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Acoustic Markers Associated with Impairment in Language Processing in Alzheimer's Disease

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This study broaches in a novel way the analysis of cognitive impairment characteristic of the early stages of Alzheimer's Disease (AD). Specifically, we attempt to determine the acoustic speech parameters that are sensitive to the onset of the disease, and their association with the language deficit characteristic of AD. Speech analysis was carried out on 21 elderly patients with AD using *Praat* software, which analyzes the acoustic components of speech. The data obtained were subjected to stepwise regression, using the overall scores obtained in the test as the criterion variable, and the scores on the frequency, amplitude and periodicity variables as predictors of performance. We found that the percentage of voiceless segments explains a significant portion of the variance in the overall scores obtained in the neuropsychological test. This component seems to be related mainly to the patient's ability in phonological fluency. This finding could permit the creation of a diagnostic test for AD through analysis of the acoustic speech parameters at very low cost in terms of both time and resources.
Keywords: Alzheimer, phonology, speech, verbal fluency.

El estudio aborda una manera novedosa el análisis de los deterioros cognitivos característicos de las primeras fases de la Enfermedad de Alzheimer (EA). En concreto, se pretende determinar los parámetros acústicos del habla sensibles al inicio de la enfermedad, y su asociación con el déficit lingüístico característico de la EA. Realizamos un análisis del habla a 21 mayores con EA, por medio del *software Praat* que analiza los componentes acústicos del habla. Los datos obtenidos se analizaron mediante la técnica de regresión paso a paso, con las puntuaciones globales obtenidas en las diferentes pruebas neuropsicológicas como variable criterio, (entre otras el test de Cuetos-Vega de procesamiento lingüístico) y las puntuaciones en las variables de frecuencia, amplitud y periodicidad del sonido como predictores de su ejecución. Obtuvimos que el porcentaje de segmentos sordos explica una parte significativa de la varianza de la puntuación global obtenida en la prueba neuropsicológica. Este componente parece estar relacionado, principalmente, con la capacidad de fluidez fonológica del paciente. Esto podría permitir la elaboración de una prueba de diagnóstico de la EA a través del análisis de los parámetros acústicos del habla con un coste temporal y material muy bajo.
Palabras clave: Alzheimer, fonología, alocución, fluided verbal.

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Early detection of AD is determined by the predictive ability of the variables used in the making of diagnostic tests (Ferri et al., 2005). These variables have usually been defined based on preclinical symptomatology related to semantic memory and verbal fluency tasks (Pérez-Martínez, Baztán, González-Becerra, & Socorro, 2005). Both of these cognitive variables are very sensitive to the impairment observed in the early stages of AD (Cuetos-Vega, Menéndez-González, & Calatayud-Noruega, 2007; Peraita, Galeote, & González, 1999), a sensitivity that is reflected in the high demand for consultations motivated by problems involving word forgetting and language fluency in elderly individuals. For this reason, attempts have been made recently to design tests that are quick and easy to apply for screening AD and are considered reliable and valid according to neuropsychological examination. A recent article presents a test that fulfills these criteria. The test by Cuetos-Vega et al. (2007; hereafter CVT), allows us to discriminate patients with AD from individuals with Mild Cognitive Impairment (MCI) and healthy individuals, with a high degree of sensitivity and specificity. This is especially important given the well known difficulty involved in differentiating patients with AD from persons with MCI using only episodic memory tests -which can only differentiate the degree and significance of episodic memory impairment in patients with AD- (Valls-Pedret, Molinuevo, & Rami, 2010). This is why many researchers (among others, Frutos-Alegría, Moltó-Jordà, Morera-Guitart, Sánchez-Pérez, & Ferrer-Navajas, 2007; Petersen et al., 1999) defend the need to use other cognitive and/or functional abilities to make a differential analysis of these two etiologies in the pre-dementia stages of the disease, especially in older individuals with MCI who already have or will subsequently have AD.

