Received: 18 October 2022 | Revised: 22 March 2023 | Accepted: 23 March 2023

DOI: 10.1002/alz.13097

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Exploring semantic verbal fluency patterns and their relationship to age and Alzheimer's disease in adults with Down syndrome

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Funding information
National Institute for Health Research networks (mental health, dementias, and neurology) and participating NHS trusts; Wellcome Trust Strategic Award, Grant/Award Number: 098330/Z/12/Z; Medical Research Council, Grant/Award Numbers: MR/S011277/1, MR/ S005145/1,

Abstract

Introduction: Adults with Down syndrome (DS) are at ultra-high risk of developing Alzheimer's disease (AD), characterized by poor episodic memory and semantic fluency in the preclinical phase in the general population. We explored semantic fluency performance in DS and its relationship to age, AD, and blood biomarkers.

Methods: A total of 302 adults with DS at baseline and 87 at follow-up from the London Down Syndrome Consortium cohort completed neuropsychological assessments. Blood biomarkers were measured with the single molecule array technique in a subset of 94 participants.

Results: Poorer verbal fluency performance was observed as age increases. Number of correct words declined in those with AD compared to those without over 2 years

MR/R024901/1; the Swedish Research Council, Grant/Award Number: #2022-01018; European Union's Horizon Europe research and innovation programme, Grant/Award Number: 101053962; Swedish State Support for Clinical Research, Grant/Award Number: #ALFGBG-71320; Alzheimer Drug Discovery Foundation, Grant/Award Number: #201809-2016862; AD Strategic Fund and the Alzheimer's Association, Grant/Award Numbers: #ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C; European Union Joint Programme – Neurodegenerative Disease Research, Grant/Award Number: JPND2021-00694; Alzheimer's Society, Grant/Award Number: AS-CP-18-0020; Jérôme Lejeune Foundation; European Commission, Grant/Award Number: 848077; Bluefield Project; Olav Thon Foundation; Erling-Persson Family Foundation; Stiftelsen för Gamla Tjänarinnor; European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie, Grant/Award Number: 860197; UK Dementia Research Institute, Grant/Award Number: UKDRI-1003; Hjärnfonden, Grant/Award Number: #FO2022-0270

and was negatively correlated with neurofilament light ($r = -0.37$, $P = .001$) and glial fibrillary acidic protein ($r = -0.31$, $P = .012$).

Discussion: Semantic fluency may be useful as an early indicator of cognitive decline and provide additional information on AD-related change, showing associations with biomarkers in DS.

KEYWORDS
Alzheimer's disease, animal subcategories, Down syndrome, glial fibrillary acidic protein, intrusions, neurofilament light, repetitions, semantic verbal fluency

1 | INTRODUCTION

Down syndrome (DS; trisomy of chromosome 21) is a developmental disability estimated to be present in ≈6 million people worldwide.[1,2] Adults with DS are at an increased risk of early-onset Alzheimer's disease (AD)[3] due to *APP* triplication with 90% eventually developing clinical features of AD in their lifetime.[4,5]

DS is characterized by impairment in multiple cognitive domains[6,7] and identifying whether decline during adulthood is attributable to normal aging or AD can be challenging.[8] While combining history, physical examination, and cognitive testing remains the best approach to diagnose AD in DS, there is still a need for tests sensitive to early AD decline.[9] There is some evidence to suggest that in people with DS, executive functioning abilities precede the typical memory loss found in sporadic AD.[10]

One measure closely related to executive functioning that is relatively easy to assess is verbal fluency,[11] a common test which engages cognitive processes and use of retrieval strategies.[12] In the general population, AD is reported to be associated with deficits in verbal fluency, especially semantic fluency,[13] with poorer performance predicting incident dementia 4 to 6 years before clinical diagnosis.[14,15] In adults with DS, deficits in verbal fluency are also associated with age and AD[16–20] with changes in performance suggested to be detected from the age of 35 to 39[21] and observed to be a strong predictor of AD over the age of 40.[17]

While verbal fluency has been identified as a robust measure of cognitive decline and dementia onset in people with DS, the associations with the development of underlying neuropathology has not been established. Plasma biomarkers such as neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) are associated with AD and show promise as diagnostic/prognostic biomarkers of AD in DS.[22–26] In DS, NfL levels have been found to be predictive of AD[26,27] and higher GFAP levels have been observed in response to abnormal brain amyloid beta (Aβ) accumulation.[28] Determining the relationship between verbal fluency and these plasma biomarkers would help illustrate how this task reflects changes in underlying neuropathology.

