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Verbal Fluency Fruits as a Predictor of Alzheimer's Disease Progression in Brazilian Portuguese Speakers

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Abstract

Objective: Verbal Fluencies (VF) animals (VFa) and VF fruits (VFf) have previously been described to be similarly effective in discriminating normal participants from patients with Alzheimer disease (AD). Both tasks were less accurate in discriminating AD-stages for unknown reasons. Based on semantic clustering scores in VFa, a literacy depending pattern has been revealed across cultures; however, no previous analysis has been performed for VFf.

Methods: Three-hundred-fourteen native Brazilian Portuguese speakers were divided in four groups: a Control Group (CG) and Mild Cognitive Impairment (MCI), Mild Alzheimer's Disease (MAD) and Moderate Alzheimer's Disease (ModAD) groups. A quantitative (total score - TE) and a qualitative (clusters – Cf) analysis were conducted for VFf and were compared to other cognitive tasks. As no semantic setting was found, a non-arbitrary classification of fruits based on Sub Categorical items (Cf), according to the articulatory point of Brazilian Portuguese was performed. The words were grouped as follows: 1) bilabial, 2) velars, 3) open vowels, 4) closed vowels, 5) lateral dental/ alveolar, 6) dental /alveolar, and 7) labio-dentals. Clustering strategies (Cf) in the AD Groups differed from those of the CG. Cf revealed differences beyond groups depending on which articulatory point was emitted.

Results: MCI had a 73% lower chance of attaining an NV than did the CG and with AD groups presented odds ratios of using the Cf /k/, /g/ velars feature 85% lower than those of the CG. Participants who used Cf bilabial had 2.04 times higher VFTE scores than those who did not. Younger subjects had a higher probability to perform better on the task. Participants with >9 years of education had a higher probability of higher performance with respect to the VFf TS.

Conclusion: Articulatory deterioration occurred in AD since the early stages. VFf seems to be a suitable task for MCI evaluation.

Introduction

Screening tools such as the Verbal Fluencies (VF) in which the participant is asked to produce as many items (animal, supermarket items, fruits, vegetables and others) as quickly as possible, in 60 s [1], are easy to administer [2] and have high sensitivity and specificity in the clinical investigation of Alzheimer's Disease (AD) [3]. They are known to detect mainly executive dysfunction [4] and semantic memory impairment [5]. Other impairments in aspects of language production, e.g. phonological and articulatory, reflecting semantic memory disruption, may occur early in AD, contrary to claims that these aspects are relatively preserved until the final stages of disease progression [6].

Radanovic et al. [7] compared the accuracy of two categories, Verbal Fluency - Animals (VFa) and Verbal Fluency-Fruits (VFf) between patients with mild cognitive impairment (MCI) and AD, in a group of Portuguese speaking Brazilian elderly. Their results showed that both categories were similar in discriminating control group (CG) participants from patients with AD. Administered together, they had improved discriminatory accuracy. The VFf best discriminated between the CG and patients with MCI and between patients with MCI and AD, for undetermined reasons.

Differences in VFa and VFf in semantic representations have also been reported, where a more relevant category (food) might be less influenced by literacy, while animal fluency, which has diverse subcategories, was more dependent on exposure to formal education [8].

Recent research has begun to separate performance measures in VFs (qualitative and quantitative) to isolate the semantic and executive performance components [9]. Troyer et al. [10] suggested that the clustering procedure, the production of words within semantic or phonemic categories, may reflect that isolation, developing measures of category clustering in addition to the total number of correct words generated-total score (TS). To our knowledge, no clustering procedure in VFf has been described worldwide.

In the current study, we analyzed clustering fruits (Cf) and TS in VFf, their sensitivity and specificity in CG participants and patients in the AD spectrum: MCI, mild Alzheimer disease (MAD) and moderate Alzheimer disease (ModAD).

Our hypothesis was that the VFf could have a typical pattern that may underline this semantic category, different from the VFa, as no literacy pattern, which could probably explain findings in the field, was found. Thus, Cf was based on articulatory points in Brazilian Portuguese [11].

