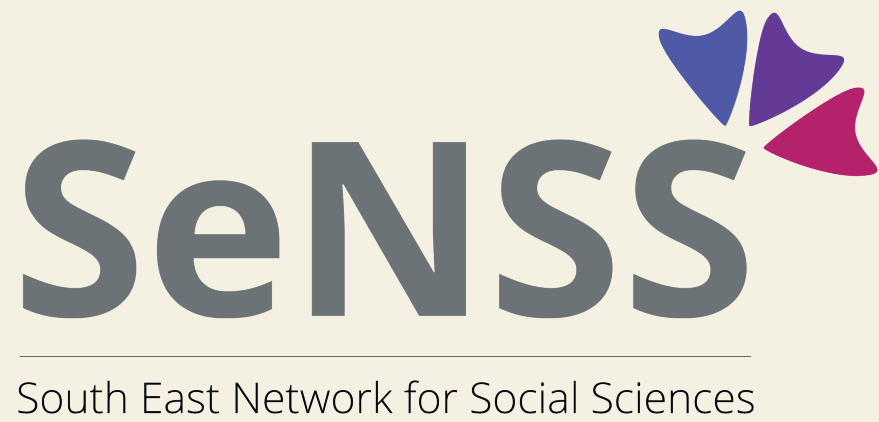




Sussex Partnership
NHS Foundation Trust



South East Network for Social Sciences



Alice Stanton & Claire Lancaster

A.Stanton@Sussex.ac.uk

C.Lancaster@BSMS.ac.uk

Introduction

Early Alzheimer's detection is crucial, but current methods are invasive and expensive. This study leverages quick verbal fluency tasks to identify subtle cognitive differences in adults with and without the APOE e4 Alzheimer's risk gene, detecting early changes associated with genetic risk. Computational analysis of raw voice recordings extracts novel metrics of memory, flexibility, and semantics.

Automated techniques garner insights beyond word counts, making detailed examination of verbal fluency performance feasible for clinical early detection and monitoring of Alzheimer's pathology.

Method

Participants

86 healthy adults aged 45-66 with known APOE genotype (43 APOE e4+, 43 APOE e4-) were recruited. Participants were genotyped previously but not preselected by genotype. Researchers were blind to genotype until after data collection.

Verbal Fluency Tasks

- Participants completed three 2-minute verbal fluency tasks:
- Traditional animal fluency: Participants listed as many animals as possible.
- Forced Switch Task (FST): Participants named animals but switched between subcategories (e.g. felines, arctic animals) when prompted after pseudorandom delays.
- Associate/Disassociate Task (A/DT): Participants named animals that were similar (green) or dissimilar (red) to prompts on a screen.

Raw voice recordings were automatically transcribed with timestamps using Whisper. Manual checking was performed for any words with a confidence score lower than 0.6.

Outcome Measures

- Disfluencies: number of filled pauses, repetitions, revisions
- Semantic clusters: manual clusters formed by two independent raters
- Switch cost: time (ms) between subcategory cue and production of first related word
- Semantic distance: Word2Vec similarity between prompt and response

Statistical Analysis

All verbal fluency tasks were analyzed using linear models with between group design and Bonferroni correction to compare performance between APOE genotype groups.

