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Recurrent Perseverations on Semantic Verbal Fluency Tasks as an Early Marker of Cognitive Impairment

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Abstract

INTRODUCTION: Our objective was to examine the association between perseverations produced on the semantic verbal fluency (SVF) task in asymptomatic individuals and the future diagnosis of cognitive impairment (CI).

METHOD: Participants were individuals participating in the Mayo Clinic Study of Aging (N: 1,269, mean age: 79.3 SD 5.1 years; 51% men). All were cognitively normal at baseline and were followed in 15-month intervals for up to 6 visits. Each neurocognitive assessment included SVF tasks (“animals”, “fruits”, and “vegetables”). Cox modeling was used to test for associations between perseverations and time to CI diagnosis.

RESULTS: Perseverations on the “animals” SVF task were associated with incident CI (hazard ratio: 1.35; 95% CI: 1.10 – 1.66). No significant association was found with perseverations on the “fruits” or “vegetables” SVF tasks. Mixed-effects modeling in cognitively normal participants revealed that the number of perseverations at baseline is significantly associated with decline in memory and visuospatial cognitive domains but is not associated with decline in attention.

CONCLUSIONS: Assessing perseverations together with standard SVF scores on the “animals” SVF task can help in early identification of asymptomatic individuals at an increased risk for CI. Perseverations are not associated with attention, but rather visual and verbal working memory mechanisms. In longitudinal settings aimed at early detection of signs of CI in pre-symptomatic individuals, SVF testing with scoring that includes counting of perseverations may potentially serve as a practical alternative to the more cumbersome memory tests.

Keywords

verbal fluency; Alzheimer’s disease; dementia; perseverations; cognitive impairment

Introduction

Subtle cognitive changes identified with comprehensive neuropsychological tests occur a decade or more preceding incident dementia (Aguirre-Acevedo et al., 2016; Rajan, Wilson, Weuve, Barnes, & Evans, 2015); however, these tests are labor-intensive to administer and score. Thus, despite their ability to detect subtle changes, the use of these instruments is limited to clinical settings that specialize in cognitive testing, which precludes their application to frequent serial monitoring of cognitive health in large pre-symptomatic populations. Recent work on early cognitive changes associated with Alzheimer's disease (AD) dementia has focused on developing alternatives to the comprehensive neuropsychological test batteries that can be computerized and are easy to administer by the clinician or self-administer by the patient (J. Kaye et al., 2014; J. A. Kaye et al., 2011; Silverberg et al., 2011). Cognitive tests of verbal fluency (VF) constitute a good candidate for an automated assessment instrument to identify early signs of cognitive impairment. Performance of the VF task relies heavily on executive function and both semantic and episodic memory (Mayr, 2002) – cognitive domains affected by AD early in the course of the disease (Silverberg et al., 2011). Thus, VF tests typically included in standard cognitive assessment batteries used to study dementia are sensitive to cognitive impairment associated with AD dementia (Henry, Crawford, & Phillips, 2004) and have been previously recommended as a clinical diagnostic tool (Canning, Leach, Stuss, Ngo, & Black, 2004).

Typical administration and scoring of VF tests is done with paper and pencil and is limited to counting the total number of correct words produced by the patient in 60 seconds that either start with the provided letter of the alphabet (PVF: phonemic verbal fluency) or belong to the specified semantic category (SVF: semantic verbal fluency). SVF performance was found to be particularly sensitive to AD dementia and superior in its diagnostic utility to letter fluency (Brickman et al., 2005; Cerhan et al., 2002). SVF tests were also found to be a good screening mechanism for early detection of dementia and amyloidosis in people with Down's syndrome (Hoyo et al., 2015), and a sensitive predictor of mortality in patients with AD dementia (Cosentino, Scarmeas, Albert, & Stern, 2006).

Errors on SVF and PVF tests, including out-of-category words and repeated correct words (perseverations) are not typically included in clinical assessments but have been extensively investigated in research settings. In particular, perseveration errors were found to be associated with multiple neurological disorders including mild and moderate Alzheimer's disease dementia (Fischer-Baum, Miozzo, Laiacina, & Capitani, 2016; McDowd et al., 2011; Pekkala, Albert, Spiro III, & Erkinjuntti, 2007). The association between perseverations produced by cognitively normal individuals as an early marker of incident dementia has not been extensively investigated.

