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# Speech pause distribution as an early marker for Alzheimer's disease

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ABSTRACT

**Background:** Pause duration analysis is a common feature in the study of discourse in Alzheimer's disease (AD) since this patient group has shown a consistent trend for longer pauses in comparison to healthy controls. This speech feature may also be helpful for early detection; however, studies involving patients at the pre-clinical, high-risk phase of amnestic mild cognitive impairment (aMCI) have yielded varying results.
**Objective:** To characterize the probability density distribution of speech pause durations in 26 patients with AD, 57 amnestic multi-domain amnestic MCI patients (29 with memory encoding deficits, a-mdMCI-E, and 28 with retrieval impairment only, a-mdMCI-R) and 29 healthy controls (HC) in order assess whether there are significant differences between them. To explore the potential differences in pause production between patients with a-mdMCI-E and a-mdMCI-R, as the former are considered to be at higher risk of progressing to dementia.
**Methods:** The 112 picture-based oral narratives obtained were manually transcribed and annotated for the automatic extraction and analysis of pause durations. Different probability distributions were tested for the fitting of pause durations while truncating shorter ranges. Recent findings in the field of Statistics were considered in order to avoid the inherent methodological uncertainty that this type of analysis entails by addressing the question of temporal thresholding and its potential repercussions on inter-annotator reliability in manual transcriptions.
**Results:** A lognormal distribution (LND) explained the distribution of pause duration for all groups. Its fitted parameters ($\mu$, $\sigma$) followed a gradation from the group with shorter durations and a higher tendency to produce short pauses (HC) to the group with longer pause durations and a considerably higher tendency to produce long pauses with greater variance (AD). Importantly, a-mdMCI-E produced significantly longer pauses and with greater variability than their a-mdMCI-R counterparts ($\alpha = 0.05$).
**Conclusion:** We report significant differences at the group level in pause distribution across all groups of study that could be used in future diagnostic tools and discuss the clinical implications of these findings, particularly regarding the characterization of a-mdMCI.

## 0. Introduction

Mild Cognitive Impairment (MCI) represents the array of syndromes at the transitional stage from healthy ageing to a variety of dementia types, characterized by normal activities of daily living alongside impairment in one or more cognitive domains in the absence of dementia (Jack et al., 2018). With nearly half of the individuals diagnosed with Mild Cognitive Impairment (MCI) due to Alzheimer's Disease (AD) developing dementia within three years (Glynn et al., 2020; Petersen,

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2018), it has been suggested that diagnosis at the prodromal stage represents the optimal time-window for onset delay and potential intervention (Livingston et al., 2017). Risk evaluation upon MCI diagnosis is considered not only more cost-effective than diagnosis at the dementia stage (Alz, 2018), but also deemed to be less distressful for those involved in comparison to general population screenings, allowing for care planning when concerns are raised and assistance is needed (Prince et al., 2011). The assessment of the constellation of cognitive deficits found in the prodromal stage of AD has proven to provide considerable diagnostic power regarding dementia progression regardless of biomarker use (Callahan et al., 2015) and seems to have clearer clinical utility (Petersen, 2018; Cui et al., 2011). Crucially, neuropsychological testing is accessible in every clinical context, which makes cognitive profiling the current focus of general clinical practice (Jack et al., 2018) and prevention efforts (Kivipelto et al., 2018). However, due to the heterogeneity in MCI's clinical profile and outcome, risk factors for Alzheimer's dementia and their association with MCI subtypes need yet to be ascertained (Clark et al., 2013).

The increased risk associated with impairment in multiple cognitive domains in comparison to single-domain MCI is still under debate due to the heterogeneity of the syndrome as well as to the fact that AD is the most common but not the only possible underlying aetiology (Clark et al., 2013; Jak et al., 2016). It has been suggested that the number of domains affected rather than the single- versus multiple-domain distinction might be a more reliable diagnostic predictor of dementia progression (Glynn et al., 2020). The presence of memory deficits – with or without accompanying impairment in other domains – was initially considered a defining feature of the clinical syndrome (Petersen et al., 1995, 1997; Smith et al., 1996) and is a consistent factor in the clinical profile of a great proportion of MCI patients with a later progression to dementia (Belleville et al., 2017; Fleisher et al., 2007; Göthlin et al., 2017; Kim et al., 2019a; Perri et al., 2007; Tabert et al., 2006; Glynn et al., 2020). More specifically, impairment in anterograde memory encoding reflected in unsuccessful cued recall and susceptibility to intrusion effects has been associated with higher probability of underlying AD (Aggarwal et al., 2005; Jacobs et al., 1995; Grober et al., 2000) even at the prodromal phase of MCI (Mistridis et al., 2015). More recent studies have demonstrated that this particular cognitive profile in MCI is compatible with positive AD biomarkers (Chiotis et al., 2018; Curiel Cid et al., 2020; Goldstein et al., 2019; Hessen et al., 2019; Putcha et al., 2019), as well as abnormal neural connectivity (Hampstead et al., 2016; Prieto Del Val et al., 2016; Sarica et al., 2018) and cerebral perfusion patterns (Xie et al., 2016) during memory encoding tasks. Moreover, declines in memory encoding have been predicted in amyloid-positive cognitively-normal individuals (Edelman et al., 2017; Hollands et al., 2014; Papp et al., 2017) alongside downstream tau increases (Hanseeuw et al., 2019; Marks et al., 2017; Sperling et al., 2019; Tort-Merino et al., 2019), as well as in patients with subjective cognitive complaint with positive AD biomarkers (Gagliardi et al., 2019). Abnormal cortical activity has also been observed in genetic carriers during memory encoding tasks (Ochoa et al., 2017; Rabipour et al., 2020), supporting the thesis of a preference of AD pathology for cortical areas devoted to memory processing and, more precisely, those involved in encoding and retrieval of newly learned information.

Language impairment has also been consistently observed in MCI patients who end up with a dementia diagnosis (Karr et al., 2018; Mura et al., 2014). AD progressors perform significantly worse than non-progressors at naming (Belleville et al., 2014; Cloutier et al., 2015; Kim et al., 2019b; Pravatà et al., 2016) and semantic fluency (Kim et al., 2019b; Mazzeo et al., 2016; Vaughan et al., 2018; Vita et al., 2014) with prediction models combining biomarkers and composite cognitive scores benefiting significantly from the inclusion of language-related scores (Belleville et al., 2017; Gainotti et al., 2014; Gleason et al., 2018). Connected speech is a highly complex process recruiting various levels of linguistic processing that has revealed substantial differences between patients with MCI due to Alzheimer's Disease (AD) and their healthy counterparts, predominantly in the form of semantic impoverishment and reduced fluency (see Filiou et al., 2020; Mueller et al., 2018a for recent reviews).

