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Article

Phonemic Verbal Fluency to predict Alzheimer's disease?

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Abstract: Background: Among the cognitive markers of Alzheimer's disease (AD), semantic and phonemic verbal fluency tasks seem to be an early indicator of deterioration. The aims of this study are 1) to evaluate both types of Verbal Fluency in the early stages of AD in order to know which of them deteriorates earlier and, 2) to investigate if Verbal Fluency Tasks can help to differentiate between patients with Mild Cognitive Impairment (MCI) who will progress to AD two years later (progresses) and those who do not (non-progresses). **Method:** A Verbal Fluency Task was administered to 25 patients with MCI and their respective control subjects. All patients underwent a neuropsychological evaluation twice in order to follow up their global cognitive status. The second time, 8 of them converted to AD. **Results:** On the one hand, Phonemic Verbal Fluency deteriorates earlier than Semantic Verbal Fluency in MCI patients; on the second hand, although we found statistically significant differences between patients with MCI and AD in both type of fluency tasks, they were not found when comparing the performance of progresses and non-progresses. **Conclusion:** These results point to a greater impairment in Phonemic Verbal Fluency in MCI patients and its potential predictive capacity to predict conversion to AD.

Keywords: Alzheimer's disease; cognitive markers; language and verbal fluency

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly, accounting for more than 60% of all cases [1]. It is characterized by a slow onset and progressive cognitive decline that affect higher functions as language, personality, memory, visuospatial perception and knowledge [2]. Consequently, this neurodegenerative disease is a serious problem that decreases the quality of life of patients and their relatives.

The stage at which a diagnosis of AD is made impacts the therapy advised, the counseling given to patients and family, and the approach to long-term care [3]. Therefore, the issue in AD diagnosis today is to recognize the disease before the cognitive deficits have reached the threshold of dementia, that is to say, at its prodromal stage. Several terms have been used to describe this pre-dementia phase. The most popular one is Mild Cognitive Impairment (MCI), proposed by Petersen et al. in the late 90s [4,5].

In the last decade, there has been unprecedented growth of scientific knowledge about early diagnosis, especially regarding biomarkers and neuroimaging techniques. However, in clinical context, the diagnosis of AD is mainly based on neuropsychological testing. The best known cognitive markers of this pathology are: 1) deterioration of episodic memory, which does not improve even with cues and involves the presence of numerous intrusions and perseverations; 2) reduced social and occupational performance; 3) anosognosia; 4) anomie or difficulty in naming; 5) spatial disorientation in unfamiliar places; 6) deficits in visual processing speed and in selective and divided attention and; 7) communicative difficulties [6]. A marked deterioration in semantic memory is a consistent finding in patients, even in the early stages of the Alzheimer's disease [7–9]. One of the earliest and most notorious manifestations are naming problems, which are usually measured by verbal fluency (VF) tasks, in which the subject is asked to produce as many words as possible in a given time [10,11]. The two forms of verbal fluency commonly assessed are phonemic - related to the

retrieval of words that begin with a certain letter or phoneme- and semantic -related to the ability to produce series of words that belong to a semantic category such as animals or fruits¹¹. It also has to be said that these tasks are not only related to the activation of processes linked to lexical access, but also to executive processes that are also altered with age, especially in cognitive impairment processes [12,13].

Several studies have found semantic verbal fluency (SVF) to be very sensitive assessment of semantic impairment at a very early stage of AD [8,14–17], but this is not a universal finding. On the one hand, Whels et al. [18,19] did not find statistic significant differences between patients with mild AD and healthy elderly control subjects in performing the SVF task, and Albert et al. [20] reported normal performance on naming and category fluency in a group of patients categorized as 0.5 on the clinical dementia rating (CDR) scale [21]. On the other hand, Goñi et al. [22] found that people with Alzheimer's disease performed worse than the control group in the phonemic verbal fluency (PVF) task, so they deduced that it deteriorates before the SVF. In this sense, there seems to be an unresolved debate about the type of fluency that deteriorates earlier in AD. For this reason, the aims of this research are, on the one hand, to evaluate both types of VF in people with early stages of Alzheimer's disease in order to know which of them deteriorates earlier and, on the other hand, to investigate whether either of them predicts the evolution of MCI to AD.