Following the taxonomy proposed by Sandson and Albert, perseverations on SVF tests can be categorized into three distinct forms - recurrent, continuous and stuck-in-set (Sandson & Albert, 1984, 1987). In the current analysis, we focus on recurrent perseverations – words that were repeated on a cognitive task but may be separated by other intervening words. The cognitive mechanisms postulated to be responsible for recurrent perseverations on VF tests include impairment in frontally-mediated working memory, attention and inhibition -

processes needed to maintain reference to the items already produced in response to the task and disallow their repetition (Azuma, 2004; Rosen & Engle, 1997). The association between the decline in working memory capacity and prevalent dementia, including in its early stages, is well documented (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; MacPherson, Della Sala, Logie, & Wilcock, 2007; Stopford, Thompson, Neary, Richardson, & Snowden, 2012). Thus, perseverations on VF tests may signal pathological changes in the brain that begin to take place well in advance of the onset of more obvious symptoms of incident dementia (Reiman et al., 2012).

The objectives of the current study were to determine a) the potential of SVF testing as a lightweight alternative to comprehensive cognitive assessment, and b) if qualitative aspects of SVF performance such as perseverations are associated with incident cognitive impairment in pre-symptomatic individuals and should be included as part of the SVF assessment strategy aimed at early assessment of dementia risk.

Methods

Participants

The initial longitudinal cohort consisted of 2,719 participants in the Mayo Clinic Study of Aging (MCSA) cohort started on October 1, 2004 (see (Roberts et al., 2008) for detailed description). These participants were all adjudicated as cognitively normal (CN) at the baseline assessment in year 2005 and were subsequently assessed at approximately 15-month intervals for up to 6 additional study visits. The present study was restricted to 1,376 of the initial cohort participants who completed at least two MCSA assessments by December 1, 2013. The present study participants had 3.26 (SD 1.76) assessments on average with a mean follow-up of 5.46 (SD 2.08) years. Participants with APOE genotypes 3/4 and 4/4 were labeled as APOE4 carriers. Of the 1,376 participants in the initial cohort, 896 remained cognitively normal throughout the study.

We performed two types of longitudinal analyses: a) survival analysis to examine the association between perseverations at the baseline assessment and incident cognitive impairment (diagnoses of MCI or AD), and b) mixed-effects modeling in a subgroup of participants who remained CN throughout the study follow-up period to examine the relationship between perseverations and domains of cognitive functioning (memory, attention, and visuospatial). The latter analysis was conducted in CN individuals in order to control for the effects of any incident cognitive impairment in one or multiple domains.

Clinical and Cognitive Assessments

At each study visit, all participants underwent clinical evaluation and neuropsychological testing. Clinical evaluation included a complete neurological examination, the Clinical Dementia Rating scale (Morris, 1993), and the Short Test of Mental Status (STMS; Kokmen, Smith, Petersen, Tangalos, & Ivnik, 1991) among other assessments previously published elsewhere (Roberts et al., 2008). A decision about diagnoses of CN, mild cognitive impairment (MCI) or dementia was based on a consensus agreement among the examining

nurse, physician, and neuropsychologist. The clinical evaluations were performed without using information from imaging or other biomarkers acquired during the study.

All participants were administered a neuropsychological testing battery consisting of nine tests. The tests were selected to assess function in four domains: *memory* (delayed free recall percent retention scores for Wechsler Memory Scale-Revised Logical Memory and Visual Reproduction tasks (Wechsler, 1981), and the Auditory Verbal Learning Test (Ivnik et al., 1992)); *language* (Boston Naming test (Kaplan, Goodglass, & Weintraub, 1983) and SVF (Lucas et al., 1998)); *attention aspect of executive function* (Trail Making Test, Part B (Reitan, 1958) and Digit Symbol Substitution subtest from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981)); and *visuospatial skills* (picture completion and block design (Wechsler, 1981)). The raw scores on each test were adjusted for age using normative data from the Mayo Clinic's Older American Normative Studies (Ivnik et al., 1992). The adjusted test scores within each domain were summed and scaled to obtain domain-specific and global z-scores (Roberts et al., 2008) used in the current analysis.

