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A study of semantic and phonological verbal fluency in Alzheimer's disease

Un estudio de la fluidez verbal semántica y fonológica en la enfermedad de Alzheimer

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia in older adults, so early diagnosis is essential to slow or delay its progression. Among the cognitive markers of AD, verbal fluency seems to be an early indicator of deterioration. The main objective of the present work is to find out whether it is phonological or semantic verbal fluency that deteriorates earlier in AD. A Verbal Fluency Task was administered to 30 patients with AD and 30 control subjects matched by age, sex and educational level. On the one hand, statistically significant differences were found in the performance of the phonological fluency task between the control and experimental group, with better performance at higher educational level. On the other hand, in patients with AD it was observed that gender did not influence the performance of fluency tasks and, although performance in phonological fluency was slightly higher than in semantic fluency, no statistically significant differences were found. These results point to a possible greater impairment in phonological fluency in the early stages of AD that should be further analyzed in larger samples in order to be taken into account at the time of diagnosis.

Keywords: Alzheimer's disease, Mild Cognitive Impairment, cognitive markers, language and verbal fluency

Resumen

La enfermedad de Alzheimer (EA) es la principal causa de demencia en los adultos mayores, por lo que el diagnóstico precoz es fundamental para frenar o retrasar su progresión. Entre los marcadores cognitivos de la EA, la fluidez verbal parece ser un indicador temprano de deterioro. El objetivo principal del presente trabajo es averiguar si es la fluidez verbal fonológica o la semántica la que se deteriora antes en la EA. Se

administró una tarea de fluidez verbal a 30 pacientes con EA y 30 sujetos control emparejados por edad, sexo y nivel educativo. Por un lado, se encontraron diferencias estadísticamente significativas en el desempeño de la tarea de fluidez fonológica entre el grupo control y experimental, con mejor desempeño en el nivel educativo superior. Por otro lado, en pacientes con EA se observó que el género no influía en el desempeño de las tareas de fluidez y, aunque el desempeño en fluidez fonológica fue ligeramente superior al de fluidez semántica, no se encontraron diferencias estadísticamente significativas. Estos resultados apuntan a un posible mayor deterioro de la fluidez fonológica en estadios tempranos de la EA que debería analizarse en muestras más amplias para tenerlo en cuenta en el momento del diagnóstico.

Palabras clave: enfermedad de Alzheimer, deterioro cognitivo leve, marcadores cognitivos, lenguaje y fluidez verbal

INTRODUCTION

According to data from the Spanish Society of Neurology (SEN), about 40,000 new cases of Alzheimer's disease are diagnosed each year in Spain. However, these figures may underestimate the real extent of the problem since around 80% of mild cases go undiagnosed.

The cognitive decline of this neurodegenerative disease usually begins slowly, advances progressively and lasts an average of 10 years -from diagnosis-, usually ending in dementia (Alcantar et al., 2011). Regarding symptomatology, a series of pathophysiological changes occur that alter neuronal functioning and affect at least three of the following higher functions: language, personality, memory, visuospatial perception and knowledge (calculation, abstraction, reasoning...) (Proaño & Aguilar, 2004).

In this context, it is essential to identify early markers that facilitate early diagnosis and early access to available pharmacological and non-pharmacological treatments, which would help to stop, or at least slow down, the progression of the disease (Tirapu-Ustárroz et al., 2008). The main ones are: 1) biological markers or biomarkers that include genetic markers; 2) molecular markers; 3) neuroimaging markers and; 4) cognitive markers. The latter have tended to be the most studied due to their accessibility, their low cost and their presence in preclinical phases. In addition, they are decisive when making the differential diagnosis between non-pathological aging -associated with age and usually manifested in subjective complaints of cognitive functioning-, and pathological aging -derived from a disease such as Alzheimer's disease. Deterioration of episodic memory is often one of the first sign of cognitive impairment due to the disease. But the decline of other cognitive markers not related to memory may also be present from the early stages of Alzheimer's, such astrouble understanding visual images and spatial relationships, impaired reasoning or judgment, reduced social interaction, anosognosia, anomia and communicative difficulties (Jiménez et al., 2013).

Among the cognitive markers mentioned, language impairment stands out. It is present from preclinical stages and its severity correlates with the severity of the disease. Naming problems can be measured by verbal fluency (VF) tests, in which the subject is asked to produce as many words as possible in a given time (Ivanova et al., 2020).