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Methods

All participants were Brazilian Portuguese native speakers and they were divided into four groups: a control group (CG) (n=126), followed at a geriatric outpatient clinic and patients with MCI (n=71), MAD (n=50) and ModAD (n=67), followed at a Behavioral Neurology Outpatient Clinic. The groups were further divided by age (60 to 69 years, 70 to 79 years and 80 to 89 years and education (0-4 years, 5-8 years and 9-18 years of formal education).

For the AD groups, the inclusion criteria were based on those suggested by the American Psychiatric Association (DSM-V) [12] and the National Institute of Neurological Disorders and Stroke, National Institute of Health [13], for probable AD. Exclusion criteria were any other neurological or psychiatric disease (except for behavioral disturbances that could be attributed to AD and non-corrected sensory deficits. The control group was defined as participants who achieved normal scores in the neuropsychological evaluation (age- and education-corrected). For controls, exclusion criteria were any neurological or psychiatric disease and evidence of cognitive or functional decline.

All participants were initially assessed for cognitive impairment using the Brazilian version of the Mini-Mental State Examination (MMSE) [14,15], Clock Drawing Task (CDT) [16,17], Verbal Fluency-Animals [18], Verbal Fluency-Fruits [19,20] and the Clinical Dementia Rate (CDR) [21].

In a pilot study, 314 volunteers were asked to generate fruit items within 60 s. Based on a confirmed cut-off (13) in VFf, TS was divided in three groups as follows: negative value >13 (NV), cut-off value=13 (CV) and positive value <13 (PV) and a Cf analysis was performed to determine the incidence of each cluster type. One cluster was defined as a minimum of three consecutive words belonging to the same subcategory produced by the patient. Cluster size was counted from the second word of each cluster (a 3-word cluster was counted as one cluster size) and errors and repetitions were not counted.

As no semantic cluster was found, words were grouped and counted in cluster subcategories based on articulatory proximity in Brazilian Portuguese. These non-arbitrary sub-categorical clusters (Cf) were then defined as follows: 1) /p/, /m/, /b/ (bilabial); 2) /k/, /g/ (velar); 3) /a/ open vowels, 4) /u/ (closed vowels), 5) /l/ (lateral dental/ alveolar), 6) /t/, /d/, (dental/alveolar); 7) /f/ /v/, (labio dental). The clustering analysis was based on these seven subcategories.

Student's t-test and ANOVA were used to compare groups if their use was deemed appropriate by the Kolmogorov-Smirnov and the Levene tests, respectively. Where the homoscedasticity assumption was violated, the statistical degrees of freedom were corrected using the Brown-Forsythe test. Where the normality assumption was violated, Mann-Whitney or Kruskal-Wallis tests were employed. When the mean differences in ANOVA or the Kruskal-Wallis test were significant, multiple comparisons were carried out using the Duncan and Dunn-Bonferroni tests.

In order to evaluate the correlation between numerical and categorical variables, Spearman's correlation coefficient was used. To evaluate the effects of group, sex, age, education, and MMSE and CDT scores (predictor variables) on TS and Cf, logistic regression models were adjusted and to the simultaneous effects of type: Cf, group, sex, age, education, MMSE and CDT on the VFf classification, we used the ordered logit regression, which corresponds to a generalization of logistic regression for ordinal polytomous responses. For the Cf formed, considered a count, the Poisson model was adjusted considering the same predictor variables for resource use. In each model, all the predictor variables were initially considered. Then, the non-significant variables at 5% were excluded one by one in order of significance (backward method).

A significance level of 5% was used for all statistical tests.

Statistical analyses were performed using the statistical software SPSS 20.0 (IBM Corp., Chicago, IL) and STATA 12 (Stata Corp., College Station, TX).

The study was approved by the Ethics Committee of the Hospital of São Paulo, Faculty of Medicine, Federal University of São Paulo. All participants (or their legal representatives) gave their informed consent before enrolment in the study, which addressed volunteer participation, anonymous handling of data, safety guidelines, and the accomplishment of good clinical practices at the local institution. All study procedures were performed in accordance with the Helsinki Declaration.