Quantitative cut-off scores were based on normative data and extensive experience with the measurement of cognitive abilities in the target population via neuropsychological domain performance scores. Values worse than -1.5 SD were considered as typical for MCI or dementia. However, based on our long-used approach (Petersen, 2004; Petersen et al., 1999), cut-off scores for neuropsychological tests were used as a guide to reach consensus for diagnosis rather than as an absolute criterion.

A diagnosis of MCI was established based on the following: a) cognitive concern was raised by the participant, informant, nurse, or physician; b) impairment in 1 or more of the 4 cognitive domains (see description of neuropsychological assessments above); c) normal functional activities; and d) absence of dementia. A diagnosis of dementia was based on *DSM-IV* criteria (American Psychiatric Association, 1994). Subjects were considered to be cognitively normal if they performed within the normative range and did not meet criteria for MCI or dementia.

For this analysis, we did not try to account for instances in which participants reverted from MCI to CN, or from dementia to CN or MCI status. The majority of people reverting to CN from a cognitively impaired status ($n=81$) did so temporarily and were subsequently re-diagnosed with either MCI or dementia (Roberts et al., 2014). Thus, once a participant was diagnosed with either MCI or dementia, he/she was assigned to the corresponding diagnostic group even if he/she was diagnosed as CN on a subsequent visit. This approach likely resulted in a more conservative analysis because those participants who temporarily reverted from MCI to CN status were likely to have milder impairment and would tend the results towards less of a difference compared to CN.

Measuring Perseveration on SVF Tests

All SVF responses were manually digitized by three University of Minnesota linguistics students who entered into a computerized database all words produced by study participants and recorded on paper by the study psychometrists. Counting of recurrent perseverations was performed by a computer program.

Statistical Analysis

The relationship between baseline perseverations and risk of cognitive impairment was tested using Cox proportional hazards modeling with age (rather than time in study) as the time scale. Perseveration counts were entered as a dichotomous variable that was set to “0” (no perseverations were found in the sample) or “1” (one or more perseverations were present). We also tested an alternative continuous representation of this variable, which yielded similar AIC values and coefficients to the model with the dichotomous representation. We chose to report the Cox modeling results obtained with the dichotomous predictor due to relative ease of interpretation and because few people had more than 2 perseverations. Since perseveration counts are not independent of the total number of words produced on SVF tests, all Cox models of perseverations also included the raw SVF score as an adjustment covariate along with APOE4 genotype, age, sex and years of education.

In order to aid in the interpretation of hazard ratios, we standardized the unit change in predictor variables (i.e. memory, attention, visuospatial, and language domains, SVF scores and perseverations) to represent the mean 5-year change in these scores that reflects the degree to which the CN population of the current study declined or improved over a 5-year period.

Testing for associations between perseverations and cognitive domains of memory, attention and visuospatial abilities was performed in a subset of participants who remained CN throughout the study. The CN subset was defined by excluding all visits for participants who received any incident diagnosis of cognitive impairment or dementia at any time during the follow-up period. Baseline perseveration counts were entered into mixed-effects regression models (one for each cognitive domain) as a predictor variable along with time (years since baseline visit), baseline SVF score, APOE genotype, age, sex and years of education. In this study we were interested in looking for possible cognitive mechanisms associated with perseverations. Thus, we only wanted to test for associations between perseverations on SVF tests at baseline and longitudinal change in cognitive domain scores rather than measure the exact nature of the impact a unit change in the perseveration variable would have on the response variables. Therefore, we chose to use continuous perseveration counts (log-transformed to account for their long-tailed distribution) for the mixed-effects analysis. A count of 1 was added to all values to avoid taking a log of zero.