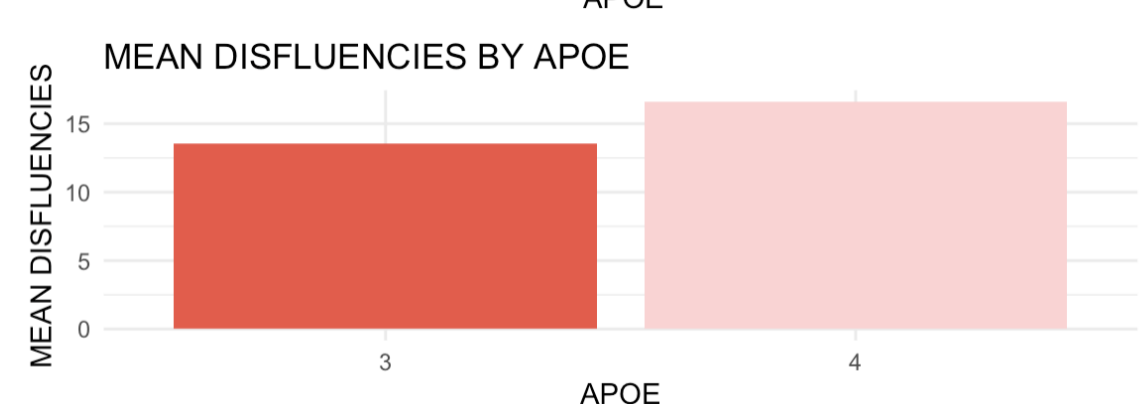
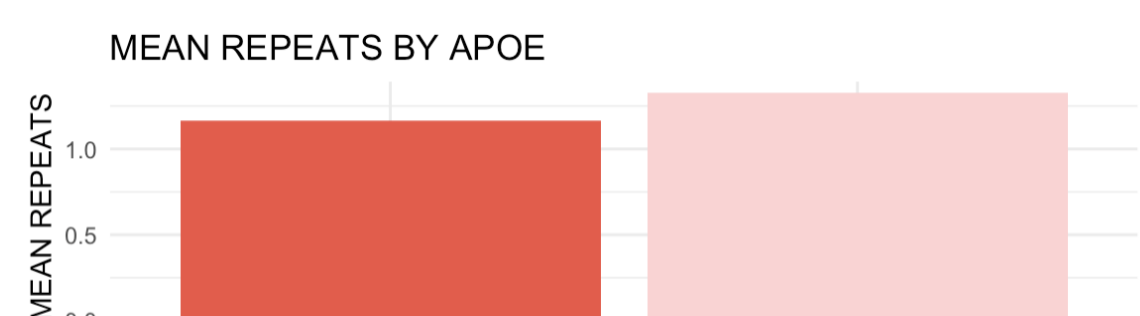
Animal Fluency Results

Participants

86 total participants: 43 e3/e3, 43 with ≥ 1 e4 allele. 89% female.

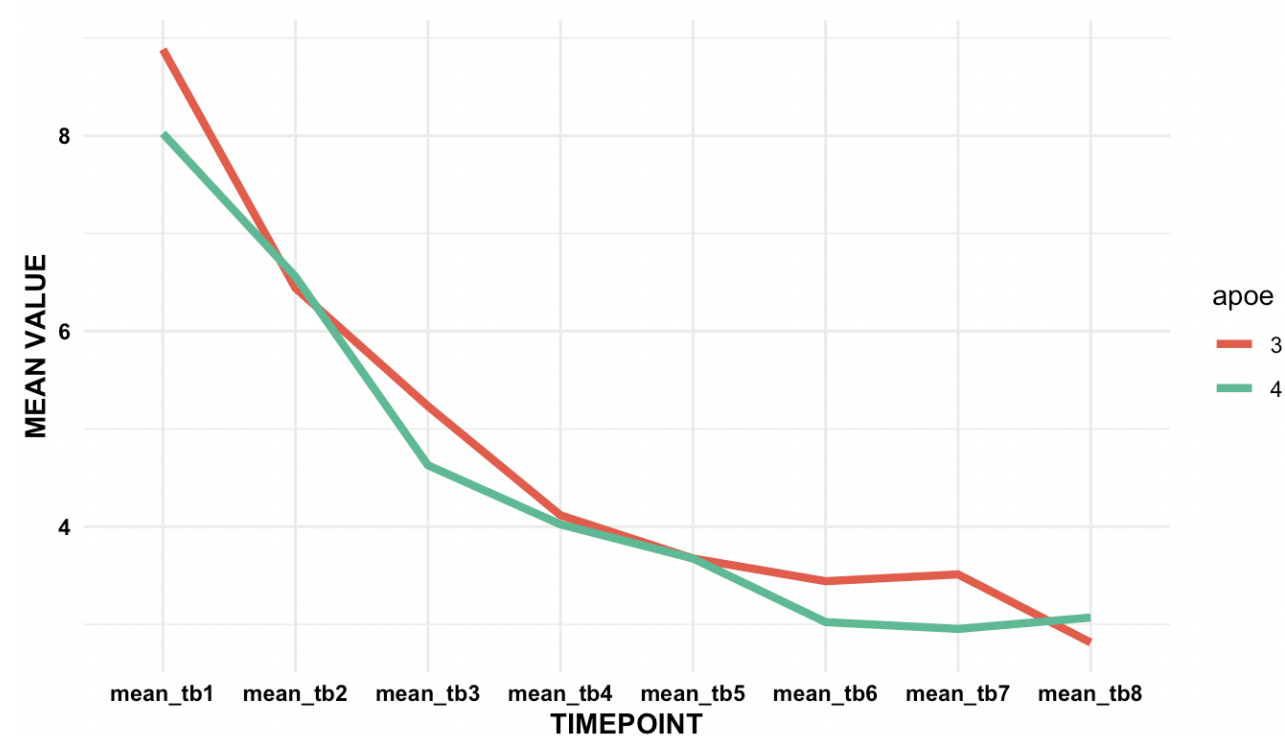
APOE	Mean Number of Words	SD Number of Words
3	36.69767	11.35684
4	35.32558	11.41578

