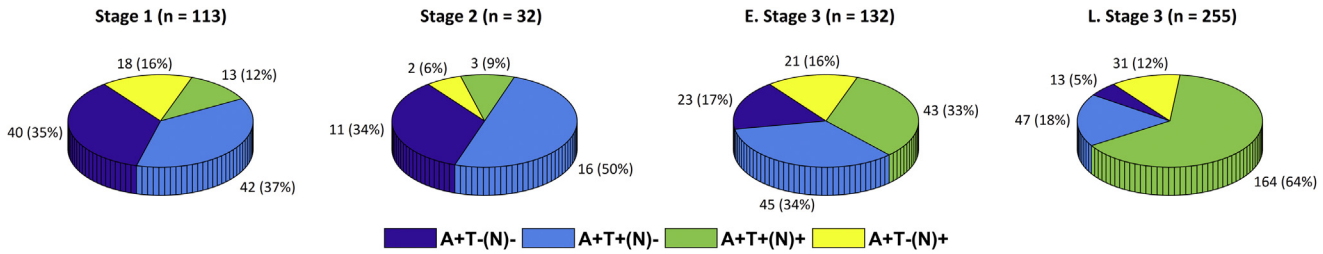


**Fig. 2.** Sample sizes and prevalence of each AT(N) profile for patients in the Alzheimer's continuum, across each numeric clinical stage. Abbreviations: E. stage 3, early stage 3; L. stage 3, late stage 3.

**Table 2**
Difference in annual change of cognitive measures in early stage 3 compared with late stage 3

| Variable | Difference in annual change (pts/y) | *p* value |
|---|---|---|
| MMSE | | |
| AT(N) | | |
| A+T−(N)− | 0.16 (−0.08–0.40) | 0.20 |
| A+T+(N)− | 0.35 (0.17–0.53) | <0.001 |
| A+T+(N)+ | 0.42 (0.19–0.64) | <0.001 |
| A+T−(N)+ | 0.20 (−0.02–0.41) | 0.07 |
| CDR-SB | | |
| AT(N) | | |
| A+T−(N)− | −0.19 (−0.34 to −0.03) | 0.02 |
| A+T+(N)− | −0.27 (−0.40 to −0.15) | <0.001 |
| A+T+(N)+ | −0.50 (−0.64 to −0.35) | <0.001 |
| A+T−(N)+ | −0.05 (−0.21 to 0.10) | 0.50 |

A positive (negative) difference in annual change of MMSE (CDR-SB) means that the decline of early stage 3 is slower than in late stage 3. Quantities between parentheses are 95% CI.
Key: L. stage 3, late stage 3; E. stage 3, early stage 3; MMSE, Mini–Mental State Examination score; CDR-SB, Clinical Dementia Rating—Sum of Boxes.

et al., 2010; Cui et al., 2015; Jessen et al., 2014; Lee et al., 2016, 2017; Petersen et al., 2010; Risacher et al., 2013; Wolfsgruber et al., 2013; Wu et al., 2012; Ye et al., 2014), this is, to our knowledge, the first study in which the comparison has been performed among subjects with biomarker confirmation of AD, as defined by the NIA-AA research framework (Jack et al., 2018). This is extremely important because recent studies have suggested that the high number of false-positive MCI diagnoses in the EMCI group might have influenced previous results (Edmonds et al., 2014, 2015, 2019; Thomas et al., 2019), leaving the efficacy of the episodic memory staging to track cognition in prodromal AD unclear.

In contribution to solving for the aforementioned problem, our cross-sectional results suggest that early stage 3 represents a transitional stage between stage 2 and late stage 3 in the pathophysiological progression of the disease (Figs. 1 and 2). Moreover, Fig. 2 indicates that biomarker abnormalities evolve according to an A+T−(N)− → A+T+(N)− → A+T+(N)+ temporal progression (Bateman et al., 2012; Jack et al., 2011; Jack and Holtzman, 2013), in which early stage 3 fits in the expected way, that is, with more (fewer) A+T+(N)+ (A+T−(N)−) profiles than in stages 1 and 2 but fewer (more) than in late stage 3. The longitudinal tracking of stage 1 and 2 patients showed that the most probable transition was to early stage 3, supporting our hypothesis that this stage represents not only a transitional phase in terms of biomarker profiles but also accurately describes the cognitive continuum of AD.