The great advances in fields such as natural language processing and automatic speech recognition in the last decades have contributed to a surge in studies reporting in most cases on a large number of linguistic and paralinguistic variables (Asgari et al., 2017; Beltrami et al., 2018; Fraser et al., 2019; Gosztolya et al., 2019; König et al., 2015; Mirheidari et al., 2019; Mueller et al., 2018b; Orimaye et al., 2017, 2018; Rentoumi et al., 2014; Roark et al., 2011; Toth et al., 2018), ranging from voice features (Lopez-de Ipina et al., 2017; Meilán et al., 2018; Themistocleous C. Eckerström and Kokkinakis, 2020) to discourse analysis (Abdalla et al., 2018; Drummond et al., 2015; Kim et al., 2019a; Pompili et al., 2018; Toledo et al., 2018) in the characterization of patients with MCI who progress to a diagnosis of AD. The measurement of voiced and unvoiced segments in connected speech has been a particularly prolific research avenue thanks to its relative methodological simplicity and the great technical precision that current technologies grant. In this regard, it has been observed that AD patients produce more silent pauses than healthy controls (HC) (Gayraud et al., 2011) and pause more frequently (Hoffmann et al., 2010; Pistono et al., 2019), although (Gayraud et al., 2011) failed to find significant differences in pause rate. Pauses in this patient group have also been found to have significantly longer mean durations than those of HC (Singh et al., 2001) – even though for instance in Gayraud et al. (2011) this difference does not reach statistical significance, – thus representing a larger proportion of total discourse time (Hoffmann et al., 2010; Pistono et al., 2019; König et al., 2015; Fraser et al., 2016) even though this difference was not significant in Singh et al. (2001).

These speech fluency features are already present in MCI, with patients producing more pauses (Toth et al., 2018) at a higher rate than HC (Beltrami et al., 2018; Roark et al., 2011), although pause rate did not differ in other studies (Toth et al., 2018; Pistono et al., 2016) and neither did the number of pauses (Sluis et al., 2020). Mean pause duration is another recurring feature of study since patients with MCI are expected to produce pauses with longer mean duration than those of healthy controls (König et al., 2015; Beltrami et al., 2018; Pistono et al., 2016), although in other studies no significant difference was found (Roark et al., 2011; Sluis et al., 2020) or this finding was task-dependent (Toth et al., 2018). Voice-to-silence ratio seems to be a more reliable feature, consistently differentiating the narratives of patients with MCI from their healthy counterparts with a lower proportion of voiced time in relation to total discourse time (Kim et al., 2019b; Toth et al., 2018; Beltrami et al., 2018; Roark et al., 2011; Sluis et al., 2020).

Differences in task choice, criteria for pause labelling, temporal thresholding, or methodology applied – manual versus automatic transcription and segmentation – may have contributed to some extent to discrepancies in the results of previous studies. Studies including different speech elicitation methods in MCI have revealed differential results in mean pause length across tasks. For instance, in Toth et al. (2018) only the post-distractor delayed recall video summary task yielded significantly longer pauses in MCI patients as compared to HC, whereas neither the distractor-free immediate recall condition nor the task based or the description of their previous day elicited significant differences. In Beltrami et al. (2018) only the picture description task and the description of a typical day at work yielded significantly longer pauses in participants with MCI, while the episodic memory-based task (a description of the last dream they remembered) did not reveal statistically significant differences between this group and HC. AD patients in the same study produced significantly longer pauses than their HC counterparts regardless of task (Beltrami et al., 2018), similarly to Pistono et al. (2019), where a picture description task and a post-distractor delayed recall narrative were used. In view of these contradicting results the role of memory deficits in the pausing behaviour of MCI patients remains yet unclear, suggesting that longer

pauses might arise due to different causes depending on the task at hand.

As technology improves and automatic speech alignment becomes more widely available potential differences amongst these techniques and their confounding effects should also be evaluated. In a study assessing the performance of HC and MCI patients at a story retelling task under two conditions (immediate and delayed recall) in which manual annotation and forced alignment were compared (Roark et al., 2011) statistically significant differences were found in the immediate recall condition only, involving standardized pause rate and total phonation time regardless of annotation method. However, phonation rate and transformed phonation rate were found to be significant in the immediate recall condition only, and, more importantly, exclusively in the forced alignment condition (Roark et al., 2011). All these findings warrant further research into potential cross-task differences in pause production – particularly in patients with MCI – as well as on the influence that methodological decisions such as minimum pause duration threshold, annotation method and cross-annotator validation strategies may bear on study results and the conclusions drawn from them.

In previous studies it has been pointed out that speech segments are not normally distributed and that, therefore, moments of the distribution – e.g. mean and variance – may be inadequate for the characterization of linguistic elements including words and speech pauses (Goldman-Eisler, 1961; Chien and Huang, 2003; Rosen et al., 2003; Rosen, 2005; Torre et al., 2017, 2019).

This line of research suggests that the lognormal distribution might be a more accurate approach to the description of speech pause duration distribution in human voice, showing consistency across studies and good sensitivity for identifying particular constraints such as distribution across discursive and syntactic boundaries or task type (Campione and Véronis, 2002; Goldman et al., 2010; Bailly and Gouvernayre, 2012). Its application to language-impaired groups in other neurological disorders such as vascular aphasia or ataxic dysarthria has confirmed these findings, revealing differences in duration and distribution between those patient groups and healthy controls (Rosen et al., 2003; Angelopoulou et al., 2018; Hird and Kirsner, 2010).

In this work we firstly endeavour the characterization of the distribution of speech pauses in AD, amnestic MCI and HC considering some limitations inherent to the segmentation of speech pauses such as higher relative errors on shorter ranges. For this purpose, we address the fitting of truncated distribution considering recent discussions on cut-off point selection on long-tail distributed data. In particular, we aim to show that patients with confirmed Alzheimer's dementia and amnestic multi-domain MCI patients with memory encoding deficits (a-mdMCI-E) at high risk of dementia progression produce significantly longer pauses and with more dispersion than healthy controls, as well as to determine the relative weight of long pauses in relation to their general pattern of pause production. Crucially, we expect to also find significant differences in pause duration and distribution between the group with a-mdMCI-E and their a-mdMCI counterparts with retrieval impairment only (a-mdMCI-R), since the former are more prone to AD progression that the latter. We discuss the validity of pause analysis in the prediction of MCI outcome in the AD spectrum, contributing to the refinement of the current clinical profile of MCI due to AD and to the race for non-invasive, low-cost diagnostic tools for dementia diagnosis.