The CVT is a short battery composed of 10 memory and language tests. As its authors conclude, the language tests it includes have been shown to have greater discriminating value for AD in the early stages of the disease (verbal fluency and object naming) than the episodic memory tests usually employed, even though the language tests in the CVT are not specific to language processing but rather basically assess semantic memory. This is a logical supposition, given that classic studies describe the language of patients with AD in the early stages as fluent, articulated speech with adequate repetition, preserved motor aspects both at the phonological and the morpho-syntactic levels (Emery, 1988) and preserved reading aloud (Bayles, 2003; Tomoeda & Bayles, 1993). Basically, speech would remain intact until the advanced stages of the disease unless there is damage or difficulty in accessing lexical semantic representations (Ullman, 2004).

Nevertheless, as early as 1907 Aloysius Alzheimer (Alzheimer, Forstl, & Levy, 1991) stated that whereas memory impairment in individuals with AD differs *quantitatively* from memory impairment in pathological aging, the traits of language impairment differ *qualitatively* and characterize the disease clearly. Pioneering studies examined spontaneous speech recorded from free conversations of patients with AD. Using normative parameters such as a count of the conversational interactions or examining phonological-articulatory impairment by means of prosodic transcriptions (Croot, Hodges, Xuereb, & Patterson, 2000; Hutchinson & Jensen, 1980) they found different early symptomatology in certain aspects of speech at the level of expression. Among others, they presented a lack of initiative as well as slowness, articulatory apraxia, exaggeratedly long phrases and sentences, paraphasia, anomie, scarce informative content owing to the use of vague and imprecise phrasing, low melodic level and low rhythm (Appell, Kertesz, & Fisman, 1982; Forbes-McKay & Venneri, 2005). As can be seen, most of these studies analyze comprehensive emotional prosody. The impairments found occur prior to and are more evident than those that affect other language abilities (Taler, Baum, Chertkow, & Saumier, 2008), and become more severe as the dementia progresses (Testa, Beatty, Gleason, Orbello, & Ross, 2001).

Other studies have highlighted the aphasic disorders characteristic of the early stages of AD (Faber-Langendoen et al., 1988). Logopenic Progressive Aphasia (LPA) associated with AD is a variant of Primary Progressive Aphasia (PPA), and they differ in that LPA does not present evident motor problems. Cognitive and neuro-imaging data provide evidence that this disorder may have its origin in impairment of the phonological loop function (Gorno-Tempini et al., 2008). The phonological loop would be in charge of actively maintaining verbal information by relating language information to working memory. LPA is characterized by a fluctuating and/or reduced output ratio, phonological errors, hesitation, overall simple, although normal, language, pauses in the access to frequent words, errors or slowing down in the comprehension of complex grammatical structures and impairment in the repetition of sentences (Kemper, Marquis, & Thompson, 2001).

All of these symptoms that seem to define the language of patients with AD stem from the presence of a major atrophy in the medial temporal lobe that may be present as from the prodromal phase of the disease. Moreover, its characteristic consequences could be detected by acoustic analysis of voice frequency, amplitude and periodicity, accompanied by time parameters such as the output ratios and hesitation. These prosodic variables can provide data about cognitive processes such as language planning, the structural organization of semantic memory, production (Hoffmann et al., 2010), word-naming (Tirado, Muñoz, Aguirre, Pineda, & Lopera, 2004) and access to lexico-sematic memory (Valls-Pedret et al., 2010). These speech variables have already been considered as prodromal biomarkers detectible in other disorders such as Parkinson's disease (Martínez-Sánchez, 2010), although the affection of the motor systems that control speech which is

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characteristic of Parkinson's Disease affects acoustic aspects such as the levels of fundamental frequency and are caused by rigidity in the muscles of the larynx. In contrast, these analyses have not yet been performed on patients with AD, in the consideration that factors associated with deficits in lexical accessing typical of AD will determine to a greater extent hesitations in voice output, changes in output ratios, and alterations in prosodic planning.

Thus, the aim of this study is to evaluate the characteristic traits of expressive language impairment in AD by regressing different acoustic voice parameters in patients with AD in its initial stages on their performance in memory and language tests obtained by applying CVT. We start from the hypothesis that the deficits in semantic memory and language reflected in the CVT by patients with AD will be significantly associated with changes that have taken place in their expressive prosodic phonetic parameters. In a regression analysis this relationship will become manifest in the powerful degree to which the acoustic parameters of language expression in patients with AD predict their deterioration in performance of language tasks based on semantic memory.