Current research primarily investigates whether the number of correct words can be predictive of decline in semantic fluency tests.[15,29,30] Less is known about whether errors including repetitions and intrusions, and the variety of animal subcategories, could be used as cognitive markers of preclinical AD in DS. The measure of subcategories is helpful to assess the ability to access a range of subcategories as well as productivity (e.g., to identify the ability to use different subcategories when one is exhausted) and may be sensitive to decline due to AD. In the general population, patients with mild cognitive impairment accessed fewer subcategories compared to healthy older adults.[31–33]

In the non-DS population, results regarding the number of errors as markers for cognitive decline have been inconsistent; one study[34] demonstrated that errors generated showed little difference between those who remain cognitively healthy and those who developed dementia. Yet others have indicated that a high number of repetitions can help in the early identification of cognitive impairment.[35] In DS, the occurrence of intrusions in memory recall tasks have been shown to predict memory decline,[36] suggesting these may warrant further attention in this population.

We aimed to explore the potential association between semantic fluency performance and age using longitudinal data from a large DS

cohort study. We were interested in the number of correct words, intrusions, repetitions, and subcategories produced in adults with DS. People with AD are more impaired on semantic fluency than healthy controls;[13] we thus investigated the ability of these measures to detect differences in participants with and without AD. Finally, we aimed to explore the relationship between verbal fluency and two plasma biomarkers for AD: NfL and GFAP.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed the literature using standard search engines (e.g., PubMed and GoogleScholar). Few studies have investigated whether poor semantic fluency performance can be a predictor of Alzheimer's disease (AD) in Down syndrome (DS) and have supported these findings with plasma biomarkers for AD. However, studies have identified that deficits in verbal fluency performance could be used as cognitive markers of preclinical AD.
2. **Interpretation**: This study indicates that the simple verbal fluency task may provide valuable additional information on early cognitive change due to AD in DS and there is a relationship between verbal fluency performance and measures of neurodegeneration and astrocytic activation.
3. **Future Directions**: These findings contribute to our understanding of the mechanisms of typical age-related declines in verbal fluency in adults with DS and provide evidence for its use as an early indicator of cognitive decline.

2 | METHODS

2.1 | Participants

A total of 327 participants were recruited from the London Down Syndrome Consortium (LonDownS) cohort (from which 25 participants were excluded) and completed baseline assessments, and 87 participants aged ≥36 at baseline completed follow-up assessments 2 years later. Participants aged ≥16 years at baseline with sufficient hearing to comfortably engage with the cognitive tests (with the threshold being the Whisper Test at conversational level), and with mild to moderate intellectual disability (ID) were eligible. Full details regarding participants and the assessments can be found in Startin et al.[37]

Participants aged ≥36 were expected to have AD neuropathology and thus to present with varying degrees of cognitive decline over time with those 16 to 35 years likely to perform near their cognitive peak. Baseline assessments (Time 1, T1) were completed between October 2013 and September 2015, with follow-up assessments ≈2 years later (Time 2, T2). Only older adults participated in follow-up assessments, as young adults < 36 years old should not show significant change in cognitive functioning. For more information regarding participants and the rationale behind the selection of the age groups, refer to Firth et al.[20]

Ethical approval was obtained from the North West Wales Research Ethics Committee (13/WA/0194).

2.2 | Procedure

Outcomes used in the current analysis include a semantic verbal fluency task, cognitive tests, ID severity score, a dementia diagnosis, and measures of NfL and GFAP.