We also investigated whether episodic memory staging of stage 3 patients was indicative of patient progression for a given AT(N) profile. We found that cognitive decline and progression to AD dementia were faster in late stage 3 than in early stage 3 patients only for AD-type profiles (profiles with A+T+) (Table 2 and Figs. 3 and 4). This finding was independent of intraprofile levels of Aβ42, p-tau, t-tau, and hippocampal atrophy, suggesting that episodic memory actually provides complementary information about the severity of the disease. It is not clear, however, to what extent these differences in progression can be attributed to a more fine-grained staging system rather than to differences in cognitive reserve (Stern, 2012, 2006) or concomitant pathology burden. Under the cognitive reserve scenario, some subjects would exhibit less impaired cognition than expected for a given burden of AD neuropathologic changes. In this context, our early stage 3 patients might represent subjects with high cognitive reserve, although it is also possible that the higher impairment of late stage 3 patients might be due to the presence of concomitant pathologies. For instance, vascular pathology is known to accelerate cognitive deterioration (Helzner et al., 2009; Li et al., 2011) and recent evidence suggest that vascular pathology might be a core AD feature (Lee et al., 2016).

Regardless of the origin of cognitive differences between early and late stage 3 patients, the significantly divergent outcomes observed in this study indicate that proper accounting for these substages might result in a better prediction of cognitive decline and, thus, in increased power for interventional trials using profile-based participant selection. In addition, the rapid progression to AD dementia observed in A+T+ LMCI suggests that these patients might be appropriate candidates for symptomatic treatment, allowing to treat symptoms earlier in the disease course.

Episodic memory staging may also help to harmonize prognosis results obtained across different stage 3 cohorts. Because current guidelines for the definition of stage 3 or MCI leave the definition of abnormality cut-points in cognitive scores to the discretion of the researcher (Albert et al., 2011; Dubois et al., 2014; Dunn, 2018; Jack et al., 2018), the proportion of patients in the early stage might vary

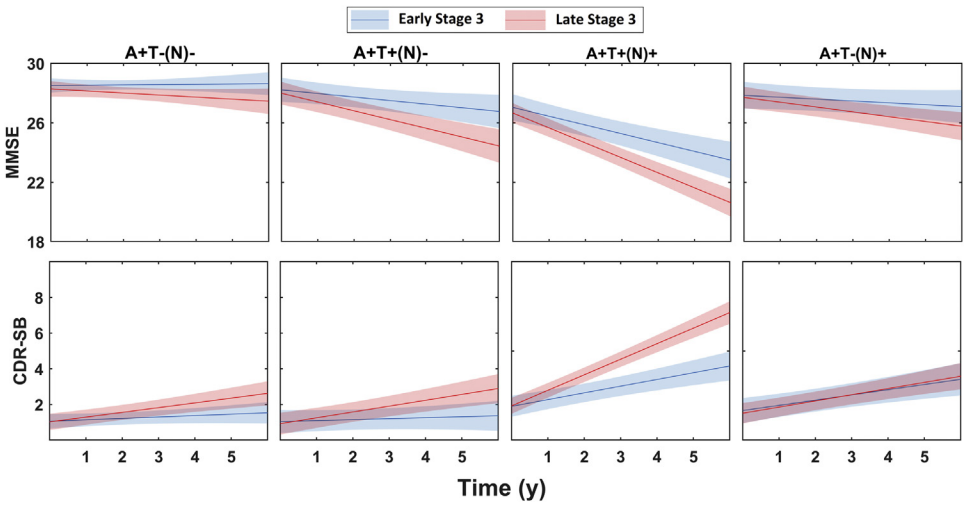


**Fig. 3.** Longitudinal progression of Mini–Mental State Examination and Clinical Dementia Rating—Sum of Boxes for each biomarker profile and substage, as predicted by the fitted linear mixed models evaluated at mean values of continuous covariates and reference categorical covariates (males and APOE ε4 noncarriers). Shaded areas represent 95% confidence intervals. Abbreviations: MMSE, Mini–Mental State Examination; CDR-SB, Clinical Dementia Rating—Sum of Boxes.