Method

Participants

A group comprising 21 (mean age = 80.68; *SD* = 5.79) *AD* patients over 60 years of age, whose native language was Spanish, with no history of drug or alcohol abuse or symptoms of depression (Geriatric Depression Scale *[GDS]* < 10). All of them were patients at the Centro de Referencia Estatal de Alzheimer y otras Demencias (CREA-IMSERSO) in Salamanca, Spain. All were diagnosed (NINCDS-ADRDA) with probable *AD* and GDS = 4 (mild AD). The patients were taking part in the Program for Integral Cognitive Activation in Dementias (PACID) of the CREA, and thus maintained their communicative system, and their ability to read and to follow instructions (mean score *MMSE* = 14.6; *SD*. = 8.31).

Materials

The temporal parameters of speech were recorded verbatim for examination. Recordings were made using professional Fostex FR-2LE monaural recording equipment, with 24 byte resolution and a sampling rate of 48 kHz, and an AKG D 3700 S microphone. The voice samples of all the participants were edited using the Praat 5.1.42 voice analysis program (Boersma & Weenink, 2010). Praat is a computer program that facilitates acoustic analyses, articulatory synthesis, statistical data processing, editing and manipulation of audio signals. When the recordings were finished they were converted to WAV format (transmission speed 705 kbps), using a file for each of the sentences.

All the participants underwent a neuropsychological evaluation focused on the study of language functions. CVT was applied (2007). This test has a high discriminating capacity for cognitive decline with sensitivity and specificity values of .960 and .86, respectively. It consists of 10 tasks, half regarding memory and half regarding language: 1) Semantic verbal fluency; 2) Phonological verbal fluency; 3) Naming by definition; 4) Object naming; 5) Verbal fluency with proper nouns; 6) Naming proper nouns; 7) Immediate recall of word list; 8) Immediate recall of personal information; 9) Delayed recall of word list; and 10) Delayed recall of personal data. Each task has maximum of 10 points, and overall scores can oscillate between 0 and 100 points.

As a control the Isaacs Set-Test was administered (Pascual-Millán et al., 1990). This is a semantic fluency test in which the patient is asked to say elements of colors, animals, fruit and cities over a three minute period, and then the number of words said per patient is analyzed. Another test of phonological fluency was added in which patients had to say words beginning with "*p*". This test has a sensitivity of 79% and a specificity of 82%. Also administered was the WAIS vocabulary subscale (Kaufman & Lichtenberger, 2006). This consists in asking for the meaning of a series of words until the patient fails in 5 consecutive words. It measures verbal fluency and the level of vocabulary handling, together with access to the meaning or semantic representation of words. The test has .80 reliability, although we do not have data as to its specificity and sensibility in the diagnosis of dementias.

Procedure

All the patients underwent individual neuropsychological evaluation in two sessions programmed on consecutive days. All the patients gave their informed consent to the evaluation according to the ethical protocol of the Center; the results of the dependent variables were never used in this study to make diagnostic decisions. In the first session they took the biographical information test, the MMSE (Folstein, Folstein, & McHugh, 1975), the Set-Test, the WAIS vocabulary test and the complete CVT consecutively; in the second session their voices were recorded. To record the acoustic voice parameters the patients were asked to read a series of sentences presented on a screen in 48 font size to make reading easier. The patients were asked to say the sentence aloud after reading it (delayed pronunciation task). They were asked to read what appeared on the screen and to complete the missing information loudly and clearly (e.g., "My name is..."). Subsequently there appeared another series of sentences that they had to repeat (e.g., "Everybody likes cats"), and finally the first paragraph of *Don Quixote* ("*El ingenioso hidalgo don Quijote de la Mancha*") by Miguel de Cervantes. The task took approximately two minutes.

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Acoustic analysis was carried out in order to obtain overall and local measures of the patients' speech-related parameters. To do so, prosodic analysis was performed with the procedure of automatic prosodic transcription employing the algorithms implemented by Mertens (2004), calculating the fundamental frequency (F_0) contours by means of Boersma's (1993) autocorrelation algorithms. Estimation of the prosodic profile was based on analysis of the melodic behavior of speech through stylization of the variation in the trajectory of the peaks and in the tonal perception of the F_0 of the vowel nucleus of the syllables. This stylization is carried out exclusively by analyzing the increases and decreases (peaks and valleys) in F_0 on the intensity of the vowel segments. The vowel nucleus was estimated by establishing a peak of intensity bounded on the left and right by –3dB and –9dB, respectively. The stylization of F_0 obtained was expected to represent the melodic movements perceived by the human ear. The value of the left boundary (–3dB) eliminates most of the microprosodic fluctuations and stylizes the beginning of the syllable, whereas the right boundary (–9dB) preserves the variations in the tone of the accented vowels.