Results

All 314 participants were included, with a mean age of 72.7 years (SD=7.2 years; range 59 to 92 years). Associations between VFf and the variables age range (p=0.001), education (p<0.001), groups (p<0.001), Cf /k/, /g/ uses (p<0.001), Cf /a/ open vowel (p=0.011), Cf /u/ closed vowel (p<0.001) and Cf /t/, /d/ (p<0.001) are shown in Table 1. PV was more common in participants 80 years old or older (24.3% vs. 12.5%), with less than 4 years of education (47.6%), in the MAD (22.2% vs. maximum 12.5%) and ModAD groups (35.4% vs. 0.0%). In addition, the ModAD group had the lowest percentages of Cf /k/, /g/ velar (5.3%), Cf /a/ open vowel (7,4%), Cf /u/closed vowel (1.1%), and Cf /t/, /d/ dento-alveolar (1.1%) compared to the other groups. The NV group included the highest percentage of younger patients (59 to 69 years) - 46.5%, higher education (45.5%), CG participants (75.2%), and use of Cf /t/, /d/ dental/ alveolars (14.8%).

Table 2 shows the simultaneous effects of sex, age, education, CDT and MSSE scores and resource types (predictor variables) on VFf (dependent variable) examined with the ordered logit regression model. PV was adopted as a TS reference category in classes. In this way, the exponentiated coefficients were interpreted as a ratio of chances of greater adequacy. Remained significant on final model: age range 59 to 69 years (p=0.001), education of 9 years or more (p=0.023), the MCI (p=0.001) and MAD (P=0.012) groups, and the use of Cf (/p/, /m/. /b/) bilabial resources (p=0.018) and Cf /k/, /g/ velar (p=0.022). Thus, it was found that the odds of higher (more adequate) TS in participants who used Cf /p/, /m/, /b/ bilabial were 2.04 times greater than in those who did not. This odds ratio was approximately 2.51 times higher for those who used Cf (/k/, /g/) velars. In this way, those who used both resources had a 5.12 (p=0.049) times greater odds ratio of attaining higher (more adequate) TS than those who did not use these two resources. It is also noted that patients with MCI had a 73% lower chance of having an NV than did the CG. This was 89% lower in patients with AD. It is also noted that younger participants had a greater odds ratio (3.06 times) to have an NV than those who were between 70 and 79 years old, and there was no difference in the odds in the TS between those aged over 80 years and those who were between 70 and 79 years old.

Concerning education, it was observed that the odds ratio of higher TS was 2.28 times higher in those with 9 years or more of education compared to those with 4 years or less. In addition, there were no differences in the odds between patients with 5 to 8 years of education and 4 years or less. The ordered logistic model assumes proportionality of odds across response categories, which was not violated.

| | VFf | | | | | | Total | | p |
| | PV | | CV | | NV | | | | |
	N	%	N	%	N	%	N	%	
Sex	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	0.823
Male	49	25.9%	5	20.8%	24	23.8%	78	24.8%	
Female	140	74.1%	19	79.2%	77	76.2%	236	75.2%	
Age in years	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	0.001
59-69	48	25.4%	7	29.2%	47	46.5%	102	32.5%	
70-79	95	50.3%	14	58.3%	45	44.6%	154	49.0%	
>80	46	24.3%	3	12.5%	9	8.9%	58	18.5%	
Education in years	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	<0.001
≤ 4	90	47.6%	10	41.7%	24	23.8%	124	39.5%	
5-8	69	36.5%	4	16.7%	31	30.7%	104	33.1%	
>9	30	15.9%	10	41.7%	46	45.5%	86	27.4%	
Groups	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	<0.001
Control	37	19.6%	13	54.2%	76	75.2%	126	40.1%	
MCI	43	22.8%	8	33.3%	20	19.8%	71	22.6%	
MAD	42	22.2%	3	12.5%	5	5.0%	50	15.9%	
ModAD	67	35.4%	0	0.0%	0	0.0%	67	21.3%	
Cf /p/./b/./m/ bilabial	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0.b.%**	0.085
No	95	50.3%	11	45.8%	37	36.6%	143	45.5%	
Yes	94	49.7%	13	54.2%	64	63.4%	171	54.5%	
Cf /k/./g/ velars	**187**	**100.0%**	**24**	**100.0%**	**100**	**100.0%**	**311**	**100.0%**	<0.001
No	177	94.7%	19	79.2%	69	69.0%	265	85.2%	
Yes	10	5.3%	5	20.8%	31	31.0%	46	14.8%	
Cf open vowel /a/	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	0.002
No	175	92.6%	19	79.2%	80	79.2%	274	87.3%	
Yes	14	7.4%	5	20.8%	21	20.8%	40	12.7%	
Cf closed vowel /u/	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	<0.001
No	187	98.9%	20	83.3%	91	90.1%	298	94.9%	
Yes	2	1.1%	4	16.7%	10	9.9%	16	5.1%	
Cf /l/ Liquid	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	0.073[a]
No	189	100.0%	24	100.0%	98	97.0%	311	99.0%	
Yes	0	0%	0	0.0%	3	3.0%	3	1.0%	
Cf /t./d/	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	<0.001[a]
No	187	98.9%	24	100.0%	88	87.1%	299	95.2%	
Yes	2	1.1%	0	0.0%	13	12.9%	15	4.8%	
Cf /f/./v/ fricatives	**189**	**100.0%**	**24**	**100.0%**	**101**	**100.0%**	**314**	**100.0%**	0.361[a]
No	185	97.9%	23	95.8%	96	95.0%	304	96.8%	
Yes	4	2.1%	1	4.2%	5	5.0%	10	3.2%	