Each participant was administered a semantic verbal fluency task at baseline (T1) and, where relevant, at follow-up (T2), and instructed to name as many different animals as possible in 60 seconds. The total number of correct words generated was recorded along with the number of errors including intrusions (i.e., non-relevant words to the semantic group) and repetitions (i.e., correct words that were repeated such as the same words, the same words with different endings, or the same words coupled with a descriptive word, such as "dog" and "cute dog"). Sex-specific and age-specific words of the same animal species were given credit and not considered a repetition if their phonemic was different (e.g., lion and lioness, cat and kitten). The number of animal subcategories (i.e., the number of subcategories produced within the higher category "animals") was also recorded and assessed using the following categories: wild animals, domestic animals, aquatic animals, reptiles, birds, and arthropods. Three members of the research team met on two occasions to first define subcategories and finally to revise them to ensure they were consistent and culturally appropriate. For example, although snakes could be both wild and domesticated, we agreed that most people would consider snakes to be wild animals. These categories were then consistently applied for all participants. While no credit was given for the word "animal," exemplars such as bird, reptile, fish, and shellfish were given credit and counted toward the number of correct words.

General cognitive abilities were assessed at the two time points using raw scores from the verbal and non-verbal subscales of the Kaufman Brief Intelligence Test Second Edition (KBIT-2).[38] Additionally, abilities and behaviors associated with cognitive decline over the last 2 months were assessed with the Dementia Questionnaire for People with Learning Disabilities (DLD).[39]

ID level was defined according to the International Classification of Diseases 10th Revision diagnostic system[40] and based on parental/caregiver report of the individual's best level of functioning. ID was classified into three levels: mild, moderate, and severe ID. These levels correspond, respectively, to the general functional abilities associated with intelligence quotient levels of 50 to 69, 35 to 49, and <35.

Dementia diagnoses were made by specialists using comprehensive assessments and were extracted from patients' medical history. These assessments were used to identify symptoms of decline in cognition,

adaptive functioning, or behavior indicative of early dementia-related change. Information regarding potential comorbidities (e.g., seizures) were collected in a semi-structured informant interview and physical health check.

In participants where blood samples were able to be collected, venipuncture of the antecubital fossa was generally performed on the same day as neurocognitive assessment. Plasma samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes using a closed Vacutainer system with a butterfly needle. Samples were centrifuged at 2000 × g at 4∘C for 10 minutes; aliquoted into 250 μL cryotubes; and stored at the Social, Genetic and Developmental Psychiatry Centre, King's College London at −80∘C until analysis. NfL and GFAP concentrations were measured with automated the single molecule array (Simoa) technique using Quanterix at the Clinical Neurochemistry Laboratory, University of Gothenburg. Repeatability for NfL was 4.5% and for GFAP 3.9%. Precision was 6% for NfL and 4.1% for GFAP. Additional details of the sample collection are described in the supplementary methods in supporting information.

2.3 | Statistical analysis

Descriptive statistics were used to summarize the sample and its characteristics. Because age in DS is strongly associated with AD, linear regressions were performed to determine an association with age as a continuous variable and verbal fluency ability adjusting for sex, ID severity, verbal knowledge (KBIT-2), and AD diagnosis, and to investigate changes in verbal fluency performance within subjects at baseline and follow-up. We tested associations between NfL and GFAP samples, and verbal fluency ability with Spearman's rank correlation tests and partial correlation tests adjusting for age, sex, and ID severity. Furthermore, an adjusted logistic regression model was used to identify differences in verbal fluency ability between those with and without AD, adjusting for sex, ID severity, verbal knowledge (KBIT-2 scores), and age.

Statistical significance was set at $P < .05$. All statistical analyses were performed using the statistical software packages SPSS (version 25.0; SPSS Inc.).