The number of **words produced** was comparable across genotype groups. There was a significant effect of time on task ($F(2,192)=57.62$, $p<.001$), with fewer words produced in later time bins. However, there was no significant main effect of APOE genotype ($p=.862$) or APOE by time bin interaction ($p=.315$).



APOE	Mean Number of Clusters	SD Number of Clusters	Mean Cluster Size	SD Cluster Size
3	9.627907	2.743158	3.005355	0.8384929
4	10.162791	2.544183	3.138187	1.3274152

MEAN VALUES BY APOE AND TIMEPOINT



- An ANOVA reported no significant main effect of APOE genotype on **repeated words** ($p=.122$).
- A significant main effect of APOE on **disfluencies** ($p=.001$) was seen across APOE, but follow-up pairwise comparisons (Bonferroni corrected) found no significant differences between specific groups.
- APOE e3/e3 and e4+ only showed a trend effect of genotype on **disfluencies** ($F(1,84)=3.59$, $p=.062$), with e4+ carriers producing more disfluencies.
- There was no significant difference between APOE e4+ and APOE e33 (control group) on the **number of clusters** produced ($p=.351$) nor the size of clusters ($p=.581$).

Switching up Verbal Fluency: Detecting APOE e4 Genotype Differences in Mid-life

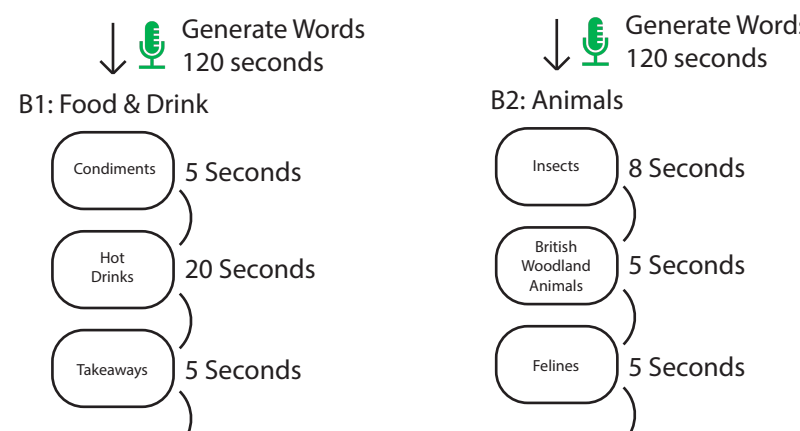
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Forced-Switch Verbal Fluency - Results