Testing for differences in proportions (e.g. proportion of participants with APOE4 genotype in the cognitively normal vs. cognitive impaired groups) was done using the parametric chi-squared test, while testing for differences in means (e.g., age) was done using 2-sample t-tests. Effect sizes reported in Table 1 were calculated as Cohen’s d for t-tests and Cohen’s h for chi-squared tests. For making statistical significance inferences, where appropriate, a threshold of $p < 0.05$ was used. All statistical computation was performed using the R statistical package (version 2.15) with the ‘nlme’ (version 3.1–128) and ‘survival’ (version 2.37–7) libraries (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2016; Therneau & Grambsch, 2000).

Results

The cohort of 1,376 participants was further restricted based on availability of SVF scores and legible hand-written psychometric worksheets. In order to examine the relationship between perseveration on three SVF tasks (“animals”, “fruits”, and “vegetables”) and incident cognitive impairment, we excluded participants who did not have a response to all three SVF tasks at baseline. After these exclusions, the final set consisted of 1,269 people (mean age 79.3, SD 5.1 years; 643 men (51%)). Of these participants, 896 (71%) remained CN throughout the study and 373 (29%) received a diagnosis of cognitive impairment (MCI or dementia) during follow-up. The study sample characteristics are summarized in Table 1. Overall, the initially CN participants who were subsequently diagnosed with cognitive impairment were slightly older (by approximately 2 years on average), had slightly fewer years of education (by less than one year on average), were more likely to be heterozygous or homozygous for the APOE4 allele, and produced fewer correct words and more perseverations on all three SVF tests at the baseline visit. There were no differences between these groups by sex.

Effect of Baseline Cognitive Performance on Time to Cognitive Impairment

Cox proportional hazards models that included z-scores for the language, memory, attention and visuospatial cognitive domains showed that all baseline individual domain scores were significantly associated with the hazard of subsequent cognitive impairment (HR: 0.43, 95% CI: 0.37 – 0.49 for memory; HR: 0.52, 95% CI: 0.46 – 0.58 for attention; HR: 0.63, 95% CI: 0.56 – 0.71 for visuospatial; and HR: 0.56, 95% CI: 0.50 – 0.64 for language).

Effect of Baseline SVF Performance on Time to Cognitive Impairment

Cox proportional hazards models that included SVF scores for each of animals, vegetables, and fruits categories showed that all baseline SVF scores were significantly associated with the hazard of subsequent cognitive impairment (HR: 0.93, 95% CI: 0.91 – 0.96 for animals; HR: 0.91, 95% CI: 0.88 – 0.94 for vegetables; HR: 0.93, 95% CI: 0.90 – 0.96 for fruits).

Effect of Perseverations on Time to Cognitive Impairment

Cox proportional hazards modeling revealed that having one or more perseverations on the baseline “animals” SVF test was significantly associated with increased hazard of subsequent cognitive impairment diagnosis by 35% (HR: 1.35, 95% CI: 1.10 – 1.66). The hazard associated with perseverations in responses to other SVF categories was in the same direction as that for the “animals” category but was smaller in magnitude and not statistically significant (“fruits” - HR: 1.05, 95% CI: 0.85 – 1.28; “vegetables” - HR: 1.07, 95% CI: 0.87 – 1.31). Combining the counts of perseverations across “animals”, “fruits”, and “vegetables” categories resulted in the same increased hazard of subsequent cognitive impairment diagnosis of 35% (HR: 1.35, 95% CI: 1.06 – 1.73) as with the “animals” category alone.

Table 2 and Figure 1 show the results of comparing time to cognitive impairment in subgroups defined by the SVF score on the “animals” test at baseline (high vs. low using the median score as the cutoff), and the presence or absence of perseverations in test responses.

The median age attained without a cognitive impairment diagnosis was highest in participants who had no perseverations and high SVF scores (91.1 y. o.) and lowest in participants with lower SVF scores with one or more perseverations (84.4 y. o.). In the high SVF group, presence of perseverations was associated with significantly increased hazard of cognitive impairment diagnosis by 53% (HR: 1.53, 95% CI 1.06 – 2.21). In the low SVF group, presence of perseverations was also associated with increased hazard of cognitive impairment but to a lesser extent and with marginal statistical significance (HR: 1.28 95% CI: 0.99 – 1.64). The Kaplan-Meier estimates from unadjusted model fits (see Figure 1) show that in this population the survival curves for the group with higher SVF scores and no perseverations (solid black line) and the group with lower SVF scores with perseverations (dashed black line) begin to diverge when participants are in their late 70s and continue to diverge into the 90s.