3 | RESULTS

The analysis included 302 participants at baseline (T1) and 87 participants at follow-up (T2) with demographic characteristics and mean scores for both younger and older adult groups presented in Table 1. From the original cohort, 25 participants (8 with AD, 14 males, mean age = 46.48, standard deviation [SD] = 14.53) were excluded from the following analysis due to the inability to produce any words during the verbal fluency task at baseline. However, participants who were able to produce words at baseline but unable to produce any at follow-up were included in the analysis because it might be indicative of cognitive decline. Additionally, 83 participants were lost to follow-up (mean age = 50.31, SD = 8.56) including 21 with a diagnosis of AD (constituting 56.7% of those with AD at baseline), 41 males (49.4%), and 7 who died between baseline and follow-up.

3.1 | Verbal fluency and age at baseline

Linear regression was performed to ascertain the relationship between the number of correct words, intrusions and repetitions, and age adjusting for sex, verbal knowledge, ID severity, and AD diagnosis at T1 (across both groups of participants). As shown in Table 2, the number of correct words had a statistically significant relationship with age, with fewer words as age increases (adjusted R square = 19.5%). Neither intrusion nor repetition scores were significantly associated with age (unadjusted results can be found in the supplementary tables in supporting information). However, because the number of errors made may be associated with the total number of words produced, intrusions and repetitions were also calculated in relation to the number of correct words proportionally. We used linear regression to assess whether a higher proportion of errors were made with aging. Adjusting for the same covariates as previously, the number of intrusions was significantly associated with age, but not the number of repetitions ($\beta = 6.5$, 95% confidence interval (CI) [0.29, 12.73], $P = .04$; $\beta = 3.35$, 95% CI [−4.32, 11.01], $P = .39$, respectively), suggesting that the number of intrusion errors proportionally increased as age increased. The number of total animal subcategories (analyzed separately) was also significantly associated with age ($\beta = -1.27$, 95% CI [−2.47, −0.06], $P = .039$) with a decrease in the number of animal subcategory production as participants aged. When subcategories were analyzed independently (e.g., wild animals), only the number of domestic animals was associated with age ($\beta = -1.17$, 95% CI [−1.81, −0.52], $P = .001$). Additional details of the results are included in the supporting information.

3.2 | Verbal fluency performance and its relationship to NfL and GFAP levels

Blood samples were collected from a subset of participants with NfL levels available for 94 participants (mean age 41.54; M = 19.509 pg/mL, SD = 18.39) and GFAP levels available for 76 participants (mean age 41.67; M = 122.535 pg/mL, SD = 91.51). NfL levels and the number of correct words were significantly negatively correlated ($r = -0.367$, $P = .001$) as well as GFAP levels and the number of correct words ($r = -0.313$, $P = .012$). There were no significant correlations between either biomarker and the number of intrusions (NfL $r = -0.053$, $P = .641$; GFAP $r = -0.175$, $P = .167$, respectively) or repetitions (NfL $r = -0.025$, $P = .82$; GFAP $r = 0.136$, $P = .283$, respectively). Adjusted for sex, ID severity, and age, the number of correct words remained significantly correlated with NfL levels ($r = -0.265$, $P = .048$) but not with GFAP levels ($r = -0.193$, $P = .15$).

Because those aged ≥36 have significantly higher NfL and GFAP levels than younger individuals, the number of correct words and the relationship to these plasma biomarkers was explored in both age groups. In younger individuals (16–35 years old), the number of

TABLE 1 Demographic data and mean (SD) neuropsychological scores for younger adult and older adult groups.