In this study we established a range of detection of F_0 from 65 to 650 Hz, on windows of .005s; for the automatic segmentation, the following intensity threshold was used in the stylization of the algorithm: Glissando = $.32/T^2$, DG = 30, dmin = .05. To determine the presence of a vowel, a threshold of $.32/T^2$ semitones/s was used, T being the duration of the vowel in seconds. If the rate of change in pitch is greater than the defined threshold, it is assigned a value proportional to the glissando threshold (continuous glide of the melodic line within a syllable), whereas if the value is lower than the threshold it is assigned the same value as the median of the voice sample analyzed. The choice of threshold is based on perceptual values of pitch detection in voice (Mertens, 2004). It is important to note that although the standard psychoacoustic threshold for isolated vowels is G = $.16/T^2$, during natural speech the voice flow is rarely linear, such that the value finally assigned has been shown to model variations in voice more adequately, especially in automatic transcriptions.

The procedure allows us to obtain overall variables related to the patient's prosody: Time of voice, Percentage with voice, Percentage of voiceless segments over speech duration, Percentage of voice interruptions, Percentage of phonation and Pauses in voice. We also obtained variables relating to F_0, the main parameter for analyzing the intonation and melodic curve of any vocalization (it represents the number of times the vocal cords open and close per second), as well as fluctuations in voice frequency (Shimmer) and amplitude (Jitter).

Data analysis

To determine the predictive value of the acoustic variables for memory and language impairment in AD, we performed a stepwise regression analysis of the values obtained in the parameters of frequency, amplitude and periodicity as predictors of the overall scores the patients obtained in the neuropsychological tests.

Results

The values obtained for the patients in the neuropsychological tests and in the recordings of acoustic parameters are shown in Table 1, and the regression analysis is presented in Table 2. It can be seen that the acoustic variables used explain 35% of the variance in the overall score obtained on the CVT (F = 10, 036, p = .005). The only predictor variable selected was "percentage of voiceless segments"; this describes the proportion of segments in which the voice signal stops being periodical and the calculation algorithm is unable to extract the fundamental frequency in relation to total voice time. This variable has a negative beta, that is, the patients who obtained a higher score on the CVT showed a lower percentage of voiceless segments during the speech sample analyzed.

In order to evaluate the consistency of the results, we performed the same analyses on three language tests of semantic network access. First, on the total score of Isaac's Set-Test of semantic categories; in Table 2 we can see that the variables used explain 21% of the variance in the overall score obtained (F = 5, 063, p = .03). As in the CVT, the predictor variable that entered was the percentage of voiceless segments. As to the total results of the category of phonological 'p' fluency, Table 2 shows that the acoustic variables used explain 34.4% of the variance in the overall score obtained (F = 9, 949, p = .005). Again, the predictor variable that entered was the percentage of voiceless segments. Finally, regarding the total scores of the WAIS vocabulary test, in Table 2 it can be observed that the variables used explain 50% of the variance in the overall score obtained. The first predictor variable that entered was the percentage of voiceless segments (F = 9, 859, p = .005), and the second was the median of F_0 (F = 8, 888, p = .002).

The results show that the percentage of voiceless segments appears as the only significant factor in predicting scores in all the neuropsychological measures in patients with dementia. In light of these findings, we sought to find what language processes were related to the percentage of voice output or voiceless segments. To do so, we analyzed which specific subscales of the CVT determine the percentage of voiceless segments. Table 3 shows the results of the stepwise regression on the "percentage of voiceless segments" variable. As can be seen, the CVT subscales used explain 57% of the variance in the value of this variable. The variable that first entered was the Phonological verbal fluency test (F = 16, 526, p = .001), and in second place came the Proper noun verbal fluency test (F = 12, 054, p = .001). The higher the percentage of voiceless segments, the lower the score in the CVT regarding the phonological verbal fluency test and the recall of proper nouns.