Cognitive Domains Associated with Perseverations

Table 3 summarizes the results of mixed-effects modeling to test for associations between the number of perseverations produced on the baseline SVF tests and the composite z-scores in each of memory, attention and visuospatial domains. Overall trajectories in the response variables show a slight improvement over time in the memory domain, a decline in attention, and no significant change in the visuospatial domain. Perseverations at baseline were associated with worse performance in all three domains but were found to be significant predictors only in memory and visuospatial domains, but not attention.

These results are corroborated by a stepwise Cox regression analysis in which we added, one at a time, the z-scores for memory, attention, and visuospatial cognitive domains as covariates along with the “animals” SVF score, perseverations, APOE4 genotype, age, sex, and years of education. This analysis showed that perseverations do not significantly contribute to the model that includes memory (perseveration HR: 1.17, 95% CI: 0.95 – 1.44) but do contribute to models that include attention (perseveration HR: 1.30, 95% CI: 1.06 – 1.59) or visuospatial (perseveration HR: 1.27, 95% CI: 1.04 – 1.57) domains.

Relative Effects of Cognitive Measures on Time to Cognitive Impairment

Mean 5-year changes in predictor variables in the study population, and the Cox hazard ratios standardized by the 5-year change in these predictor variables (sHR), are shown in Table 4. A decrement in the attention domain scores equivalent to a mean 5-year change shows the greatest effect on time to dementia diagnosis (sHR: 1.29), followed by language (sHR: 1.17), visuospatial (sHR: 1.12), and memory (sHR: 1.05) domains. The hazard ratio associated with performance on the SVF (animals category) test with perseverations included in the model (sHR: 1.15) was half of the sHR for the attention domain but three times larger than sHR for the memory domain.

Discussion

Our results confirm findings from prior studies (Aguirre-Acevedo et al., 2016; Rajan et al., 2015) that performance in several cognitive domains is significantly associated with future cognitive impairment. The novel contribution of our analysis is that recurrent perseverations

on the “animals” SVF test in cognitively normal older individuals portends a significantly higher hazard of cognitive impairment diagnoses. This finding extends previous studies showing that perseverations are more prevalent in mild and moderate dementia (Miozzo, Fischer-Baum, & Caccappolo-van Vliet, 2013; Pekkala et al., 2007). Our analysis also confirms the findings of multiple previous studies that identified VF tests as sensitive to dementia (see (Henry et al., 2004) for review) and provides additional evidence that decreased SVF performance (in the form of perseverations) in cognitively normal individuals is associated with incident cognitive decline (Baddeley et al., 1991; MacPherson et al., 2007; Stopford et al., 2012).

No association was found between incident cognitive impairment and perseverations on SVF tests that used “fruits” and “vegetables” categories. This is likely due to the fact that “fruits” and “vegetables” categories contain fewer exemplars than the “animals” category. In a prior study, Pekkala (Pekkala et al., 2007) found that cognitively normal participants and patients with dementia produce fewer words and more perseverations in response to the “vegetables” category as opposed to the “animals” category. Our results (Table 1) are consistent with Pekkala’s (2007) findings and show that participants produced almost half as many words and double the density of perseverations on “fruits” and “vegetables” as compared to their performance on the “animals” category, suggesting that larger categories such as “animals” may provide a more sensitive mechanism for early detection of cognitive decline than smaller categories. An effective strategy in clinical settings may be to lengthen the time allotted for naming animals to increase the load on working memory. This potential strategy is consistent with work by Holtzer et al. (2009) on letter fluency tasks showing that extending administration time to 2 minutes increases the discriminative ability of the test to distinguish between controls and cognitively impaired groups.