		Young adults (aged 16–35)	Older adults (aged 36–74)	
		Baseline	Baseline	Follow-up
Participants	Age	26.08 (5.39)	49.59 (7.95)	50.90 (7.30)
	N	132 (43.7%)	170 (56.3%)	87 (51.2% of baseline)
	Ethnicity			
	White	112 (37.1%)	162 (53.6%)	82 (94.3%)
	Other ethnicity	20 (6.6%)	8 (2.6%)	5 (5.7%)
	ID level			
	Mild	54 (40.9%)	80 (47.1%)	44 (50.6%)
	Moderate	78 (59.1%)	90 (52.9%)	43 (49.4%)
	Sex: male	59 (44.7%)	91 (53.5%)	50 (57.5%)
	Dementia diagnosis	0 (0.0%)	37 (21.8%)	23 (26.4%)
Tests	*Verbal fluency*			
	Correct words	10.63 (5.27)	8.31 (5.01)	7.02 (5.95)
	Wild animals	3.79 (3.21)	2.93 (2.78)	2.67 (3.12)
	Domestic animals	3.73 (2.22)	3.18 (2.19)	2.40 (2.39)
	Aquatic animals	0.73 (1.17)	0.46 (0.92)	0.34 (0.73)
	Reptiles	0.79 (1.11)	0.43 (0.77)	0.31 (0.65)
	Birds	1.17 (1.37)	1.00 (1.23)	1.13 (1.74)
	Arthropods	0.40 (0.84)	0.26 (0.85)	0.17 (0.59)
	Repetitions	1.01 (1.50)	1.01 (1.64)	0.87 (1.39)
	Intrusions	0.23 (0.65)	0.28 (0.70)	0.55 (1.04)
	Total number of subcategories	3.40 (1.38)	2.94 (1.36)	2.29 (1.76)
	KBIT-2 raw verbal	*n* = 131; 36.34 (14.78)	*n* = 163; 30.32 (16.12)	*n* = 73; 30.86 (18.76)
	KBIT-2 raw non-verbal	*n* = 131; 15.81 (5.54)	*n* = 163; 12.70 (6.13)	*n* = 75; 12.41 (6.62)
	DLD (cognitive scores)	*n* = 97; 5.51 (6.15)	*n* = 99; 10.55 (9.64)	*n* = 83; 13.79 (12.86)
	DLD (social scores)	*n* = 101; 8.25 (5.73)	*n* = 100; 10.43 (6.95)	*n* = 83; 12.37 (10.52)

Note: Baseline includes young and older adults and excludes participants unable to produce any words. Follow-up includes older adults only and those unable to produce any words at follow-up. Adults < 36 years old were not included in the follow-up.
Abbreviations: DLD, Dementia Questionnaire for People with Learning Disabilities; ID, intellectual disability; KBIT-2, Kaufman Brief Intelligence Test Second Edition; SD, standard deviation.

TABLE 2 Relationship between verbal fluency performance and age.

	β	95% CI	*P*-value
Number of correct words	−0.38	(−0.75, −0.01)	.049*
Intrusions	0.69	(−1.49, 2.86)	.53
Repetitions	−0.29	(−1.55, 0.97)	.66
Sex (female)	3.55	(0.67, 6.44)	.016*
Intellectual disability (mild)	−5.33	(−8.40, −2.25)	.001***
Verbal knowledge	−0.13	(−0.26, −0.01)	.037*
AD diagnosis (with)	−11.31	(−16.08, −6.55)	.001***

Note: Linear regression included sex, verbal knowledge, intellectual disability severity and AD diagnosis as covariates, and age as an outcome.
Abbreviations: AD, Alzheimer's disease; CI, confidence interval.
*$p < .05$; ***$p < .001$.

correct words was not significantly correlated with NfL (M = 8.920 pg/mL, SD = 4.40; $r = 0.098$, $P = .57$) nor were GFAP (M = 68.260 pg/mL, SD = 27.73; $r = -0.016$, $P = .93$) levels. However, in the older adult group, the number of correct words was significantly negatively correlated with NfL (M = 26.383 pg/mL, SD = 20.66; $r = -0.398$, $P = .007$) and there was a weaker negative correlation with GFAP (M = 157.933 pg/mL, SD = 101.07; $r = -0.317$, $P = .064$) levels, as shown in Figure 1.