CV: Cut-Off Group Value; PV: Positive Group Value; NV: Negative Group Value
P<0.05–chi-squared or Fisher's exact tests (a). Descriptive level of the chi-squared or Fisher's exact tests (a)

Table 1: Patients distribution by sex, age, education, AD groups and Cf according to the cut-off groups of VFf.

Table 3 shows the simultaneous effects of sex, age, education, CDT and MSSE scores, and resources types (predictor variables) of VFf (dependent variable) examined with the ordered logit regression model: Cf /p/, /m/, /b/, Cf /k/, /g/, / Cf vowel /a/ and Cf vowel /u/. Remained significant in the final model: age range 59 to 69 years (p=0.011) and >80 years (p=0.042), CDT score (p<0.001) and the use of Cf /k//g/ velars (p<0.001). Education (p=0.059) was maintained in the model because it was marginally significant. Thus, it was found that the odds of higher NV in participants who used Cf /k/, /g/ velars were 4.11 times greater than in those who did not. This odds ratio was approximately 9 times higher for those who used Cf (/t/, /d/) dento-alveolar. Additionally, younger patients had higher chances (2.22 times) of having NV than did patients who were between 70 and 79 years old. This chance was 57% lower in those aged over 80. Finally, it was found that for every 1 additional points on the CDT, there was an increased chance of 67% of the participant having a higher TS. The ordered logistic model assumes proportionality of odds across response categories, which was not violated.

ROC Curve Analysis

VFf adequately discriminated CG from MCI, MAD and ModAD, also MCI from MAD and MCI x ModAD in the total sample. The accuracy was moderate in discriminating the CG from the MCI group and the MCI from the MAD group, but good in discriminating the CG from the MAD group and the MAD from the ModAD group, and excellent in discriminating the CG from the AD groups when considered together (Table 4).

	Initial model		Final model	
	ODDS RATIO (CI 95%)	**p**	**ODDS RATIO (CI 95%)**	**p**
Man (ref.=Woman)	1.23 (0.62-2.44)	0.556	-	ns
Age (ref.: 70-79) in years				
59-69	3.08 (1.57-6,05)	0.001	3.06 (1.56-5.99)	0.001
>80	0.48 (0.21-1.12)	0.09	0.48 (0.21-1.12)	0.09
Education (ref.: ≤ 4 years)				
05-08	1.12 (0.54-2.32)	0.752	1.12 (0.55-2.27)	0.762
>9	2.28 (1.10-4.75)	0.028	2.28 (1.12-4.63)	0.023
Group (ref.: CG)				
MCI	0.26 (0.12-0.57)	0.001	0.27 (0.13-0.58)	0.001
MAD and ModAD	0.10 (0.04-0.30)	<0.001	0.11 (0.04-0.30)	<0.001
MSSE	0.98 (0.86-1.10)	0.683	-	ns
CDT	1.33 (1.07-1.66)	0.01	1.32 (1.06-1.63)	0.012
Cf /p/,/m/,/b/ bilabial (ref.: no use)	2.08 (1.15-3,77)	0.016	2.04 (1.13-3.67)	0.018
Cf /k/,/g/ velars (ref.: no use)	2.61 (1.17-5.82)	0.019	2.51 (1.14-5.51)	0.022