## 1. Materials and methods

### 1.1. Participants

Patients were recruited prospectively and retrospectively through the Neurology units of the Hospital General de Hospitalet de Llobregat (Hospitalet de Llobregat), Hospital Moisés Broggi (Sant Joan Despí) and Hospital Clínico San Carlos (Madrid) during the period 2015 to 2019. Healthy controls included patients' relatives and volunteers. A total of 112 participants aged 58 to 91 were recruited for the purpose of this study. The recruitment and classification protocol is summarized in 1.

Probable AD diagnosis was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) and the National Institute on Ageing and Alzheimer's Association (NIA-AA) (McKhann et al., 2011) for the retrospective and prospective cohort, respectively. All patients included in this group ($n = 26$) had a Clinical Dementia Rating (CDR) (Hughes et al., 1982) score of 1.

56 subjects with MCI were diagnosed according to Petersen criteria (Petersen, 2004) in the initial cohort and NIA-AA criteria (Albert et al., 2011) for prospective participants. More specifically, patients were of the amnestic-multidomain MCI subtype (a-mdMCI) with a CDR score of 0.5. Patients in this group were further classified into two groups according to their memory impairment profile at the Rey Auditory Learning Test (RAVLT) (Rey, 1964). One subgroup displayed impaired delayed recall but normal recognition memory (deficit in retrieval processes, a-mdMCI-R, 28 participants), and the other one showed both impaired delayed recall and recognition memory (deficit in encoding processes, a-mdMCI-E, 29 participants) (Aggarwal et al., 2005). As explained in the introductory section, the latter pattern of impairment has been observed to be more prone to AD progression (Jacobs et al., 1995; Folstein et al., 1975). Follow-up of 16 of the 29 a-mdMCI-E patients and of 18 of the 28 a-mdMCI-R participants revealed that 10 (55%) of the former progressed to AD diagnosis within three years, whereas only one a-mdMCI-R patient (6%) followed the same course.

Additionally, 29 age-matched cognitively unimpaired participants, with no history of neurological disease and a minimum Mini Mental State Examination (MMSE) (Folstein et al., 1975) score of 25 were also recruited as healthy controls (HC). Confirmation of any other neurological condition, history of psychiatric disorder, alcohol abuse or the use of any medication or systemic disease that might justify the observed cognitive impairment was considered a motive for exclusion. None of the participants suffered any visual or hearing impairment that could affect their performance.

### 1.2. Standard protocol approval and patient consent

The study was approved by the Bioethics Committee of Universitat de Barcelona (*IRB00003099*), by the clinical research ethics committees of Hospital Clínico San Carlos (ref. *19/046-E*) and by the Consorci Sanitari Integral-Hospital Universitari de Bellvitge in the case of Hospital General de l'Hospitalet de Llobregat (ref. *19/43- PR222/19*). All participants signed a written informed consent form prior to enrolment in the study.

### 1.3. Neuropsychological protocol

Patient assessment included, in addition to MMSE (Folstein et al., 1975) and the Rey Auditory Verbal Learning Test (Rey, 1964), the 60-item version of the Boston Naming Test (BNT) (Kaplan and Goodglass, 1983), direct and reverse WAIS digits and Block Design test (Wechsler, 1997), category (animals) and letter fluency (letter p), the clock-Drawing test (Sunderland et al., 1989) and Poppelreuter's Overlapping Figures Test (Della Sala et al., 1996). Biographic memory was evaluated by means of a five-item questionnaire requesting two important dates – usually a wedding and a relative's birthday – and the names of three famous people. During the same testing session participants were asked to complete the picture description task of the Bilingual Aphasia Test (Paradis, 1987), based on a simple six-picture story depicted on a single sheet of paper (see Fig. 1). Participants were asked to provide as many details as possible about the pictures while encouraged to shape their speech into the form of a narrative rather than imparting static descriptions of independent frames. Testing sessions were held at the practitioners' office in hospital and oral narratives were recorded by means of a SONY IICDSX78 recorder at a sampling frequency of 44.1 kH.

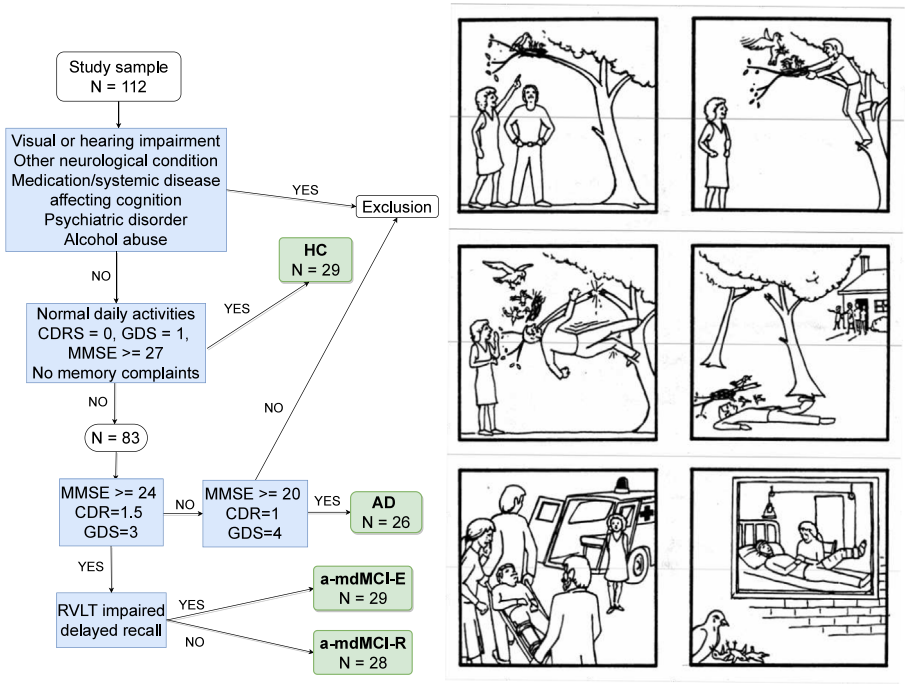


**Fig. 1.** (Left) CONSORT diagram where the protocol described is common to both the retrospective and prospective cohorts. (Right) Picture description task, Bilingual Aphasia Test, (Paradis, 1987).