Contrary to prior studies postulating that inhibition and attention involved in monitoring verbal output are major components of cognitive mechanisms responsible for perseverations (Rosen & Engle, 1997), our findings suggest that perseverations may be more strongly associated with verbal and visual components of working memory than attention. These findings are supported by recent work by Fischer-Baum et al. (Fischer-Baum et al., 2016) suggesting that perseverations in traumatic brain injury patients stem from the same working memory mechanisms as those proposed in AD dementia and findings that, in general, impairment in episodic memory is one of the most robust early markers of cognitive decline associated with pre-clinical dementia (Howieson, 2016). The results of the current study are also consistent with work by Azuma (Azuma, 2004) in healthy participants showing that working memory loads during VF tasks have a profound effect on the rate of perseverations. Previous studies have also shown that performance on SVF recruits brain areas in the right hemisphere (Katzev, Tuscher, Hennig, Weiller, & Kaller, 2013; Stuss et al., 1998) in addition to the left frontal and temporal regions. It is possible that the cognitive processes responsible for perseverations on SVF rely on the right hemisphere, similarly to the processes involved in visual design tasks (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001), thus providing a potential link between verbal and non-verbal memory mechanisms.

By being strongly associated with memory performance, presence or absence of perseverations was not a significant contributor to predicting cognitive impairment over and above performance on memory tests but was found to significantly contribute to prediction models with attention and visuospatial performance measures. This finding has practical relevance because memory tests exhibit practice effects in serial administration to pre-symptomatic individuals; memory tests without a sufficiently large number of items could also exhibit ceiling effects. Our results indeed show that in CN individuals, memory z-scores actually improved over time (see Table 3) and exert the weakest effect on time to dementia diagnosis (see Table 4) likely due to effects of practice, consistent with prior work (Goldberg, Harvey, Wesnes, Snyder, & Schneider, 2015). Furthermore, some standard memory tests highly sensitive to dementia (e.g. the logical memory test) do not lend themselves well to remote or self-administration and are difficult to score, limiting their application in large longitudinal settings. On the other hand, SVF and attention tests are much easier to administer and score and can be automated or semi-automated using mobile and speech recognition technology (Pakhomov, Marino, Banks, & Bernick, 2015). Prior work also shows that while serial administration of VF tests results in robust practice effects, the effects are small and plateau over multiple trials (Cooper, Lacritz, Weiner, Rosenberg, & Cullum, 2004). The results of the current study suggest that, in longitudinal settings aimed at early detection of signs of cognitive impairment in pre-symptomatic individuals, SVF testing with scoring that includes counting of perseverations may potentially serve as a practical alternative to the more cumbersome memory tests.

Limitations

The participants were older adults (mean age 79), thus our results need to be replicated in younger populations. However, the age range of the current study group spans a major segment of the age-of-onset of dementia due to AD. PVF tests were not administered as part of cognitive assessment in MCSA; however, based on prior literature, we would anticipate similar results with perseverations on PVF as in SVF responses. The participants in this study were almost entirely of European extraction for whom English was their first language. This potentially limits the generalizability of our findings that will need to be replicated in more ethnically diverse populations. Lastly, a number of other measurements such as the degree to which participants use clustering and switching strategies on SVF responses are possible to obtain but were not included in the current study; they may provide further insights into the language manifestations of early prodromal stages of dementia.

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Figure 1.

Kaplan-Meier survival curves showing time to cognitive impairment diagnosis in subgroups defined by high vs. low SVF score and presence vs. absence of perseverations on the “animals” category fluency test. SVF score median is 19 words.

Table 1.

Sample characteristics.

	Not Cognitively Impaired	Cognitively Impaired (MCI or Dementia)	Effect size	p- value#
N	896	373		
Age at baseline, y, mean (SD)	78.5 (5.0)	81.1 (5.0)	−0.54	<0.001
Sex, No. (%)				
Male	51.0	49.7		
Female	48.9	50.3		
Education, y, mean (SD)	14.1 (2.9)	13.5 (3.0)	−0.22	<0.001
Presence of at least one APOE ε4 allele, No. (%)	687 (23)	262 (30)	0.07	0.006
Follow up time in visits, mean (SD) *	3.3 (1.8)	3.2 (1.7)	−0.05	0.059
SVF score at baseline, mean words (SD)				
Animals	20.8 (4.6)	18.7 (4.1)	−0.46	<0.001
Fruits	12.6 (3.5)	11.4 (3.2)	−0.35	<0.001
Vegetables	12.4 (3.5)	11.0 (3.3)	−0.40	<0.001
Perseveration density at baseline (% of total words), mean (SD)				
Animals	7.7 (4.3)	9.1 (5.0)	0.31	<0.001
Fruits	13.1 (8.4)	14.8 (9.3)	0.20	0.003
Vegetables	12.5 (7.7)	14.9 (9.9)	0.29	<0.001