3.3 | Verbal fluency and AD diagnosis

A logistic regression model was able to distinguish groups with and without dementia with the number of correct words being a significant predictor ($P = .02$) adjusting for age, sex, verbal knowledge, and

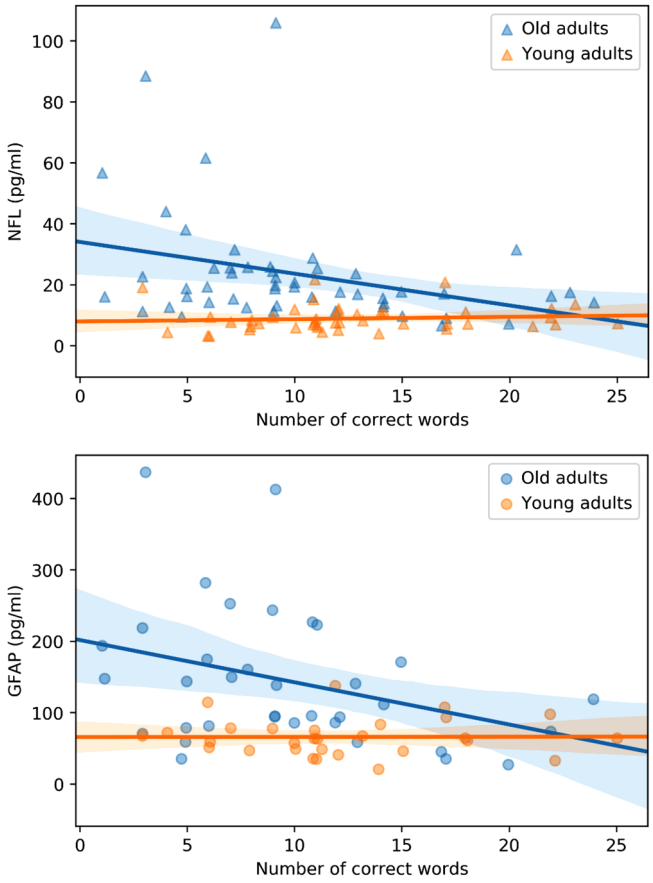

FIGURE 1 Correlation of the number of correct words with plasma biomarkers, and the relationship in both younger adults (≤35 years old) and older adults (≥36 years old). The graphs demonstrate that there is a relationship between the number of correct words and plasma biomarker levels mainly in older adults. NfL, neurofilament light; GFAP, glial fibrillary acidic protein.

ID severity as presented in Table 3 (unadjusted results can be found in the supplementary tables). Using the same covariates and analyzed separately, the number of total animal subcategories did not predict the presence of AD (β = 0.11, exp[β] = 1.12, 95% CI [0.76, 1.66], P = .57).

3.4 | Longitudinal change in verbal fluency performance over 2 years

To understand the progression of verbal fluency over time and whether it may be a predictor for cognitive decline, we examined the effect of age at T2 on verbal fluency with a linear regression model. To do so, we subtracted scores at T1 from T2 for each subject to obtain a change score for the numbers of correct words, intrusions, repetitions, and total number of subcategories. While the number of intrusions, repetitions, and subcategories did not differ over time, the number of correct words generated significantly decreased after 2 years when accounting for sex, ID, verbal knowledge, and AD diagnosis at T2 (Table 4; unadjusted results and covariates are supplied in the supplementary tables).

TABLE 3 Prediction of presence of Alzheimer's disease by verbal fluency performance.

	β	Exp(β)	95% CI exp(β)	*P*-value
Number of correct words	0.17	1.18	(1.03, 1.36)	.02*
Intrusions	0.43	1.54	(0.76, 3.11)	.23
Repetitions	−0.30	0.74	(0.52, 1.06)	.10
Sex (female)	−0.06	1.06	(0.39, 2.27)	.89
Intellectual disability (mild)	0.66	1.93	(0.74, 5.00)	.18
Verbal knowledge	0.04	1.04	(1.00, 1.09)	.05
Age	−0.08	0.92	(0.89, 0.96)	.001***

Note: Logistic regression included sex, verbal knowledge, intellectual disability severity, and age as covariates, and Alzheimer's disease as an outcome.
Abbreviation: CI, confidence interval.
*$p < .05$; ***$p < .001$.

TABLE 4 Longitudinal change in verbal fluency performance (Time 2 – Time 1).