**Table 1**
Demographic information.

| | HC | a-mdMCI-R | a-mdMCI-E | AD | Omnibus test | Pairwise comparisons |
|---|---|---|---|---|---|---|
| Female \| Male | 21\|8 | 20\|8 | 19\|10 | 18\|8 | – | – |
| Age (yrs.) | 76 ± 8 | 75 ± 7 | 76 ± 5 | 81 ± 6 | 4.59[a] | AD > HC, a-mdMCI-R |
| Education (yrs.) | 8.1 ± 2 | 6.8 ± 2.8 | 6.1 ± 2.9 | 5.6 ± 2.5 | 16.11[b] | HC > a-mdMCI-E, AD |
| MMSE | 29 ± 1.2 | 27.4 ± 2.3 | 25.4 ± 2.6 | 22 ± 2.6 | 64.23[b] | HC > a-mdMCI > AD |

Including Healthy Controls (HC), amnestic multimodal MCI group with memory encoding deficits and a high proportion of AD converters (a-mdMCI-E), MCI with only memory retrieval issues (a-mdMCI-R) and AD patients (AD).
[a]Bonferroni and Tukey/Tamhane corrected one-way ANOVA followed by two-independent sample T test if applicable.
[b]Bonferroni and Dunn corrected K samples Kruskal–Wallis test followed by Mann–Whitney U if applicable. All test performed significantly with $p < 0.05$.

### 1.4. Participant characteristics

Participant mean age was 76 ± 7 years of age and mean years of education was 6 ± 3 years. Patients in the AD group were significantly older (81 ± 6) than HC (76 ± 8) and both the a-mdMCI-R (75 ± 7) and the a-mdMCI-E (76 ± 5) groups, $F(3, 111) = 4.58$, $p < 0.05$. There were significant differences in years of education across groups ($H(3) = 16.11$, $p < 0.05$) since AD patients (5.6 ± 2.5) and participants in the a-mdMCI-E group (6.1 ± 2.9) had significantly less years of education than HC (8 ± 2). MMSE scores differed significantly ($H(3) = 64.23$, $p < 10^{-3}$), with individuals with AD obtaining the lowest mean score (21.8 ± 2.5), which was significantly lower than that of HC (29 ± 1.2), a-mdMCI-R patients (27.4 ± 2.3) and individuals with a-mdMCI-E (25.5 ± 2.6). a-mdMCI-E patients scored significantly lower than HC at MMSE (Bonferroni correction and Dunn post hoc test, $p < 10^{-3}$). More detailed information on the demographic characteristics of the sample are provided in Table 1.

### 1.5. Neuropsychological profile

Regarding the two a-MCI groups, statistically significant differences were observed concerning general cognitive performance and verbal memory. Thus, patients with a-mdMCI-E performed significantly worse than subjects with a-mdMCI-R at MMSE and RAVLT, with the former obtaining significantly lower total and delayed recall scores. No significant differences were found between the two groups in any other cognitive domain as per their scores at BNT, WAIS digit span (direct and reverse), semantic and phonological fluency, WAIS III blocks, Clock Drawing Test, Poppelreuter's Overlapping Figures Test and remote memory. Patients with AD performed significantly worse than patients in the two a-MCI groups at every test except the two WAIS digits tasks, where no differences were observed amongst the groups of study. Full details and pairwise comparison results are provided in Table 2.

### 1.6. Data acquisition and segmentation

Oral narratives were processed in Praat (Boersma and Weenink, 2007) at the same sampling frequency used for audio collection. Audios were transcribed and annotated manually by the first author to allow pause tally and duration extraction by means of a script designed ad hoc.

Pauses were defined as any filled or silent interruption of the speech flow that could not be identified as a linguistic item (such as a disfluency) or as a false start. Filled pauses were thus standardized place-holders that were not lexicalized such as "uhm" or "erm", as opposing filler expressions such as "bueno" ("well") or the strategic lengthening of conjuctions, which were labelled as fillers and included in the disfluency tally. While some authors consider these vocalized pauses disfluencies (López-de Ipiña et al., 2018; Buchanan et al., 2014) or fillers (Verfaillie et al., 2019; Fraundorf and Watson, 2013; Clark and Fox Tree, 2002), most studies in the speech and dementia literature

**Table 2**
Neuropsychological profile.

| | a-mdMCI-R | a-mdMCI-E | AD | Omnibus test | Pairwise comparisons |
|---|---|---|---|---|---|
| RAVLT-total | 26 ± 6.9 | 21.6 ± 6.5 | 15.4 ± 4.9 | 19.31[a] | a-mdMCI-R > a-mdMCI-E > AD |
| RAVLT-delayed | 3.7 ± 2.2 | 0.6 ± 1.3 | 0.08 ± 0.39 | 51.1[b] | a-mdMCI-R > a-mdMCI-E, AD |
| WAIS (direct) | 4.4 ± 0.6 | 4.2 ± 0.5 | 4 ± 0.8 | 5.83[b] | – |
| WAIS (reverse) | 2.7 ± 0.9 | 2.8 ± 0.7 | 2.4 ± 0.6 | 3.63[b] | – |
| BNT | 48.9 ± 4.6 | 46.3 ± 3.5 | 34.6 ± 5.9 | 67.60[a] | a-mdMCI-R, a-mdMCI-E > AD |
| Poppelreuter | 10 ± 0 | 10 ± 0 | 9.7 ± 0.5 | 13.99[b] | a-mdMCI-R, a-mdMCI-E > AD |
| Clock Drawing Test | 3.6 ± 0.8 | 3.6 ± 0.8 | 2 ± 1.3 | 28.62[b] | a-mdMCI-R, a-mdMCI-E > AD |
| WAIS block design | 20.9 ± 9.6 | 18.5 ± 8.9 | 12.1 ± 6. | 7.04[a] | a-mdMCI-R, a-mdMCI-E > AD |
| Letter fluency | 8.3 ± 3.8 | 9.2 ± 4.2 | 5.7 ± 3.1 | 11.69[b] | a-mdMCI-R, a-mdMCI-E > AD |
| Category fluency | 10.1 ± 4.8 | 10.8 ± 4.5 | 6.8 ± 2.6 | 7.3[a] | a-mdMCI-R, a-mdMCI-E > AD |

[a]Bonferroni and Tukey/Tamhane corrected one-way ANOVA followed by two-independent sample T test if applicable.
[b]Bonferroni and Dunn corrected K samples Kruskal–Wallis test followed by Mann–Whitney U if applicable. All test performed significantly with $p < 0.01$ except WAIS (direct) with $p \sim 0.54$ and WAIS (reverse) with $p \sim 0.16$.