FST

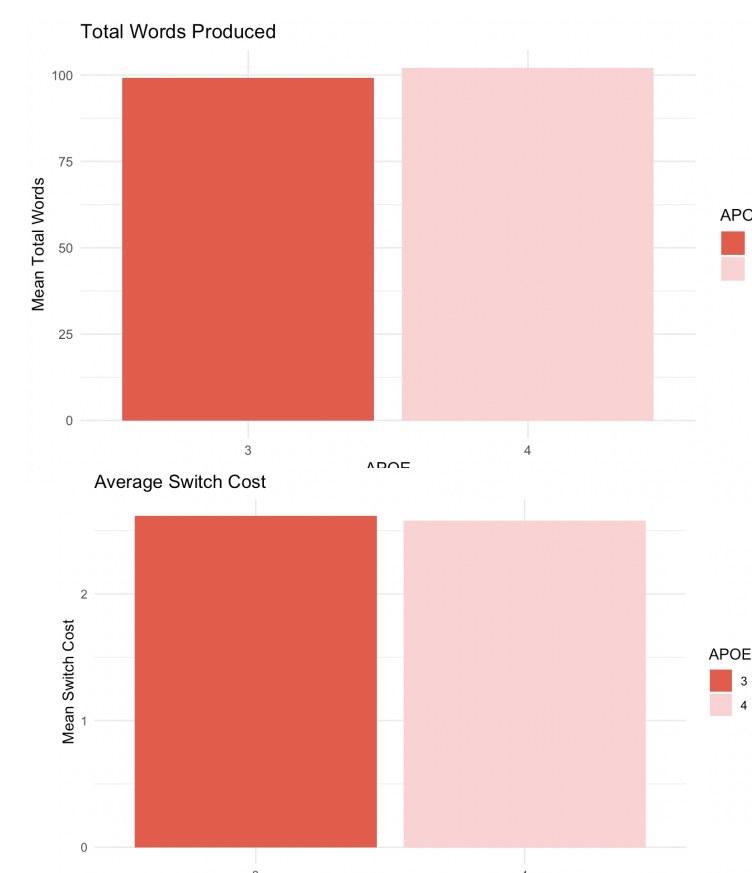


Participants

39 total participants: 20 e3/e3, 19 with ≥ 1 e4 allele. 87% female.

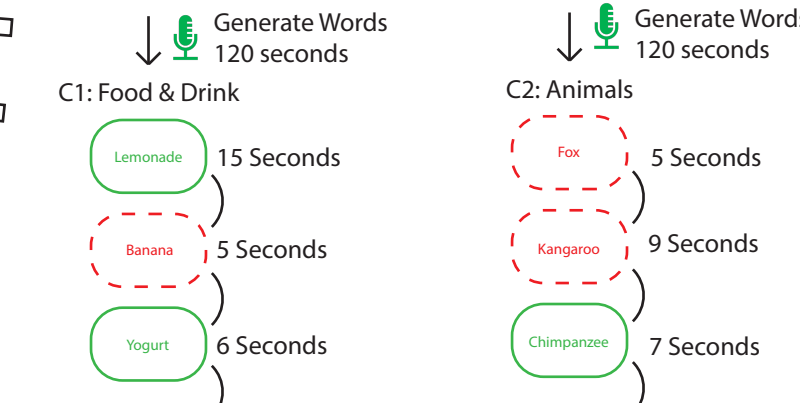
For **total words produced**, there was no significant main effect of apoe status on the number of responses ($p=.42$).

For **average switch cost**, there was also no significant main effect of apoe status on mean response length ($p=.747$).