Table 1
Descriptive statistics of the acoustic and cognitive variables used

	Minim	Maxim	Mean	*SD*
Age	67	90	80.68	5.79
Total duration (seconds)	27.04	171.35	69.42	38.62
Mean F0 (Hz)	110.35	275.84	187.18	35.52
sd F_0 (Hz)	22.41	94.16	56.60	17.23
minimun value F_0 (Hz)	63.35	77.93	69.97	3.68
Maximun value F_0 (Hz)	443.65	639.52	605.57	47.37
Phonation Time (seconds)	26.52	171.07	69.13	38.63
percentage of voiceless segments	27.06	71.75	48.72	12.47
Percentage of voice interruptions	29.04	73.16	51.22	12.35
Percentage phonation	24.35	80.26	52.57	16.08
Percentage pauses	19.74	75.65	47.42	16.08
Jitter (loc) (Hz)	1.35	4.53	2.46	.79
Jitter (loc.abs) (Hz)	68.93	274.38	137.69	52.44
Jitter (rap) (Hz)	.60	2.12	1.15	.38
Jitter (ppq5) (Hz)	.65	2.34	1.28	.46
Shimmer (loc)	7.40	19.28	12.00	3.07
Shimmer (loc.dB)	.93	2.21	1.44	.33
Shimmer (apq3)	2.94	9.39	5.62	1.79
Shimmer (apq5)	3.99	11.59	6.82	2.03
Shimmer (apq11)	7.13	17.04	10.74	2.60
Harmonic to Noise ratio	.06	.21	.11	.03
Noise to Harmonic Ratio	9.76	16.39	13.38	1.98
Cognitive Reserve	0	24	7.08	4.53
MMSE score mean	2	27	15.81	8.14
Cuetos-Vega Test Total Score	4	54	27.86	13.87
C-VT Semantic verbal fluency scale	0	10	5.19	2.40
C-VT Phonological verbal fluency scale	0	7	2.86	2.30
C-VT Naming by definition scale	0	10	6.52	3.50
C-VT Object naming scale	0	10	7.38	3.13
C-VT Verbal fluency with proper nouns scale	0	2	.43	.74
C-VT Naming proper nouns scale	0	8	1.38	1.91
C-VT Immediate recall of word list scale	0	5	1.62	1.56
C-VT Immediate recall of personal information scale	0	4	1.00	1.04
C-VT Delayed recall of word list scale	0	4	.48	.98
C-VT Delayed recall of personal data scale	0	6	1.00	1.64

Table 2
Acoustic Variables identified by stepwise regression analysis as predicting the scores in the Cuetos-Vega test, Isaac's Set-Test of semantic categories, Phonological "P" fluency test and the WAIS vocabulary test

Criteria Variables	Parameters	R^2	Beta	*p*
C-VT Total Score	1. % voiceless segments	.346	–.588	.005
Isaac's Set-Test	1. % voiceless segments	.210	–.459	.036
Phonological "P" fluency test	1. % voiceless segments	.344	–.586	.005
WAIS Vocabulary Test	1. % voiceless segments	.342	–.497	.010
	2. Median F_0	.497	–.404	.030

Table 3
Sub-Scales of Cuetos-Vega Test identified by stepwise regression analysis as predicting the scores in the "percentage of voiceless segments" variable

Criteria Variables	Parameters	R^2	Beta	*p*
% voiceless segments	1. C-VT Phonological verbal fluency	.465	–.682	.001
	2. C-VT Verbal fluency with proper nouns	.573	–.379	.048

Discussion

This study was intended to analyze the difficulties in expression shown by patients with AD in the early stages of the disease, and whether they are impairments that are characteristic of the development of the disease. The objective is to be able to discriminate these preclinical biomarkers that will allow us to initiate treatments that can modify the progression of the disease before extensive and irreversible brain damage occurs. We have found that the increase in the percentage of voiceless segments in patients' speech is a sign that explains more than 34% of the variance in the scores obtained in a specific language and memory test.