It is well-established that two types of VF can be distinguished: phonological verbal fluency (PVF) and semantic verbal fluency (SVF). The former is related to the retrieval and search of words that begin with a certain letter, which reflects executive functioning, and mainly involves activation of temporal regions. The latter is related to the ability to produce lists of words that belong to a semantic, which reflects semantic knowledge, and mainly involves activation of frontal regions (Baldo et al., 2020; Faroqi-Shah & Milman, 2018; Horcajuelo et al., 2014; Montañés et al., 2005). Therefore, these tasks are not only related to the activation of processes linked to lexical access, but also to executive processes such as inhibition of incorrect responses, working memory, focal and sustained attention, concentration, verbal retrieval, response initiation, executive control and planning the retrieval of the required words (Carballo et al., 2015; García et al., 2012). To date, there are still few studies that investigate the relationships between performance on the verb fluency task and neuroimaging parameters in population with neurodegenerative diseases. In this line, authors as Meinzer et al. (2012) and Paek et al. (2020) have recently shown that poorer verb fluency performance of individuals with dementia compared to healthy older adults leads to greater activation in left hippocampus and right supramarginal gyrus. Also Paek et al. (2020) observed that individuals with dementia activate their frontal lobe regions more strongly than healthy older adults, possibly as a way to counteract loss of attention control, decline in executive functioning skills, semantic degradation, and poor access to semantic representations.

The aim of this research is, on the one hand, to evaluate VF in people with Alzheimer's disease in order to know which of them deteriorates earlier; and, on the other hand, to confirm or not the possible influence of other sociodemographic variables such as gender and educational level on task performance.

The evaluation of the SVF is very sensitive to semantic deterioration, even in a very early stage of AD, according to different studies. For instance, Monsch et al. (1992) conducted a study in which they analyzed the performance in verbal fluency tasks of 142 participants, some with AD and others without any impairment. They concluded that the SVF best predicts the onset of this neurodegenerative disease. The same findings were found by Clark et al. (2009), Gómez and White (2006) and Henry et al. (2004) in their studies on verbal fluency and AD. In contrast, the results of the research done by Comesaña and Coni (2013), Goñi-Sarriés et al. (2015), Montañés et al. (2005) and Rosen (1980) conducted under similar conditions, are different. The latter found that people with Alzheimer's disease performed worse than the control

group in the PVF task, which suggests that the phonological task provides more accurate discrimination than the semantic one. Bearing in mind that the task of evoking words belonging to a certain category activates the semantic connections, and the task of searching words that begin with a certain letter requires a greater executive functioning, last studies are in contradiction with the idea that executive functions act as a compensatory mechanism against age-related memory decline (Faroqi-Shah & Milman, 2018; Hurks et al., 2006).

In relation to gender, the results are also inconsistent. Some studies such as Laws et al. (2016) and Moreno-Martínez et al. (2008) revealed that, within the group of people with Alzheimer's disease, women scored lower than men in most verbal fluency subcategories —specifically, women are slower to name nonliving things, and men are slower to name living things—. In contrast, Hyde and Linn (1988) conducted a meta-analysis to analyze sex differences with a sample of almost 1.5 million subjects and found better performance of the female gender in verbal ability. Not only the results but also the hypotheses explaining both types of results are diverse. On the one hand, Laws (2004) suggested that evolution may have produced small sexual asymmetries that would explain the preferential processing of stimuli belonging to certain categories; Marra et al. (2007) claim that these differences are due to the different roles usually assigned to men and women in daily activities; and Moreno-Martínez et al. (2008) hypothesized a particular vulnerability in female AD to develop a profound lexical–semantic impairment. On the other hand, Hyde and Linn (1998) concluded that gender differences in cognitive abilities are *nonexisten*. Therefore, it is still unclear which type of fluency deteriorates earlier in AD and how gender influences task performance. On the contrary, there seems to be a wide consensus on the influence of the educational level. Rodriguez et al. (2019) suggest that, given the same level of brain pathology, individuals with a higher education (cognitive reserve) benefit from a superior performance in semantic memory and executive functioning. In other words, the higher the educational level, the better the VF task performance.

2. Methods

2.1 Participants

A total of 60 subjects divided into two groups participated in the present study (see Table 1). On the one hand, the experimental group consisted of 30 patients with early AD, recruited at the University Hospital of Cabueñes (Gijón, Asturias) and at neurocognitive rehabilitation center in Pamplona (Navarra) and diagnosed according to the diagnostic criteria developed by the National Institute of Aging (NIA) and the Alzheimer's Association (AA) (McKhann et al., 2011). On the other hand, the control group, formed by 30 subjects matched by age, identified gender and educational level (see Table 1) with the experimental group, and recruited in cultural centers, Day

Centers for the Aged and in the University Program for the Elderly of the University of Oviedo.