Associate/Dissociate - Results

A/DT

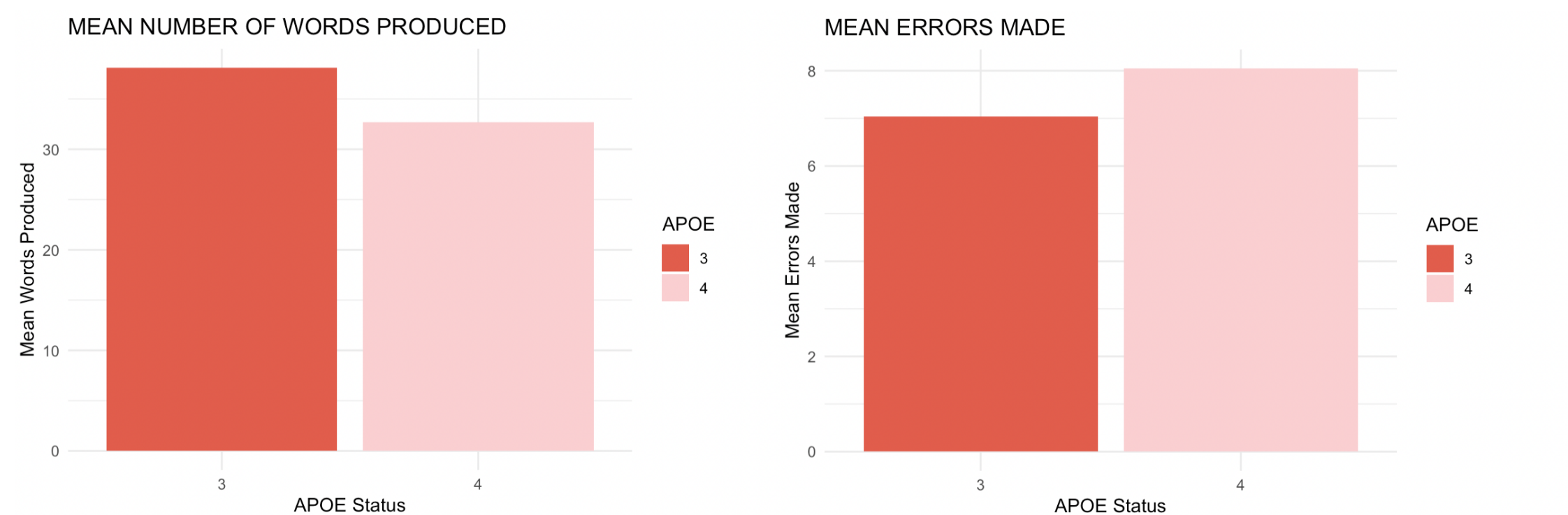


Participants

45 total participants: 23 e3/e3, 22 with ≥ 1 e4 allele. 87% female.

There was a significant difference in **words produced** ($t(df=84) = 2.3$, unadjusted $p = .024$ (With Bonferroni correction: Adjusted $p = .033$) between APOE e33 and APOE e4+, with e4+ producing fewer.

APOE e4+ and e3/e3 did not exhibit a significant difference in **errors** defined as associating with red cues intended for dissasociation and dissasociating with green cues intended for association ($p = .594$).



Word2Vec

Mean Word2Vec score for 2-minute animal fluency

A significant effect of APOE genotype on semantic similarity of generated animal names ($F(1,84)=11.69$, $p<=.001$). APOE e4 carriers had lower mean Word2Vec scores (0.30) than e3 carriers (0.35), indicating e4 carriers produced animal names with lower semantic similarity compared to e3 carriers.

APOE	Mean Semantic Distance Within Categories	SD Semantic Distance Within Categories	Mean Semantic Distance Between Categories	SD Semantic Distance Between Categories
3	0.35	0.09	0.29	0.04
4	0.31	0.04	0.27	0.04

APOE	Mean Semantic Distance	SD Semantic Distance
3	0.35	0.07
4	0.30	0.06

Mean Word2Vec score for FST

No significant effect of APOE genotype on either within cluster mean Word2Vec score or between cluster mean Word2Vec score. However, a significant difference between the 'Within' and 'Between' scores ($t = 3.936$, $p=.0003413$).

Conclusions

- On a traditional 2-minute animal fluency task, APOE e4+ carriers generated words with lower semantic similarity than non-carriers, indicating subtle differences in access and/or organization of semantic memory. In addition, e4 carriers were disadvantaged in their ability to give associated or dissociated animal examples under timed conditions, further supporting differences in controlled semantic access.
- There was a suggestion of APOE genotype influencing disfluencies (e.g., umms and ahhs), emphasizing the importance of speech features as an early risk marker for future Alzheimer's disease.
- These results provide preliminary evidence that novel techniques like Word2Vec and analyzing disfluencies may illuminate subtle verbal fluency differences associated with Alzheimer's genetic risk, that traditional metrics do not capture.
- Future research will evaluate these computational semantic and speech production measures across the lifespan in a larger sample differentiated by genetic risk for Alzheimer's. This will clarify the cognitive profile linked to genetic vulnerability for dementia. Automating the computational methods developed will facilitate clinical implementation of these tasks for early dementia diagnosis and monitoring.



References