* Follow up time was measured in terms of visits that occurred at variable intervals approximately every 15 months. Thus, for example, a mean follow-up time of 3.2 visits is equivalent to approximately 48 months.

Table 2.

Median survival times (attained age with no cognitive impairment) and hazard of cognitive impairment (see Kaplan-Meier curves in Fig 1) associated with perseverations on the “animals” category SVF test. High vs. Low SVF groups defined based on median score of 19 words.

Subgroups	Counts of participants in subgroups, No. (No. events)	Median age attained with no cognitive impairment*, y	Multivariate-adjusted HR (95% CI) **
All participants			
High SVF score	553 (118)	90.0	0.61 (0.49 – 0.77)
Low SVF score	716 (258)	85.7	--
All participants			
No perseverations	728 (198)	88.3	--
Perseverations	541 (178)	86.1	1.29 (1.05 – 1.58)
High SVF score			
No perseverations	282 (51)	91.1	--
Perseverations	271 (67)	87.2	1.53 (1.06 – 2.21)
Low SVF score			
No perseverations	446 (147)	86.5	--
Perseverations	270 (111)	84.4	1.28 (0.99 – 1.64)

• Median age was obtained from the Kaplan-Meier survival fits and is not adjusted for any covariates.

** Hazard ratio estimates are based on Cox proportional hazards models' coefficients in the corresponding subgroups adjusted for sex, education, and APOE4 status. Models that include perseverations were also adjusted for the raw SVF score.

Table 3.

Results of mixed-effects modeling in CN participants showing associations between baseline SVF characteristics (“animals” SVF test only) and cognitive domains of memory, attention and visuospatial abilities.

	Cognitive domain		
N = 896	Memory	Attention	Visuospatial
	Coeff. (p-value)	Coeff. (p-value)	Coeff. (p-value)
Change over time (per year) in response variable independently of predictors	0.030 (<0.001)	−0.042 (<0.001)	−0.001 (0.858)
Predictors			
Age at baseline, y	−0.028 (<0.001)	−0.058 (<0.001)	−0.046 (<0.001)
Sex, male	−0.449 (<0.001)	−0.403 (<0.001)	0.266 (<0.001)
Education, y	0.057 (<0.001)	0.057 (<0.001)	0.061 (<0.001)
APOE4 status, yes vs. no	0.024 (0.731)	−0.049 (0.402)	−0.066 (0.329)
SVF score at baseline, count	0.049 (<0.001)	0.033 (<0.001)	0.039 (<0.001)
Perseverations at baseline, log(count+1)	−0.271* (<0.001)	−0.059 (0.255)	−0.290 (<0.001)

* −0.271 coefficient for perseverations and memory means that participants with perseverations at baseline had a memory domain z-score on average lower by 0.271.

Table 4.

Mean change in cognitive measures over 5 years in the study population and Cox hazard ratios standardized to reflect the hazard of dementia diagnosis associated with the 5-year change.

Variable	Change over 1 year (Slope coeff.)	Change over 5 years (Slope X 5)	Standardized Cox hazard ratio for a 5-year change (sHR)
SVF test (animals)			
SVF score	−0.330	−1.648	1.124
Perseverations (yes/no) *	0.0137	0.069	1.021
SVF Score + Perseverations	--	--	1.147
Cognitive Domains			
Memory	−0.191	−0.954	1.051
Attention	−6.684	−33.418	1.293
Visuospatial	−0.504	−2.518	1.124
Language	−0.725	−3.624	1.171

* Since this is a dichotomous variable, this quantity represents an estimate of the change in proportion of participants with one or more perseverations over a 5-year period.