Table 1
Demographic data and t-Student age, MMSE and MoCA.

Variables	Control	Experimental	t	p
N	30	30		
Age (Mean ± SD)	74.07 ± 6.11	76.17 ± 7.72	1.161	.247
Education (B/P/S)	8/15/7	8/15/7		
Gender (M/F)	13/17	13/17		
MMSE (Mean ± SD)	28.28 ± 1.13	25.53 ± 2.79	9.592	.000
MOCA (Mean ± SD)	25.50 ± 2.98	15.67 ± 3.67	11.392	.000

N: Sample number; SD: Standard Deviation; B: Basic; P: Primary; S: Superior; M: Male; F: Female.

The members of experimental group had to be over 65 years of age and have been diagnosed of Alzheimer's disease in an early stage. The controls had to be over 65 years of age and have an MMSE score equal to or higher than 26. None of the participants had to have a medical or psychiatric illness (except AD in the case of the experimental group).

Before starting the research, the characteristics of the study were explained to all participants. Once they had understood the details, they signed the informed consent. In addition, the research also 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

To describe the general cognitive functioning of the sample, two screening tests were used: the Spanish adaptation of the Mini-Mental State Examination or MMSE (Folstein et al., 1975) and the Spanish version of the Montreal Cognitive Assessment or MoCA by Lozano-Gallego, et al. (2009). It should be noted that the latter test includes the evaluation of PVF.

To evaluate each type of fluency the instructions were as follows. For semantic fluency assessment, the subject was given the following instruction: "I want you to tell me for one minute as many animal names as possible that you know, whether they are domestic animals, live in the forest, in the sea, in the jungle..."; and for the phonological fluency assessment, the subject was given the instruction from the language subtest of the MoCA: "I want you to tell me for one minute all the words you know that begin with the letter 'P' but neither names of people nor names of cities are allowed".

2.3 Procedure

The subjects were evaluated by a psychologist who administered the questionnaires in the following order: 1) MMSE; 2) MOCA and; 3) verbal fluency tasks. An isolated and individual room was used to avoid any type of distraction.

2.4 Statistical analysis

The results obtained were analyzed statistically using the statistical software package (IBM SPSS Statistics 21, Chicago, IL, USA). One-way multivariate analysis of variance (MANOVA) was used to analyze the statistical differences in the two types of verbal fluency in the control and experimental groups and in relation to educational level. The Student's t-test was also used to compare the scores obtained as a function of gender in the experimental group.

3. Results

When analyzing the performance of the subjects in the fluency tasks, it is observed, on the one hand, that the control group obtained higher scores than the experimental group in both types of fluency (see Table 2). And, on the other hand, although in both cases the means of the SVF were higher than those of the PVF, in the experimental group the difference between the two was minimal.

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

Variables	Control Group	Experimental Group
PVF (Mean ± SD)	13.73 ± 4.06	11.53 ± 4.77
SVF (Mean ± SD)	16.30 ± 4.79	11.97 ± 3.24

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

To determine whether the differences between the scores of both fluency types in the control and experimental groups were statistically significant, a one-way multivariate analysis of variance (MANOVA) was performed. The results revealed statistically significant group differences in the dependent variables PVF and SVF (Wilks' Lambda = .774, F (2, 57,000) = 8.31, $p < .001$). As a consequence, belonging to the experimental or control group affects performance on verbal fluency tasks. Likewise, the test for inter-subject effects indicated the presence of statistically significant differences between the control and experimental group for PVF and SVF. To test in which type of fluency the performance of the experimental group is worse, a t-Student of related samples was performed (see Table 3).

Table 3
Comparison of the PVF and SVF performance of the experimental group.

	Mean	SD	t	p
PVF	11.53	4.77	.539	.594
SVF	11.97	3.24		

PVF: Phonological Verbal Fluency; SVF: Semantic Verbal Fluency; SD: Standard Deviation.
*p < .05

Although the mean of the SVF is slightly higher than that of the PVF, there are no statistically significant differences between both types of fluency (t = -.539, p = .594).

Next, in order to compare the scores of females and males in the experimental and control group, the t-Student test was used (see Table 4 and Table 5).