Test of proportionality of odds across response categories: initial model (p=0.425) and final model (p=0.694)
ns: non-significant; MMSE: Mini-Mental State Examination; CDT: Clock-Drawing Task, MCI: Mild Cognitive Impairment; MAD: Mild Alzheimer Disease; ModAD: Moderate Alzheimer Disease, N=311

Table 2: Initial and final ordered logit models for Cf.

	Initial Model		Final Model	
	Odds Ratio (CI 95%)	**p**	**Odds Ratio (CI 95%)**	**p**
Man (ref=Woman)	1.04 (0.54-2.02)	0.902	-	ns
Age (ref: 70-79 years)				
59-69 years	2.33 (1.24-4.36)	0.008	2,22 (1.20-4.08)	0.011
80>	0.43 (0.19-0.98)	0.045	0.43 (0.19-0.97)	0.042
Education (ref.: ≤ 4 years)				
5-8	0.89 (0.44-1.80)	0.742	0.93 (0.47-1.86)	0.846
9>	1.78 (0.88-3.63)	0.110	1.88 (0.96-3.70)	0.066
MSSE	1.08 (0.97-1.21)	0.167	-	ns
CDT	1.57 (1.18-2,08)	0.002	1.67 (1.29-2.18)	<0.001
Cf /p/,/m/,/b/ bilabial (ref.: no use)	1.64 (0.92-2,91)	0.092	-	ns
Cf /k/,/g/ velars (ref.: no use)	3.70 (1.67-8,21)	0.001	4.11 (1.97-8.54)	<0.001
Cf Vowel /a/(ref.: no use)	1.22 (0.57-2,65)	0.607	-	ns
Cf vowel/u/ (ref.: no use)	1.31 (0.37-4.65)	0.672	-	ns
Cf /t/,/d/dento alveolar (ref.: no use)	8.46 (1.67-42.83)	0.010	8.87 (1.79-43.79)	0.007
Cf /f/,/v/ fricatives (ref.: no use)	2,52 (0.61-10.39)	0.202	-	ns

Parallelism test: Initial model (p=0.313) and initial model (p=0.292)
ns: not significant; N=311

Table 3: Initial and final ordered logit models for Cf.

	Cut-off scores	Sensitivity%	Specificity%	AUC ± (SD)	p (2-tailed)	CI% AUC
CG × MCI	13	0.706	0.606	0.729 (0.038)	<0.001	0.655-0.803
CG × MAD	12	0.817	0.82	0.865(0.33)	<0.001	0.800-0.930
CG × ModAD	8	0.968	0.806	0.984 (0.008)	<0.001	0.968-1.0
CG × AD	10	0.96	0.795	0.933(0.017)	<0.001	0.899-0.967
MCI × MAD	10	0.746	0.56	0.720(0.048)	<0.001	0.626-0.815
MAD × ModAD	7	0.82	0.657	0.838	<0.001	0.764-0.912

SD: Standard Deviation; AUC: Area Under the Curve; CI: Confidence Interval; AD=MAD+ModAD

Table 4: Cut-off scores, sensitivity and specificity for the VFf category in the discrimination between CG, MCI, MAD and ModAD.

Discussion

In this study, we evaluated the performance in TS and Cf among elderly control participants and patients in the AD spectrum and examined the underlying cognitive structure of their verbal fluency. The VFf in CG had an articulatory pattern that underlined the semantic category that progressively decreased in patients with AD. Measures of VF, such as Animal Fluency, are often thought to be measures of executive functioning (EF). However, some studies have indicated that there is also a language component to these tasks. Several studies have tried to separate these two components. These studies did not exclude EF as a determinant of verbal fluency, but they did suggest that language processing is the critical component for this task [22,23].