**Table 3**
Speech data.

| | HC | a-mdMCI-R | a-mdMCI-E | AD | Omnibus test | Pairwise comparisons |
|---|---|---|---|---|---|---|
| Total number of words | 149.9 ± 71.2 | 132.9 ± 97.9 | 133.3 ± 76.8 | 142.6 ± 56.3 | – | – |
| Relevant words | 146.6 ± 58.0 | 128.9 ± 70.7 | 127.9 ± 53.6 | 129.9 ± 42.4 | – | – |
| Total number of pauses | 35.6 ± 25.3 | 35.0 ± 33.0 | 28.9 ± 14.4 | 34.0 ± 15.7 | – | – |
| Number of filled pauses | 2.8 ± 3.0 | 2.2 ± 1.5 | 1.9 ± 1.5 | 1.6 ± 1.1 | – | – |
| Total locution time | 72.3 ± 41.5 | 70.7 ± 57.6 | 63.6 ± 32.7 | 74.02 ± 28.6 | – | – |
| Total silence time | 26.2 ± 18.9 | 30.0 ± 27.3 | 25.8 ± 13.7 | 35.2 ± 18.4 | – | – |
| Verbal rate | 2.2 ± 0.5 | 2.1 ± 0.4 | 2.1 ± 0.5 | 2.0 ± 0.5 | – | – |
| Transformed phonation rate | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.8 ± 0.1 | 14.65** | HC > a-mdMCI-E, AD |
| Standardized phonation time | 3.3 ± 0.4 | 3.3 ± 0.5 | 3.5 ± 0.5 | 3.7 ± 0.4 | – | – |
| Standardized pause rate | 4.8 ± 1.7 | 4.7 ± 2.0 | 4.8 ± 1.4 | 4.4 ± 1.3 | – | – |

*Bonferroni and Tukey/Tamhane corrected one-way ANOVA followed by two-independent sample T test if applicable. **Bonferroni and Dunn corrected K samples Kruskal–Wallis test followed by Mann–Whitney U if applicable.
*Total n of words* is the raw count of words including disfluencies (repetitions, repaired and abandoned sequences); *relevant words* exclude disfluencies and utterances that are not task-relevant; *total locution time* is the sum of all the phonation and pause segments in the recording; *total silence time* is the sum of pause time only; *verbal rate* is the result of total number of words uttered divided by total locution time; *transformed phonation rate* is the arcsine of the result of dividing total phonation time by total locution time; *standardized phonation time* is obtained by dividing total number of words by total phonation time, and *standardized pause rate* is the result of dividing total number of words by number of pauses.

count them as filled pauses when explicitly described (Toth et al., 2018; Gosztolya et al., 2019; Pakhomov et al., 2010).

The lower temporal threshold for pause segmentation was set at 50 milliseconds (ms) for several reasons. Firstly, due to the unavailability of soundproof rooms in the participating hospitals that could guarantee optimal recording conditions. Secondly, transcription and annotation were done manually. Previous research on the human minimal perception threshold for pauses occurring in the speech flow have situated this limit at a minimum of approximately 300 ms for accurate pause detection (Duez, 1985; Chiappetta et al., 1987) and optimal interrater agreement (Wang et al., 2012). However, non-phonetic pauses – that is, those originated by speech planning processes and not due to articulatory phenomena – have been identified at durations as low as 100 ms (but not below that cut-off point) (Matzinger et al., 2020). These limitations motivated the assessment of interrater reliability at different lower thresholds in an attempt to establish a non-arbitrary cutoff point that ensures maximum data integrity and adequacy in 2.1 below. A summary of several speech fluency metrics (Singh et al., 2001) is provided in Table 3.

### 1.7. Interrater agreement

With the purpose of testing the coherence and replicability of the annotation system 10% of the original 112-narrative corpus (10 narratives) were transcribed and annotated by the fifth author. Comparison of word-by-word transcriptions reached an agreement level of 97.5%, whereas interrater agreement at pause identification was 99.04%. The mean absolute difference of duration measures between the two annotators was 17 ms with a Pearson correlation coefficient of 0.99.

### 1.8. Truncated distributions

Following previous work (Torre et al., 2019), we here consider three possible candidate families of long tail probability density distributions, being all of them defined with two parameters: Lognormal distribution (LND), Gamma distribution and Weibull distribution. LND is known to be generated by multiplicative processes but also additive processes when some conditions are met, as seems recently shown to happen in speech (Torre et al., 2019). LNDs are present in many natural systems (Crow and Shimizu, 1987) and have as a property that, being $X$ an independent continuous random variable generated by a LND, then the logarithm of $X$ is normally distributed. LND, Gamma and Weibull distribution functions are defined as follows:

(i) Lognormal distribution:

$$LND(x;\mu,\sigma) = \frac{1}{x\sigma\sqrt{2\pi}} e^{-\frac{(\ln(x)-\mu)^2}{2\sigma^2}} \quad (1)$$

(ii) Gamma distribution:

$$Gamma(x;k,\theta) = \frac{1}{\Gamma(k)\theta^k} x^{k-1} e^{-\frac{x}{\theta}} \quad (2)$$

being $\Gamma$ the gamma function.

(iii) Weibull distribution:

$$Weibull(x;k,\lambda) = \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} e^{-\left(\frac{x}{\lambda}\right)^k} \quad (3)$$

A truncated probability distribution is a distribution whose observations are reduced to some specific range. This technique is particularly useful when it is not possible to have reliable samples for the entire range but the underlying generating dynamic is expected to remain stable, so that the full distribution can be fitted into the

truncated observed range. This may be the case for speech segmentation, where shorter samples are subject to higher uncertainty due to factors including Automatic Speech Alignment limitations (Hernández-Fernández et al., 2019), manual segmentation bias (Torre et al., 2019) and speaker-driven mixed statistical artifacts (see SI in Torre et al., 2019).

### 1.9. Statistical analysis

Omnibus between-group differences were assessed using one-way ANOVA or Kruskal–Wallis tests as appropriate, followed by pairwise testing with Student $T$ or Mann–Whitney U where applicable.

Lower cut-off point selection when fitting long tail distributions – as those that appears in speech pause duration – is a challenge that has been widely discussed over the last years (Clauset et al., 2009). In this regard, there has been some agreement on fitting the parameters of the distribution by maximum likelihood estimation (MLE) (Eliason, 1993) and using Kolmogorov–Smirnov distance for cut-off point selection (Pawitan, 2001). First, for model selection we pick several lower cut-off candidates and fit by MLE the three families of probability density function with the two parameters explained above (Lognormal, Weibull and Gamma). Then Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were used for model selection. Goodness of fit is checked by Kolmogorov Smirnov (KS) testing as to whether reject the distribution or not at the significance level of $p = 0.05$.

Then, we refine the search for the lower cut-off point for the Lognormal distribution by using the method proposed by Corral and González (2019), which is a modified version of Clauset et al. (2009). The procedure is as follows. (i) First pick any lower cutoff threshold value, (ii) Fit, by MLE the truncated lognormal distribution to the range $x >$ threshold. This lead to the fitted parameters $\mu$ and $\sigma$. (iii) Compute Kolmogorov–Smirnov distance $D$ between the theoretical distribution with estimated parameters and the real data. (iv) Stochastically generate the same number of samples but from the fitted distribution. (v) Compute Kolmogorov–Smirnov distance $D_r$ between stochastic data and the theoretical distribution. (vi) Repeat 1000 times steps iv and v counting the number of times where $D_r < D$. Repeat this process for different lower cut-off points and select the one where $D_r < D$ happens fewer times. Note that Clauset et al. (2009) showed that there will be a minimum.