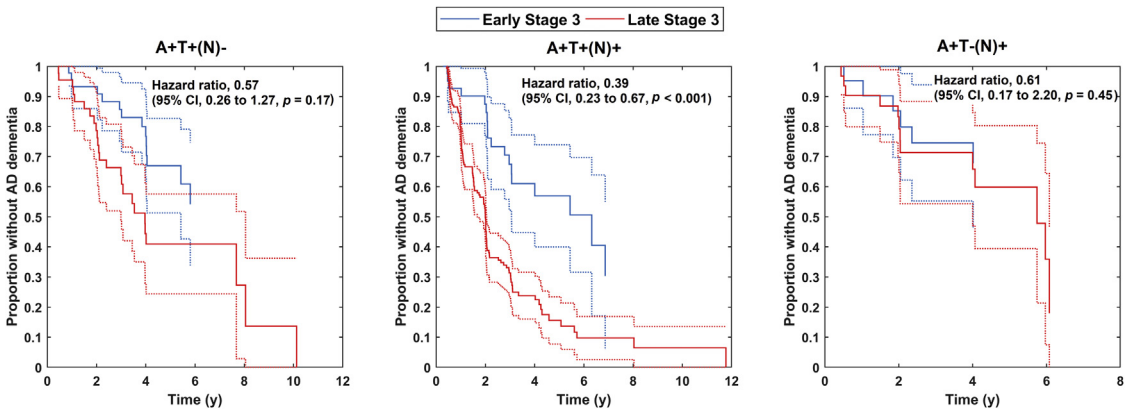


**Fig. 4.** Survival curves for the progression to AD dementia, according to AT(N) profiles and substages. Hazard ratios are defined as early versus late stage 3. We did not include the A+T−(N)− because only 3 conversions to AD were observed for each substage. Dashed lines represent 95% confidence intervals.

dramatically from cohort to cohort, resulting in a wide range of estimates of prognostic accuracy for the different biomarkers of AD (Prestia et al., 2015, 2013). This variability was one of the main factors that hampered the development of recommendations regarding the use of CSF and imaging biomarkers in predicting short-term decline (Herukka et al., 2017). Differences might be even more disparate in community cohorts, in which EMCI prevalence is much higher than in the clinic (Jessen et al., 2014; Petersen et al., 2010). In this regard, accounting for substages seems to be a promising approach to reduce variability across different stage 3 cohorts, improving the quality of the evidence for the development of new guidelines.

Our analysis has also revealed the heterogeneous nature of the A+T−(N)+ profile. Regarded as a combination of early AD pathologic changes and other non-AD conditions (Jack et al., 2018), this profile has proven to be equally likely across the different stages (Fig. 2) and, therefore, seems to lie outside the biomarker progression observed in the other 3 profiles of the Alzheimer's continuum. Not to mention, rates of progression were similar in early and late stage 3, suggesting that episodic memory is not useful in predicting progression when the impairment is caused by other non-AD conditions. Furthermore, Figs. 3 and 4 show that cognitive decline and conversion to AD dementia was faster for A+T+(N)+ profiles in comparison to A+T−(N)+, confirming that the addition of the T biomarker predicts faster progression (Cummings, 2018; Jack et al., 2018) compared with previous amyloid-neurodegeneration schemes (Albert et al., 2011; Dubois et al., 2014).

This study has strengths. First, by comparing early and late MCI subjects with biomarker evidence of AD we excluded false-positive MCI diagnoses that potentially contaminated the findings of previous studies, increasing the reliability of our findings. Second, by performing an analysis based on the AT(N) framework we provided first-time evidence indicating that episodic memory is an accurate descriptor of the AD cognitive pathway only in patients with the NIA-AA research framework definition of AD (A+T+). Third, our findings might help to refine the NC staging scheme, describing symptom progression more accurately at the MCI stage.

Our study was not without its limitations. Given the lack of autopsy-validated cut-points reflecting tauopathy or neurodegeneration in published literature, we used an alternative method which does not reflect brain pathology directly, but that provides similar imaging cut-points to those obtained when discriminating between cognitively normal young and A+ cognitively impaired subjects (Jack et al., 2017). Biomarker values close to the cut-point were commonly found, which might limit the applicability of our results for subjects with borderline biomarker levels. We combined 1.5T and 3T data in our analyses, which, despite the statistical corrections we used, might have influenced our results. Although many cognitive tests can be used to objectively assess a memory deficit, only the Logical Memory II Delayed Recall test from the Weschler Memory Scale-Revised was used in this study. It is not clear whether the categorization into early and late stage 3 might vary using different tests, leading to better or worse staging and prognostic information. Another limitation is that ADNI MCI cohorts represent only a highly preselected fraction of patients with MCI and, therefore, conclusions made here regarding different MCI cohorts and community MCI samples are plausible but need future confirmation. Further investigations are needed to confirm the observed differences in early stage 3 versus stage 2, given the low number of the latter studied here.

In conclusion, our findings might help to describe the symptomatic progression in AD more accurately, leading to a potential refinement of the NC staging scheme that will result in power increases for profile-based clinical trials.

## Disclosure

The authors have no actual or potential conflicts of interest.

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## Appendix A. Supplementary data

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