2. Materials and Methods

2.1. Participants

Twenty-five MCI patients and their respective control subjects matched by age, sex and educational level took part in the study (see Table 1). The experimental group was recruited at the Neurology Unit of the University Hospital of Cabueñes (Asturias, Spain) and the control group was enrolled in cultural centers, Day Centers for the Aged and in the University Program for the Elderly of the University of Oviedo.

Two years after the first evaluation, the MCI patients were followed up and eight of them had converted to probable AD (MCI-AD).

The educational level was separated into three groups: Low (from 0 to 4 years), Medium (from 5 to 10 years), and High (more than 10 years).

Table 1. Demographic data.

Variables	Control Group	Experimental Group
N	25	25
Age (Mean ± SD)	73.68 ± 5.12	74.60 ± 5.12
Education (L/M/H)	7/12/6	7/12/6
Gender (M/F)	15/10	15/10
MMSE (Mean ± SD)	28.96 ± 1.17	26.13 ± 2.50
MOCA (Mean ± SD)	26.44 ± 2.40	20.10 ± 3.95

N: Sample number; SD: Standard Deviation; L: Low; M: Medium; H: High; M: Male; F: Female.

The inclusion criteria used in the University Hospital of Cabueñes for MCI patients were: 1) objective memory impairment on neuropsychological evaluation; 2) normal activities of daily living; 3) evidence of concomitant dementia; 4) clinical and indirect evidence of depression; 5) other psychiatric diseases, epilepsy, drug addiction, and 6) current or previous uncontrolled systemic diseases or recent traumatic injuries. Medical history, neurological examination and brain scans (TAC or RM) were also reviewed for all patients. For their part, control subjects had to meet two conditions: 1) to be over 65 years of age and 2) to have an MMSE score equal to or higher than 26. As exclusion criteria for both groups; 1) not presenting any psychiatric, neurological (except MCI in the case of the experimental group) or medical disease that could interfere with the performance of the tests in this study.

The NIA-AA criteria (2011), proposed by the National Institute of Aging (NIA) and the Alzheimer's Association (AA), were used to identify those MCI patients who converted to probable AD [23].

All participants signed the informed consent after being informed of the study characteristics by their regular neurologist or psychologist. It should also be mentioned that the research complied with the standards established by the National Health Council on research involving human subjects and the study was approved by the Clinical Research Ethical Committee of Asturias.

2.2. Material

Two screening tests were applied to describe the general cognitive functioning of the participants: the Spanish adaptation of the Mini-Mental State Examination (MMSE) [24] and the Spanish version of the Montreal Cognitive Assessment (MoCA) [25]. The former is the most commonly used screening method in the assessment of the severity of dementia in both clinical and research field; but the latter is better detecting MCI among patients over 60 years of age than MMSE [26].

After cognitive screening, verbal fluency was assessed. First, participants were asked to produce words in the animal category -to assess SVF. Then, participants were asked to generate words that start with the letter P but neither names of people nor names of cities were allowed -to assess PVF. On each trial, they were told to generate as many words as possible within a minute.

In the phonological verbal fluency task, the choice of the letter depends on the language of the participants. In this case, the letter "P" was selected since it is the most informative [27].

2.3. Procedure

The subjects were evaluated in one single session in an individual room in order to avoid possible distractions that could bias the results.

The neuropsychological evaluations were conducted entirely by a psychologist paying attention to the behavior of the subjects under testing. All the evidences of unexpected behavioral response during testing has been registered and taken into account.

The questionnaires were administered in the following order: 1) MMSE; 2) MOCA and; 3) verbal fluency tasks. Subsequently, the results obtained were statistically analyzed using the statistical software package (IBM SPSS Statistics 21, Chicago, IL., USA).