## 2. Results

### 2.1. Speech pause duration distribution analysis

We fit pause duration observations from each patient group into three possible theoretical truncated distributions using MLE: Lognormal (LND), Gamma, and Weibull. We use goodness of fit AIC and BIC for model selection (where the lowest the better, see Table 4), confirming that, for all cases, pause duration distribution is better explained by a LND. These results are in line with previous reported analysis in speech (Torre et al., 2019; Hernández-Fernández et al., 2019).

Lower cut-off point has been calculated following the procedure explained in Section 1. Inset panel of Fig. 2 shows that there is a minimum on the times that $D_r < D$ ($\rho$) at 160 ms which will be chosen as lower threshold. Moreover, main panel of Fig. 2 shows the mean relative error between speech pause annotations (blue bars and line) is drastically reduced for speech pauses longer than approximately 150 ms, while interrater disagreement (1-interrater agreement) rapidly decreases for pauses longer than 100 ms. Total number of pauses for each group after the truncation is reflected in Table 4, being 736 for HC, 679 for a-mdMCI-R, 618 for a-mdMCI-E and 669 for AD.

In addition to this, Kolmogorov Smirnov testing confirms the goodness of fit of the LND at a 95% confidence interval. This can be observed in Fig. 3 with the empirical probability of pause duration distribution

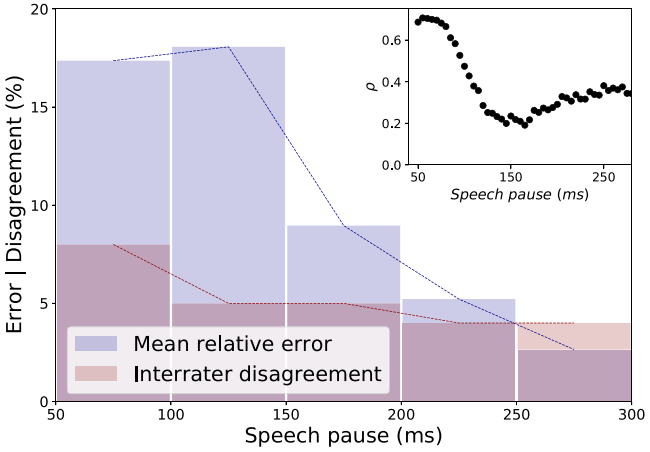


**Fig. 2.** Relative error, interrater disagreement and lower cut-off point estimation. Interrater disagreement (1-interrater agreement) quickly decreases after 100 ms, while mean relative error of speech pauses that coincide between annotators is quickly reduced after 150 ms. The inset panel shows cut-off point selection where $\rho$ reach a minimum at 160 ms (Clauset et al., 2009; Corral and González, 2019). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
LND parameters and goodness of fit.

| | LND | | | Goodness of fit AIC \| BIC | | |
|---|---|---|---|---|---|---|
| | Samples | $\mu$ | $\sigma$ | LND | Gamma | Weibull |
| HC | 736 | $-0.56 \pm 0.03$ | $0.75 \pm 0.02$ | 779 \| 789 | 792 \| 801 | 794 \| 803 |
| a-mdMCI-R | 679 | $-0.51 \pm 0.03$ | $0.85 \pm 0.03$ | 992 \| 1000 | 979 \| 988 | 979 \| 988 |
| a-mdMCI-E | 618 | $-0.42 \pm 0.04$ | $0.86 \pm 0.03$ | 958 \| 967 | 977 \| 987 | 974 \| 983 |
| AD | 669 | $-0.36 \pm 0.04$ | $0.92 \pm 0.03$ | 1241 \| 1250 | 1272 \| 1281 | 1264 \| 1273 |

(Left) Estimated LND parameters ($\mu$, $\sigma$) for speech pause duration distributions in each patient group and truncated below 160 ms. (Right) AIC and BIC goodness of fit for different alternative distributions (the lower the AIC and BIC the better). All tested distributions are defined by two parameters and within each patient group they are evaluated under the same conditions, so goodness of fit values can be used for model selection. For almost all cases LND is the most plausible distribution and in all cases LND passes the Kolmogorov Smirnov goodness of fit test at a 95% confidence level.

represented in bars for each group and their fitted truncated LND with solid lines. For the sake of clarity we also provide log-linear representations in the inset panels, where the shape of the LND turns to Gaussian. Estimated LND parameters are listed in Table 4, showing that:

$$\mu: \quad HC < a-mdMCI-R < a-mdMCI-E < AD \tag{4}$$

$$\sigma: \quad HC < a-mdMCI-R < a-mdMCI-E < AD \tag{5}$$

where $\mu$ represents in LND the multiplicative mean and $\sigma$ is related to more sparse samples, clearly showing that the HC group has a higher probability of making short pauses with a lesser deviation than AD patients (Table 4), being mild cognitive impairment groups between them with a-mdMCI-E closer to AD.

Finally, in Fig. 4 we represent truncated LNDs with estimated parameters for each group revealing that HC shows higher likelihood of making pauses at range 200 ms – 700 ms in relation to their total pause production than the AD group, with firstly a-mdMCI-E and subsequently a-mdMCI-R interestingly standing between AD and HCs in the probability gradation. This is just the opposite at longer ranges ($t >$ 1.5 s), where AD patients reveal higher probability than HCs to make long pauses, with the two a-mdMCI groups again performing mid-range and a-mdMCI-E participants displaying a more resembling performance to that of AD patients. Dotted lines represent the continuation of the LNDs out of the truncated range and inner panels express the same results through their log-linear representation.