Table 4
Gender comparison – verbal fluency in the experimental group.

		Experimental Group (mean ± SD)	t	p
PVF	Total (Mean ± SD)	11.53 ± 4.77	.375	.710
	Female (Mean ± SD)	11.15 ± 3.21		
	Male (Mean ± SD)	11.82 ± 5.77		
SVF	Total (Mean ± SD)	11.97 ± 3.24	.063	.950
	Female (Mean ± SD)	11.92 ± 3.14		
	Male (Mean ± SD)	12.00 ± 3.41		

PVF: Phonological Verbal Fluency; SVF: Semantic Verbal Fluency; SD: Standard Deviation.
*p < .05

Table 5
Gender comparison - verbal fluency in the control group.

		Control Group (mean ± SD)	t	p
PVF	Total (Mean ± SD)	13.73 ± 3.28	.955	.348
	Female (Mean ± SD)	12.92 ± 3.28		
	Male (Mean ± SD)	14.35 ± 4.57		
SVF	Total (Mean ± SD)	16.3 ± 4.79	1.401	2.42
	Female (Mean ± SD)	14.92 ± 3.59		
	Male (Mean ± SD)	17.35 ± 5.39		

PVF: Phonological Verbal Fluency; SVF: Semantic Verbal Fluency; SD: Standard Deviation.
*p < .05

As can be seen in both tables, males have a higher mean on both types of fluency than females. However, although the scores are slightly higher, the difference cannot be said to be statistically significant. In comparison with the two groups, people in the control group have higher scores in both types of fluency.

Regarding the educational level variable of the experimental group, higher scores are observed when the educational level is higher than primary or basic for both types of fluency (see Table 6).

Table 6
Fluency scores as a function of educational level for the experimental group.

		N	Median	SD
PVF	Basic education	8	9.25	4.80
	Primary education	15	10.80	3.32
	Higher education	7	11.53	5.34
SVF	Basic education	8	9.97	1.88
	Primary education	15	11.67	2.79
	Higher education	7	15.00	3.42

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

Thus, in order to analyze whether the level of educational level influenced verbal fluency performance, a MANOVA was performed taking educational level divided into three subgroups (elementary, primary and higher) as the independent variable and verbal fluency (PVF and SVF) as the dependent variable. In the experimental group, these multivariate contrasts indicated that there are significant interaction effects between predictors (Wilks' Lambda = F (4, 52,000) = 3.95, P < .007). Next, a Tukey post hoc analysis was performed to analyze the homogeneous subsets of the educational level of the experimental group through simple comparisons (see Table 7). In subset 1 —which includes basic and primary educational level— the means do not differ significantly (p-value=.723). By contrast, primary and secondary educational level are considered homogeneous subsets (p-value=.053). In contrast, in the control group these contrasts did not show significant prediction-interaction effects between the variables.

Table 7
Comparison of verbal fluency and schooling in the experimental group.

	(I) Educational Level	(II) Educational Level	Difference in means (I-J)	Sig.
PVF	Primary	Basic	1.55	.686
	Secundary	Basic	6.46	.018*
		Primary	4.91	.045*
SVF	Primary	Basic	1.79	.312
	Secundary	Basic	5.12	.003*
		Primary	3.33	.035*

PVF: Phonological Verbal Fluency; SVF: Semantic Verbal Fluency; Sig.*: significance. p < .05

After analyzing the data, statistically significant differences were found between higher and primary educational level, and between higher and basic educational level for both phonological fluency and semantic fluency.

4. Discussion

The results show that the experimental group performed worse than the control group in both types of fluency. We found that the SVF scores of the experimental group were a little higher than that of the PVF, but no statistically significant differences were found. This may be due to the fact that the sample of the

experimental group is in an early stage of Alzheimer's disease; that is, they do not yet present a great cognitive impairment, as reflected by the mean score obtained in the MMSE 23.53 (SD 2.78). Montañes et al. (2005) seems to confirm this hypothesis in his longitudinal study with 12 people with AD in which he assessed verbal fluency on four occasions. As time progressed, there was a decrease in word production in both modalities. Likewise, he related the MMSE and the two VF modalities finding a positive correlation in the fourth passage between said questionnaire and PVF, concluding that the screening test predicts the performance of the subjects in this type of fluency. Some authors such as Comesaña and Coni (2013) and Goñi-Sarriés et al. (2015) and Montañes et al. (2005) suggest that SVF is better preserved over time than PVF. This could be because SVF tasks are easier than PVF tasks as they do not require greater performance of executive functions. Therefore, they have higher complexity than the retrieval of concepts belonging to a given semantic category (Martins et al., 2007). However, there are studies that contradict these results. Henry et al. (2004), for example, conducted a meta-analysis aimed at comparing the deficits suffered by people with Alzheimer's disease and groups of healthy controls in relation to both types of verbal fluency. They found that most studies have found more significant cognitive impairment in SVF tasks than in PVF tasks.