Deficits are frequently noted in AD in the lexical semantic [24] and pragmatic domains of language in the early stages of the disease,

while the articulatory phonological and syntactic aspects of language production are often reported to be relatively well preserved until the late stages of the c. Therefore, the VF is mostly used to investigate semantic problems, although semantic retrieval may be intact, but psychomotor speed may justify impaired performance. Our data showed a progressive loss in Cf performance in patients on the AD spectrum, as category-specific deficits were enhanced, but also in the early stages of the disease. In addition, the PV group had the lowest percentages of Cf /k/, /g/ velar (5.3%), Cf /a/ open vowel (7,4%), Cf /u/ closed vowel (1.1%) and Cf /t/, /d/ dento-alveolar (1.1%) compared to the other groups, indicating a degree of degradation on the articulatory level. Moreover, the use of bilabials and velars, together, guaranteed greater TS. Participants who used Cf /p/, /m/, /b/ bilabial had 2.04 times higher total scores than those who did not. This odds ratio was approximately 2.51 times higher for those who made use of Cf (/k/, /g/) velars, perhaps because of sub-articulation, that assured greater velocity on the opposite emission site in passive/active points.

It was also observed that patients with MCI had a 73% lower chance of attaining an NV than did the CG; a finding that exposes early semantic/articulatory degradation and the great relevance of the use of the VFf in clinical practice regarding its cognitive screening sensitivity in detecting AD at the early stage.

Odds ratio of higher TS was 2.28 times higher in those with 9 years or more of education compared to those with 4 years or less. These findings may be explained by the fact that individuals with high levels of literacy have similar cerebral organization, as shown in studies combining neuroimaging techniques and neuropsychological tasks, which provided significant evidence of the association between education level and cognition. There was more evidence of the impact of formal education on test performance. Specifically, lower performance was noted in those with less than 4 years of education (47.6%) and in ModAD group (35,4%); the appropriate group presented 46.5%, higher education (45.5%). Controversial findings have shown that highly educated participants outperform those with less education in verbal fluencies tasks, but other investigations have presented different findings [25-27], most likely due to population sampling and heterogeneous data analysis methods, such as reduced time for word searching.

The effect of age on VFf was also noted as younger participants had a greater odds ratio (3.06 times) of attaining an NV than did those who were between 70 and 79 years old; even though, there was no difference in the odds ratio for TS between those aged over 80 years and those who were between 70 and 79 years old. Age has been shown to impact verbal fluency performance [28-32]. Several studies have shown an age-related decrease in the total number of words produced in the category fluency task. Some studies have shown an age-related decrease in the total number of words produced, whereas other studies have reported that performance was stable across the tested age range. Studies regarding articulation in the Brazilian population have shown disruption rates and a decrease in the speech rate only in individuals aged 80 years old or older.

The NV group presented the highest percentage of use of Cf /t/, /d/ dental/ alveolars (14.8%). The MCI and AD groups presented odds ratios of using the Cf /k/, /g/ velars feature 85% lower than those of the CG. In addition, with each increase of 1 unit in the CDT, there was a 27% increase in the probability of using Cf /k/, /g/ velars, which showed that the use of velars provided a gain in performance in the VFf.

Our results are consistent with previous studies conducted in Brazil with respect to the mean scores of controls, MCI, and patients with AD in VFf. In addition, our results showed that VFf had better sensitivity with the progression of the disease (in MAD and ModAD) and better specificity in discriminating the CG from the ModAD group when articulatory degradation progresses more intensely. Articulatory components in patterns that underline VFf may explain differences in sensitivity and specificity between variants on Vfs among AD stages.

Conclusion

In conclusion, the VFf seems to be a suitable task for AD evaluation, which could be further, verified in future studies by assessing a larger sample with additional executive tests. The Cf analysis revealed a pattern of language organization based on memories of sensory and motor action arranged in clusters that seems to be sensitive to the progressive impact of AD on language and executive function, and may typically differ from other SVF tasks. Some limitations of our study should be mentioned; namely, the absence of previous studies in Brazilian Portuguese on articulation points in CGs and patients with AD. Furthermore, a more detailed analysis of clustering strategies in other fluency tasks should be conducted. The VFf task results indicated this may be the most promising paradigm for investigating certain language structure issues, such as how category semantic items are grouped in the brain.

In addition, neuroimaging studies have shed light on the different activated areas depending on the SVF modality and could probably enhance the knowledge of the language and executive function mechanisms underlying SVFs.

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