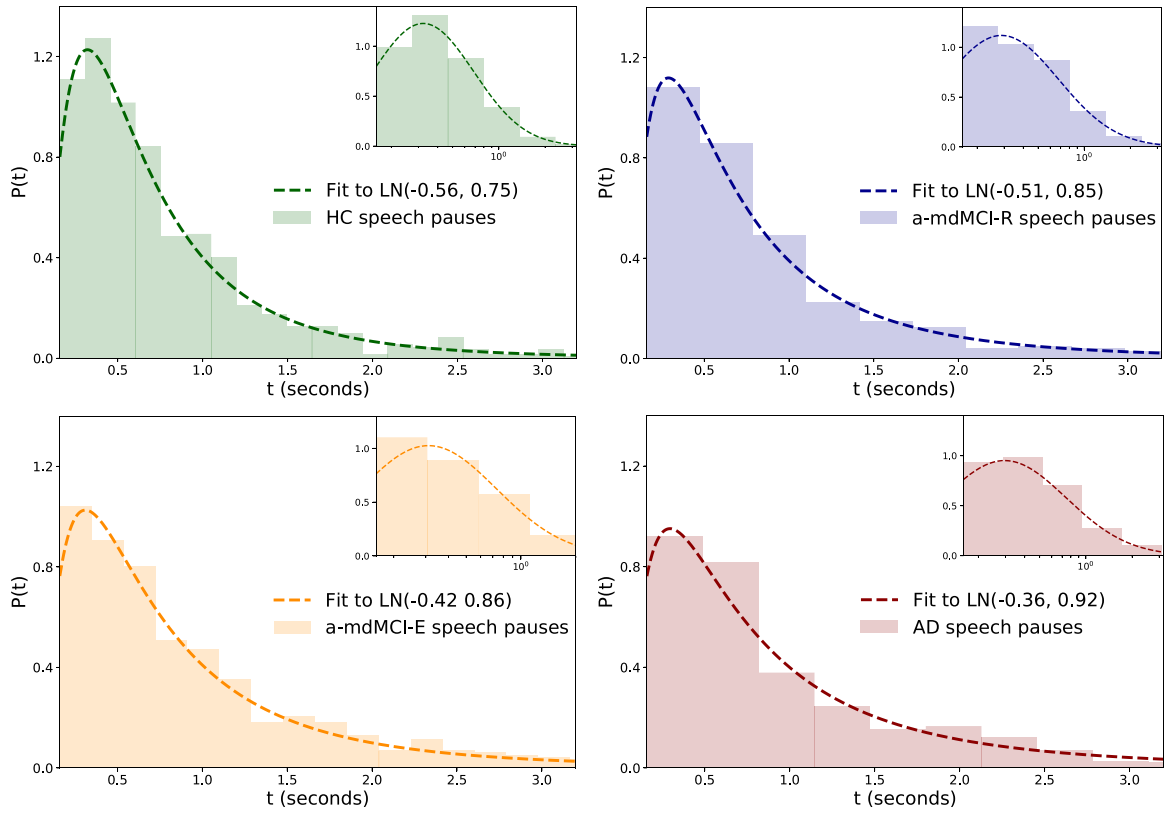


**Fig. 3.** Probability time duration distribution of pauses in each group. For each patient group, the main panel shows in linear axes the probability time duration distribution of pauses – bar representation – and the ML fitted truncated LND. The inner panels are a visual representation of the same results with logarithmic binning and log-linear axis.

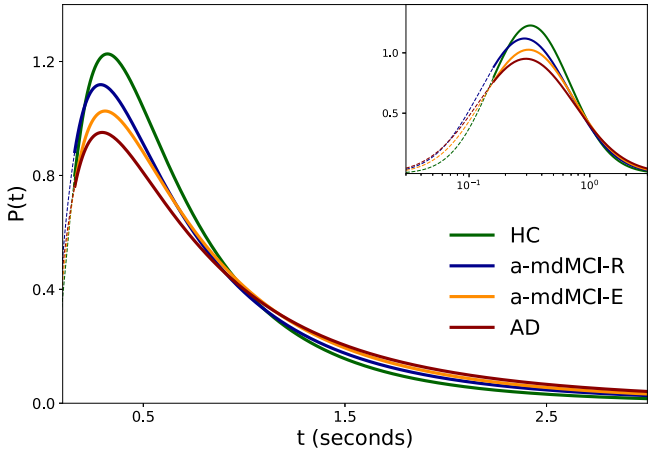


**Fig. 4.** Comparison of time duration distribution between controls and patients groups. The main panel displays the truncated LND-fitted time duration distribution for each group. The HC group shows a higher probability of making short pauses (200–600 ms) than the AD group, while AD patients show the opposite pattern with a higher probability of making long pauses (1.5 s–2.5 s) than HC (tail of the distribution). Interestingly, a-mdMCI-E and a-mdMCI-R always stand in the middle of the continuum for both pause types. Solid lines represent the range with reliable observations, while the dotted line represents the continuation of the LND to shorter timescales. The inner panel shows the same results on the log-linear axis.

Two sided Kolmogorov–Smirnov testing has been used under the null hypothesis that different group samples come from the same distribution and that differences are due to stochastic variations, confirming in all paired cases that differences are significant, therefore rejecting the null hypothesis (see Table 5).

**Table 5**
Two sided KS test between groups.

| | KS test |
|---|---|
| HC-amdMCIr | $p < 0.05$ |
| HC-amdMCIe | $p < 10^{-3}$ |
| HC-AD | $p < 10^{-3}$ |
| amdMCIr-amdMCIe | $p < 0.05$ |
| amdMCIr-AD | $p < 10^{-3}$ |
| amdMCIe-AD | $p < 10^{-3}$ |

## 3. Discussion

We have characterized the probability density distribution of speech pauses in AD, healthy controls, and two a-mdMCI groups with differential memory impairment profiles, being able to show significant differences across all groups. A gradation has been found in the parameters and shape of the LNDs from AD to HCs, with a-mdMCI-E and a-mdMCI-R standing in the middle of the continuum between those groups (inequations 4 and 5). Moreover, this issue has been addressed in a censoring context affecting shorter pauses which, as it has been shown, lack the reliability of longer pauses in terms of interrater agreement. For this purpose, we have considered the latest discussions on the fitting of long-tailed distributions (Clauset et al., 2009; Corral and González, 2019), successfully recovering LNDs for pauses longer than 160 ms.

Previous discussions addressing the use of this distribution type have proposed temporal thresholds differentiating short pauses from long speech pauses setting this barrier at 268 ms (Hird and Kirsner, 2010), 323 ms (Rosen et al., 2010) or more recently at 338 ms (Angelopoulou et al., 2018). However, other authors have suggested up to three pause types: short (<200 ms), intermediate (200 – 1000 ms) and long pauses (>1000 ms) (Campione and Véronis, 2002). The classification of "short" and "long" pauses was long reduced to a conceptual

discussion about articulatory and/or respiratory (short) pauses on the one hand, and (long) cognitive pauses on the other (Goldman-Eisler, 1972; Dalton and Hardcastle, 1989). This theoretical positioning has long gone undisputed – save for some exceptions, see Hieke et al. (1983) and Picheny et al. (1986) – but is currently under question as technical improvements allow for more precise location and measurement of pauses (Angelopoulou et al., 2018; Rosen et al., 2010) and, importantly, advances in other fields are helping to dilucidate their functional and communicative nature. In this vein, experiments applying functional magnetic resonance imaging during speech production have shown differential brain activity depending on whether pauses took place at syntactic junctions or within grammatical constituents (Kircher et al., 2004; Ramanarayanan et al., 2009). The use of electromagnetic articulometry during a reading task has also revealed pause-specific articulatory postures occurring at utterance boundaries whose frequency and kinematic features are linked by the authors to utterance planning purposes (Krivokapic et al., 2020).