	β	95% CI	*P*-value
Number of correct words	−0.18	(−0.31, −0.05)	.007**
Intrusions	−0.00	(−0.05, 0.04)	.97
Repetitions	0.02	(−0.04, 0.08)	.50
Subcategories	−0.01	(−0.06, 0.04)	.63

Note: Linear regression included sex, verbal knowledge, intellectual disability severity, and AD diagnosis as covariates, and age at Time 2 as an outcome.
Abbreviations: AD, Alzheimer's disease; CI, confidence interval.
**$p < .01$.

4 | DISCUSSION

Using data from 302 adults with DS at baseline, we investigated whether various semantic verbal fluency outcomes were associated with age and AD in this population. To our knowledge, this is the first in-depth study of verbal fluency performance in adults with DS using a standardized approach and including the number of correct words, repetitions, intrusions, and animal subcategories generated. A significant decline in verbal fluency as age increases was observed, using the metrics of the number of correct words, animal subcategories, and intrusions proportionate to the number of correct words, controlling for sex, verbal knowledge, ID severity, and AD diagnosis. Adjusting for AD, we were able to demonstrate that verbal fluency is sensitive to significant changes relative to aging as well as dementia-related changes. This is in line with previous work[19] showing poorer performance on the number of correct words in older adults with DS. A decline in the number of subcategories was also observed potentially reflecting poorer abstract thinking ability and difficulty using more complex strategies during word generation. The findings on intrusions are also consistent with a previous study that found the production of intrusions made during a working memory task was a characteristic of middle-aged

adults with DS.[36] In this line of investigation in the general population, intrusions in a semantic verbal fluency task were found to be a trait of mild AD.[41] However, in that study, a healthy older group committed more repetitions than the younger group, but the older group did not commit more repetitions than those with mild AD, suggesting that this might also be a feature of aging rather than a distinctive feature of AD. Our analysis did not demonstrate a higher proportion of repetitions to the number of correct words in adults with DS with increasing age. Given the association of intrusions with AD in the general population, a high number of intrusions proportional to the number of correct words might be an early sign of cognitive decline in people with DS.

Individuals with and without a diagnosis of AD were differentiated by the number of correct words controlling for age and other factors. This is in line with other studies which identified semantic verbal fluency to be a strong predictor of AD in DS.[16,17] These findings are further supported by the negative association between the number of correct words and levels of NfL and GFAP, with fewer words in the verbal fluency task being correlated with elevated levels of NfL and GFAP, and driven by age (predominantly by older adults). Because these biomarkers pinpoint onset of neurodegeneration (NfL), reflect astrocytic activation (GFAP), and are predictive of dementia status in both individuals with DS and the general population,[27,28,42,43] these findings suggest that verbal fluency ability, and especially the number of correct words, is closely associated with the underlying neurodegeneration and astrocytic injury/activation that are typical of AD.

Considering the elevated risk of developing AD with age in DS, we examined the time course of verbal fluency performance over a 2-year period in the adult group aged ≥36 years who are expected to have some degree of AD neuropathology.[21,44] Although the numbers of intrusions, repetitions, and animal subcategories were not observed to significantly change over this time period, the number of correct words significantly decreased over time even when controlling for AD and verbal knowledge. This is different from the findings of Rondal and Comblain,[45] which did not show a change in the number of correct words over a 4-year period in adults with DS aged between 37 and 49 years, although their sample size was small.

4.1 | Strengths and limitations

We have used data from a large, diverse community sample of adults with DS, and standardized ratings of verbal fluency before analyzing their relationship to age, dementia diagnosis, and longitudinal change, then confirmed findings using plasma biomarkers of neurodegeneration and astrocytic injury. However, the follow-up sample was smaller and limited to 2 years of follow-up. Furthermore, there was no follow-up for younger adults (<36 years of age). Although cognitive decline in the younger group is unlikely, additional follow-up may be necessary to establish practice effects in this group. In addition, exploring verbal fluency over a longer period in older adults with DS might provide additional information regarding changes in verbal fluency and whether they can be predictive of dementia at an early stage. It is nonetheless the largest study of longitudinal change in verbal fluency in DS to date. We took care to ensure the validity of results by only including participants with sufficient hearing, and mild to moderate ID to ensure they could comfortably engage with the cognitive tests. To ensure that participants who did not understand the task were not included in the analysis, those who did not produce any relevant words at baseline were excluded. Additionally, we adjusted for verbal knowledge throughout our analyses as it can be an important contributory factor in verbal fluency performance and prevents conflicting results due to differences in education between young and older adults.