It is in the early stages of AD when patients begin to produce a lower number of words in both semantic fluency and phonological fluency. Therefore, this fluency impairment should be taken into account in neuropsychological assessments since the performance of tasks related to language skills is highly sensitive to Alzheimer's disease (Comesaña & Coni, 2013; Gómez & White, 2006; Lozano-Gallego et al., 2009; Montañés et al., 2005) and represents neuropathological changes due to the neurodegenerative disease (Paek et al., 2020). These data are consistent with the study by Galeote-Moreno and Peraita-Adrados (1999), who examined language production in three different groups: young subjects, elderly people without pathologies, and elderly people with Alzheimer's disease. They found a greater deterioration in the responses produced in the group of people with AD in relation to the other two groups. Likewise, they found that the elderly without pathology showed a decrease in concepts emitted compared to the young.

Regarding the gender variable, the results of this research are not conclusive. Although males scored higher in both types of fluency with respect to females in both groups, the differences were not statistically significant. This fact was also observed in the research of Navarro et al. (2018), where performance in tasks related to SVF was very similar in both males and females. For their part, Hyde and Linn (1988) also found in their meta-analysis slightly higher performance than women, and proposed that these differences in verbal fluency are dissipating as the years go by due to flexibility in gender roles. Capitani et al. (1999) add that these sex differences depend on the type of task to be performed; that is, they are not universal. Consequently, they

conducted a study in which they observed that there were differences in semantic categories, with women performing better for 'fruits' and men for 'tools'. These findings refer to the importance of word retrieval through mental imagery strategies and in the context, habits and occupation of individuals, such as working in a factory or being the person in charge of buying the fruit at home. Goñi-Sarriés et al. (2015), in contrast, consider that the lower schooling of women could justify these lower results in verbal fluency tasks. In fact, only one of the seven subjects with higher education was a woman.

In relation to educational level, people with a higher educational level obtained better VF scores. Subjects with a higher education produced more words in both types of fluency than those with a basic or elementary education. This finding confirms previous studies such as those of Montañés et al. (2005), Galeote-Moreno and Peraita-Adrados (1999) and Rubinstein et al. (2014) who mention that VF is sensitive to the effects of educational attainment. Navarro et al. (2018) confirm this idea and add a positive correlation between SVF and educational level. He found that people with a higher educational level produced more words belonging to a semantic category. This significant influence of education on verbal fluency tests may be due, in the first place, to the cognitive effort required to perform this type of activity. Semantic memory plays a fundamental role in searching through retrieval cues in the lexical store. Secondly, the level of education has a positive impact on the creation of lexical stores and, consequently, on the existence of a wider range of words that can be used. Likewise, there seems to be a positive relationship between education and cognitive reserve, a neuropsychological construct that refers to the ability to tolerate age- or pathology-related brain changes without presenting clinical symptoms, making it a protective factor against the development of cognitive impairment (Marino & Alderete, 2010).

As future research, a longitudinal study could be carried out to investigate the possible effects on verbal fluency in people with Alzheimer's disease at different stages of the disease. Other variables such as ethnicity, socioeconomic level, pharmacological treatment, age at onset of AD, comorbidity with other conditions, lifestyle, occupation and marital status could also be introduced. It would be also interesting to explore the components of clustering and switching as they manifest across the AD spectrum and evaluate their potential as a diagnostic indicator for AD.

CONCLUSIONS

The great variability in the symptomatology of patients with Alzheimer's disease generates heterogeneous neuropsychological profiles. Our results support the fact that there are linguistic alterations already in early stages, in addition to the more known symptoms such as, for example, memory problems. Thus, in order to make an early diagnosis, verbal fluency tests should be included, especially phonological fluency - on

which further research is needed. To emphasize the great importance of early detection of this neurodegenerative disease in order to establish an adequate treatment of the cognitive deficits that exist and that can be addressed as soon as possible through pharmacological and non-pharmacological treatment.

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