Pause duration distribution in speech is adequately explained with a LND that can be inferred with the help of truncated distributions, even when information on shorter ranges is incomplete or censored. To the best of our knowledge, this is the first study where the shape of the lognormally-fitted pause duration distribution is used in the classification of different groups with cognitive impairment in the context of AD. More concretely, the shape and parameters of the LND allow the detection of significant differences in the probability distribution of pauses according to duration across all groups of study (HC, a-mdMCI and AD patients). This pause duration distribution reveals the existence of a continuum from the group with the highest probability of producing short pauses (HC) to the group with the highest probability of making long pauses (AD patients), with a-mdMCI-R performing in the range between HCs and a-mdMCI-E and the latter showing a production pattern more resemblant to that of AD (Fig. 4). The confirmation of a higher likelihood to produce more long pauses and less short pauses for those in the group with higher probability of AD progression (a-mdMCI-E) in comparison to the a-mdMCI-R group suggest a new promising tool for dementia prognosis that should be addressed in further studies.

The finding that patients with a-mdMCI-E produce significantly longer pauses with more variance than HC confirms our initial hypothesis and is in line with previous findings (Toth et al., 2018; Beltrami et al., 2018; Pistono et al., 2016). The gradation found along the AD spectrum and more specifically within the a-mdMCI subtype initially suggests a central role of memory degradation as reflected in the impaired delayed recall and recognition observed in the a-mdMCI-E group in comparison to a-mdMCI-R. Previous studies including correlation analyses of neuropsychological scores and pause duration suggest that longer pause durations arise from difficulties in the retrieval of relevant information from episodic anterograde memory both in AD (Pistono et al., 2019) and in MCI due to AD (Pistono et al., 2016), a cognitive domain particularly affected in AD that is compatible with the impaired encoding and consolidation processes observed in our a-mdMCI-E participants.

The fact that other studies using memory-taxing speech tasks failed to find significant differences in mean pause duration (Beltrami et al., 2018; Roark et al., 2011) invites for further enquiry as to criteria for pause labelling and analysis. Our picture description task (Paradis, 1987) does not exert the same level of demand on recent anterograde memory while still managing to capture fluency impairments in a-mdMCI patients, in line with previous studies also implementing picture description tasks (Beltrami et al., 2018; Sluis et al., 2020; Fraser et al., 2019; Mueller et al., 2018b). In light of this evidence and considering the well documented constellation of semantic and lexical processing deficits in AD (Duong et al., 2006; Gardini et al., 2015; Joubert et al., 2008; Pineault et al., 2018; Taler et al., 2019), our results suggest a generalized, more profound deterioration of the memory system from the preclinical stages of Alzheimer's disease. Our elicitation task successfully taps onto these emerging deficits by imposing a controlled lexico-semantic setting that is also demanding on working memory for discourse building and task maintenance, testing other dimensions of memory in addition to episodic anterograde memory and verbal learning, – which are clearly impaired in these patients – avoiding thus circularity in their diagnosis, which is already based on verbal memory assessment. In MCI the fluency factor is highly correlated with memory measures but to an even greater degree with BNT score (a picture-based test of lexical and semantic memory integrity) (Fraser et al., 2019). However, another study failed to find such correlations between fluency parameters and psycholinguistic measures in very early MCI (Mueller et al., 2018b). These differences may be the reflection of different stages of the progressive degradation of memory and language that takes place in AD, that in the case of our a-mdMCI-E sample would be at a more advanced phase given their neuropsychological profile and the fact that a considerable number of these individuals progressed to Alzheimer's dementia within three years (see 1.1 above). Our two a-mdMCI groups only differed significantly in their memory and pause profile while there were no significant differences in number of months since MCI diagnosis, which suggests that they represent two distinct subtypes with not only differential progression rates, but also eventual outcome and, therefore, prognosis.

Some important limitations of this study are sample size and the significant differences found in years of education between the a-mdMCI-E and AD groups compared to a-mdMCI-R and HC, which might have had confounding effects on our findings. Larger group sizes with balanced educational backgrounds and the inclusion of biomarkers for patient classification are necessary to confirm the diagnostic and prognostic validity of these measures, which thus far we consider very promising while addressing some key methodological issues in the field.

While LNDs are very common manifestation in natural sciences, the particular generative process involved in showing this manifestations in speech pause distributions are still not known. Further than being the reminiscence of an unknown multiplicative process, they could be the result of an additive process under some specific constrains (Torre et al., 2019) or a pattern result of specific neural activity (Buzsáki and Mizuseki, 2014). However, further studies should be carried out in order to fully understand production processes and how their alterations may relate to health disorders. Future studies should also consider the inclusion and comparison of different speech-eliciting tasks in order to clarify the role of memory in the linguistic behaviour of patients in the AD spectrum and evaluate the relative weight of other deficits that might also be at play, in addition to confirming the applicability of this methodology in the design of tests that may serve as early low-cost markers in dementia detection.

## 4. Reproducibility and replicability

The speech pause duration corpus used in this study and scripts that ensure reproducibility of all results are public available in https://github.com/ivangtorre/Speech-pause-distribution-as-an-early-marker-for-Alzheimers-disease and https://github.com/PatriciaPast/Speech-pause-distribution-as-an-early-marker-for-Alzheimers-disease. The full complete corpus may be accessible under some considerations upon request to the main author. *Python 3.8.2* and *R 3.6.3* have been used for the analyses. MLE fit, Kolmogorov–Smirnov AIC and BIC make use of *fitdistrplus 1.1.1* and *truncdist 1.0.2*. *Numpy*, *Pandas* and *Matplotlib* libraries have also been used. Some other statistical analyses were performed on *IBM SPSS 25.0*.

Replicability of the study is addressed through Section 1 (*Material and Methods*) of the present paper.

## CRediT authorship contribution statement

**Patricia Pastoriza-Domínguez:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Data curation, Software, Funding. **Iván G. Torre:** Conceptualization, Methodology, Formal analysis,

Writing – original draft, Data curation, Software, Visualization, Funding. **Faustino Diéguez-Vide:** Supervision, Funding. **Isabel Gómez-Ruiz:** Resources, Data curation, Supervision. **Sandra Geladó:** Validation. **Joan Bello-López:** Resources. **Asunción Ávila-Rivera:** Resources. **Jordi A. Matías-Guiu:** Resources, Data curation. **Vanesa Pytel:** Data curation. **Antoni Hernández-Fernández:** Conceptualization, Writing – review & editing, Supervision, Funding.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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