While we have used several components of verbal fluency, including the number of errors produced, one limitation might have been the categorization of animals used to assess the ability to access a range of subcategories during word generation. A higher number of animals were included in the subcategory of wild animals compared to other subcategories such as arthropods, which may have potentially skewed the outcome. Future research should explore different subcategorizations.

5 | CONCLUSION

In summary, these findings contribute to our understanding of the mechanisms of typical age-related decline in semantic verbal fluency in adults with DS and provide evidence for its use as an early indicator of cognitive decline. Given that frontal functions and in particular executive functioning have been shown to be affected relatively early by AD in adults with DS[46,47] but are difficult to assess in individuals with intellectual impairment, the simple verbal fluency task (used with standardized scoring) may provide valuable additional information on early cognitive change due to AD in DS.

ACKNOWLEDGMENTS

The authors would like to thank all the participants and their parents and caregivers in this study for their time. This research was supported by the National Institute for Health Research networks (mental health, dementias, and neurology) and participating NHS trusts. We would like to thank our NHS network of sites that helped to identify participants. This research was funded by Wellcome Trust Strategic Award (grant number: 098330/Z/12/Z) conferred upon The London Down Syndrome (LonDownS) Consortium; Medical Research Council grant MR/S011277/1, MR/ S005145/1, and MR/R024901/1; European Commission (H2020 SC1 Gene overdosage and comorbidities during the early lifetime in Down Syndrome GO-DS21- 848077); and Alzheimer's Society AS-CP-18-0020 (fellowship to S.E.P). R.A.B was supported by a Jérôme Lejeune Foundation postdoctoral research fellowship. H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2022-01018), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav

Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). For the purposes of open access, the author has applied a Creative Commons Attribution (CC BY) license to any Accepted Author Manuscript version arising from this submission.

CONFLICTS OF INTEREST STATEMENT

HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). The other authors declare that they have no conflicts of interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Written informed consent was obtained from individuals who had capacity to consent. Where individuals did not have capacity to consent, a consultee was asked to approve the individual's inclusion based on their knowledge of the individual and their wishes, in accordance with the UK Mental Capacity Act 2005.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mgaieth F, Baksh RA, Startin CM, et al. Exploring semantic verbal fluency patterns and their relationship to age and Alzheimer's disease in adults with Down syndrome. *Alzheimer's Dement*. 2023;1-9.
https://doi.org/10.1002/alz.13097

APPENDIX 1

Collaborators

The LonDownS Consortium principal investigators were Andre Strydom (chief investigator), Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, and Division of Psychiatry, University College London, London, UK; Elizabeth Fisher, Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, UK; Dean Nizetic, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK, and Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; John Hardy, Reta Lila Weston Institute, Institute of Neurology, University College London, London, UK, and UK Dementia Research Institute at UCL, London, UK; Victor Tybulewicz, Francis Crick Institute, London, UK, and Department of Medicine, Imperial College London, London, UK; Annette Karmiloff-Smith, Birkbeck University of London, London, UK (deceased); Michael Thomas, Birkbeck University of London, London, UK; and Denis Mareschal, Birkbeck University of London, London, UK. We would like to thank Tamara Al-Janabi, Division of Psychiatry, University College London, London, UK, for initial project management. Baseline data admin and data coding support was provided by Nidhi Aggarwal, Tommy Coyle, Amy Davies, Lucy Fodor-Wynne, Bryony Lowe, and Erin Rodger, all Division of Psychiatry, University College London, London, UK.