3. Results

Descriptive statistics are provided in Table 1. On the one hand, as expected, the control group obtained higher scores than the experimental group in both types of fluency. On the other hand, the means of the SVF were higher than those of the PVF in both groups (see Table 2).

Table 2. Mean and SD of PVF and SVF in the control groups and experimental groups.

Variables	Control Group	Experimental Group
PVF (Mean \pm SD)	14.36 \pm 3.47	12.08 \pm 3.53
SVF (Mean \pm SD)	16.76 \pm 4.30	14.88 \pm 4.20
PVF (Mean \pm SD)	14.36 \pm 3.47	12.08 \pm 3.53

PVF: Phonological Verbal Fluency; SVF: Semantic Verbal Fluency; SD: Standard Deviation.

Individual test scores for Verbal Fluency Task were transformed into Z-scores based on larger sample mean and standard deviation (see Table 2). Next, to determine whether it is SVF or PVF that deteriorates earlier in subjects with MCI, a Student's t-test was performed (see Table 3).

Table 3. Comparison of the PVF and SVF performance of the MCI and control group (Z-scores).

VF	Group	N	Mean	SD	t	p
ZPVF	MCI	25	-0.18	± 0.88	-2.30	.026*
	MCI-C	25	0.38	± 0.86		
ZSVF	MCI	25	-0.34	± 0.87	-1.56	.124
	MCI-C	25	0.35	± 0.89		

ZPVF: Z-score of Phonological Verbal Fluency; ZSVF: Z-score of Semantic Verbal Fluency; *p < 0.05.

As can be seen in Table 3, there are statistically significant differences between experimental and control group in PVF (t = -2.30 p = .026) but not in SVF performance (t = -1.56 p = .124). Hence, it seems that PVF deteriorates earlier.

Finally, to investigate if Verbal Fluency Tasks can help to predict the conversion from MCI to probable AD two years later, we analyze the differences between the eight patients who converted to AD (MCI-AD) from those seventeen who did not (MCI-nonAD) at the time in which they all maintained the original diagnosis (see Table 5). Due to the small sample size and non-compliance with the normality criterion, Mann-Whitney U test was calculated. Descriptive statistics are provided in Table 4.

Table 4. Demographic data and Z-scores of PVF and SVF.

Variables	MCI-AD	MCI-nonAD
N	8	17
Age (Mean ± SD)	72.38 ± 4.34	75.65 ± 5.23
Education (L/M/H)	2/4/4	5/8/4
Gender (M/F)	4/4	11/6
MMSE	24.75 ± 1.83	26.94 ± 2.51
MoCA	17.25 ± 2.60	21.41 ± 3.81

It is worth mentioning the age difference between both groups. Although all subjects are diagnosed with Mild Cognitive Impairment, some developed symptoms at an early age while others at an older age. Nevertheless, the difference of almost 3 years between both groups is not statistically significant.

Table 5. Comparison of the PVF and SVF performance of the MCI-AD and MCI-nonAD group (Z-scores).

VF	Group	Mean ± SD	U	p
ZPVF	MCI-nonAD	-0.01 ± 0.72	38.50	.086
	MCI-AD	-0.55 ± 1.12		
ZSVF	MCI-nonAD	-0.07 ± 0.87	56.50	.511
	MCI-AD	-0.27 ± 0.89		

*p < 0.05.

After analyzing the data, no statistically significant differences were found between PVF and SVF in both groups. Nevertheless, if we compare the VF task performance between the eight patients with the diagnosis of probable AD –two years after the first evaluation- from those seventeen who maintained the original diagnosis of MCI, we find statistically significant differences between PVF and SVF in both groups (see Table 6).

Table 6. Comparison of the PVF and SVF performance of the MCI-nonAD and AD group (Z-scores).

VF	Group	Mean \pm SD	U	p
ZPVF	MCI-nonAD	-0.01 \pm 0.72	17.50	.002*
	AD	-1.26 \pm 0.84		
ZSVF	MCI-nonAD	-0.07 \pm 0.87	8.50	.000*
	AD	-1.38 \pm 0.53		

*p < 0.05.