The "percentage of voiceless segments" refers to the proportion of segments in which the voice signal stops being periodical and the calculation algorithm is unable to extract the fundamental frequency in relation to total voice time. In vowel-sustaining phonation tasks performed by normal voices, values other than 0 should not be found. In normal conditions, voice occurs when air flow coming from the lungs is forced through the glottis and produces tension in the vocal cords, making them vibrate, generating a quasi-periodic wave of air pulses that provoke resonance in the rest of the vocal tract. In contrast, during voiceless segments, even though the signal is produced by the same process, the vocal cords are not aroused, and thus the signal has less amplitude caused by turbulence, similar to a source of noise without harmonic structure since the voice signal lacks periodicity (Ravindran, Shenbagadevi, & Salai Selvam, 2010).

In normal aging, many physiological changes gradually take place in the phonatory system: changes in the larynx, in the respiratory system, in the resonance cavities, and in the organs of articulation as a consequence of deterioration in the muscles, cartilage, articulations, ligaments and laryngeal mucous membrane (Fernández, Ruba, Marqués, & Sarraqueta, 2006; Linville, 2004). The speech of elderly individuals is perceived as slower and more imprecise, with long pauses, is less intense and has less pitch, and more hoarse and shaky (Linville, 2001), characteristics owing to fluctuations in the amplitude of the fundamental frequency (shimmer) and spectral noise (Noise-to-harmonics ratio) (Brückl, & Sendlmeier, 2003).

Our results show that the increase in voiceless segments is related to AD and to some of the cognitive impairments associated with it. Study of the voiceless segments in speech has recently been used as one of the most important parameters in distinguishing between normal voice and voice pathology (Paulraj, Sazali, Ahamad, & Sathees, 2010; Goddard, Schlotthauer, Torres, & Rufiner, 2009), since many voices with pathologies present difficulties in making periodic glottal stops (Alonso, de León, Alonso, & Ferrer, 2001). As regards the duration of voiceless periods in relation to age, different studies have not found significant differences when comparing performance in the percentage of voiceless periods over a broad age range (Schötz, 2007; Shipp, Qi, Huntley, & Hollien, 1992).

It must be pointed out that in the task used in our study, which involved reading a relatively long paragraph, the percentage of voiceless segments must necessarily be greater than 0, unlike what should occur in tasks involving sustained vowel vocalization. In Spanish, the vowel sounds [a, e, i, o, u] and certain consonants such as [b, d, g, l, m, n] are considered voiced (except when whispered). Vocal cord vibration is not necessary for pronouncing certain consonants, and that is why the sounds [x, p, t, k, s, f] are called voiceless.

The results also show that the language parameters involved in this prediction are basically phonological. Performance in a phonological verbal fluency test explains 46% of the percentage of variance of the voiceless segments. Moreover, verbal fluency with proper nouns (a familiar word seeking task) adds 10% more to the explained variance. Both tasks seem to determine a language deficit associated with the phonological search for words typical of Logopenic Progressive Aphasia (LPA), an aphasia characterized by fluctuating speech caused by impairment of the phonological loop processes and their relation to working memory. This phonological loop seems to be essential in both the verbal fluency task and the proper name task.

Using a test that only necessitates recording the patient's voice would seem to be clearly useful given the increase in neurological consultations motivated by memory and language problems. Likewise, the existence of simple voice analysis programs could facilitate oral language assessment in the specific parameters sought, even with specific technology for doing so. In this sense we would have to define the briefest language stimuli that best bring to light the variables that discriminate phonological change.

However, these results are not definitive and require longitudinal studies to clarify which acoustic and speech parameters are most sensitive to the deterioration and the progression of the disease, and to establish the levels of impairment needed with respect to the population without the pathology in order to delimit the onset of the disease as accurately as possible. Studies with participants from different pathological groups must also be performed in order to be able to make a quantitative and/or qualitative differential analysis of the acoustic speech patterns in AD with respect to other types of degenerative disorders such Parkinson's disease and dementia with Lewy bodies. In this sense, recent clinical evidence shows that subtle differences in semantic processing can be detected in spontaneous speech production in the early stages and would be useful for predicting the progression of the disease (Forbes-McKay, Ellis, Shanks, & Venneri, 2005). In this vein our study presents a speech analysis of the most basic, and therefore the most sensitive, levels of language patterns: acoustic parameters that are highly sensitive to this clinical evidence, in order to contribute tools that permit early diagnosis of AD and as a result an increase in patients' quality of life.

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