Taking all these results together, it could be that either a larger sample size would allow statistically significant differences to be obtained, or that the deterioration of PVF could help predict the conversion of MCI to probable AD.

4. Discussion

Efforts at earlier detection of AD face significant challenges such as improving assessment of earliest symptoms. Memory impairment is typically the most common manifestation of early AD, but growing evidence suggests that other cognitive domains such language dysfunction begins several years before the onset of dementia, suggesting this could be a possible prognostic marker [9,28] that should be taken into account in neuropsychological assessments.

Language impairment initially affects verbal fluency and naming. Regarding fluency, although it is well known that patients with AD begin to produce a lower number of words in both semantic and phonemic verbal fluency compared with age-and education-matched elderly control subjects, controversy exists regarding the type of fluency measure that best discriminates patients with an early AD from healthy elderly. In this sense, our results show that the experimental group performed worse than the control group in both types of fluency. What is more, the SVF scores of the experimental group were slightly higher than that of the PVF and statistically significant differences were found.

These data are consistent with authors such as Goñi et al, Montañés, and Comesaña and Coni [22,27,29]. They suggest that SVF is better preserved over time than PVF due to the executive impairment of AD patients. SVF tasks are considered to be easier to perform than PVF tasks because retrieval of words beginning with a certain letter involves searching a high subset number of categories and requires higher executive functioning performance.

Regarding assessing the progression of MCI to AD, although we found statistically significant differences between patients with MCI and AD in both type of fluency tasks, they were not found when comparing the performance of subjects with MCI and MCI who converted to AD two years later. Similarly, Vaughan et al. [30] could not differentiate between progresses and non-progresses using individual fluency measures. Tracking progression from MCI to AD requires not only accurate diagnosis but also cognitive measures sensitive to change over time³¹. In this sense, Vaughan et al. [30] proposed using discrepancy scores at baseline to discriminate between MCI who maintained stable and MCI who converted to AD after two years. Discrepancy scores were calculated for each participant by subtracting the letter fluency from the animal fluency score. They conclude that individuals with MCI with a phonemic advantage at initial assessment present a high index of suspicion for progression to AD. But the truth is that other studies of relative semantic-phonemic

discrepancies in MCI have yielded discordant results. Therefore, future research is needed to determine the specificity of such findings to AD and their utility in serial assessments over time.

The current study is subject to certain limitations, in particular the small sample size that makes it difficult to generalize the results. Secondly, it is known that there is great variability in fluency performance depending on which fluency task is used, and our study focuses only on “letter p” and “animals” because these are frequently used in clinical practice. In addition to this, the use of combined categories is more reliable than use of single letters or categories, nevertheless, we believe that our results remain applicable clinically because “letter p” fluency is part of the Montreal Cognitive Assessment - a commonly administered cognitive screening test- and animal fluency can be easily added to any assessment protocol. Supporting our choice of category test, some investigators report that semantic fluency tasks that use large categories (e.g., animals) contain more disease-associated variance and are more sensitive for detecting AD [32]. Finally, it is also worth mentioning the strengths of the study. First, the diagnosis was undertaken by a specialized neurologist using standardized neuropsychological assessments and the latest published AD diagnostic criteria [23]. Second and last, promote more research on a topic that continues to generate great controversy.

5. Conclusions

Despite the advances in the identification of AD-related biomarkers, neuropsychological assessment remains essential for diagnosis. Although memory dysfunction is the most common manifestation of early AD, some cases first present with executive, language or visuospatial disturbances. Our results support the fact that there are linguistic alterations already in early stages. Thus, in order to make an early diagnosis, verbal fluency should be taken into account, especially phonemic verbal fluency which is worse preserved over time than semantic verbal fluency. Additionally, further longitudinal studies are needed to clarify whether this may be clinically relevant in predicting progression of MCI to AD

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Informed Consent Statement: The research complied with the standards established by the National Health Council on research involving human subjects and the study was approved by the Clinical Research Ethical Committee of Asturias.

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