Towards personalized prediction of ALS disease progression trajectories using digital speech biomarkers

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Introduction

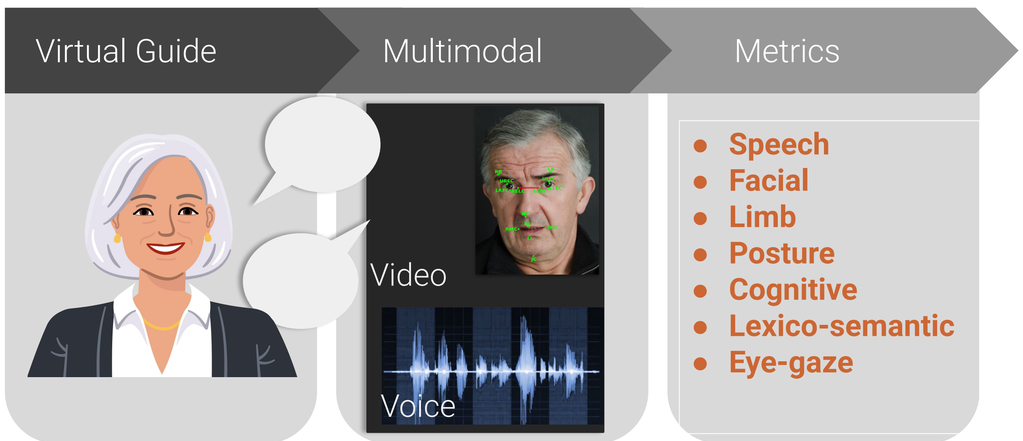

Figure 1. Schematic of the Modality.AI dialogue platform

- **Progression of disease in ALS is heterogeneous** due to the varying presentation of clinical symptoms.
- This heterogeneity makes it **difficult to accurately quantify longitudinal disease severity** in people with ALS (pALS), thereby making it **difficult to determine the efficacy of therapeutic interventions**.
- **Most of the work done** to model disease progression in ALS **assumes** that the clinical gold standard to measure disease state, the **ALSFRS-R, declines in a linear manner**.
- However, there is **evidence** that **ALS progression can be non-linear** and that **progression may vary longitudinally**.

Can **non-linear modelling** help **predict individual disease trajectories in people with ALS**?

Data and Methods

Onset	Number of participants	Mean age ± SD (years)	Mean time span ± SD (months)
Bulbar	27 (13 female)	64.33 ± 8.69	10.2 ± 7.9
Non-bulbar	92 (44 female)	61.06 ± 9.49	15.5 ± 7.9

Table 1: Demographics

- Data collected from 119 pALS using a **cloud-based multimodal dialogue platform** (Figure 1). Participants were recruited by EverythingALS and the Peter Cohen Foundation. For each participant, their **first and last assessment plus a third sample** that was closest in time to the midpoint of the interval between the first and last session were selected.
- **Tina, a virtual guide,** walked participants through **structured speaking exercises** and **objective metrics** were extracted.
- Tasks:
  - Read speech (**sentence intelligibility test (SIT)**; **Reading Passage** (**RP**; Bamboo passage 99 words)
  - **Oral diadochokinesis (DDK)**
  - **Single breath counting (SBC)**
  - **Picture description task (PD)**
- We used ***leaspy***, a software package for the statistical analysis of longitudinal medical data in the form of repeated observations at various time-points.
- We trained a **nonlinear logistic mixed effects model** to predict **individual trajectories of 11 features** - **7 timing-related speech metrics**, a **perceptual rating of speech impairment** (**PSI**; derived using a visual analogue scale and multiple raters), the **total ALSFRS-R score**, **ALSFRS-R bulbar subscore** and the **ALSFRS-R speech score**.
- We used a **leave-one-out cross validation approach** to test the performance of the model in **predicting the values of these 11 features at the third time-point of all participants**.
- Model performance was evaluated using **normalized root mean squared error (nRMSE)** which accounts for the difference in ranges across features.

Results and Discussion

- We found that **nRMSE < 0.2** for **all automatically-extracted speech metrics**, for **PSI** and for the **ALSFRS-R bulbar subscore**.
- We observed the **best performance** for **speaking duration, rate, PSI** and **canonical timing alignment** - a number between 0% (non-alignment) and 100% (perfect alignment), measured as the normalized inverse Levenshtein edit distance between words and silence boundaries, **associated with intelligibility** - computed from a reading passage (**nRMSE < 0.12**).
- Model performance was the **worst** in predicting **ALSFRS-R total score** (**nRMSE = 0.22**) and **speech score** (**nRMSE = 0.31**).

Conclusions

The results suggest that that non-linear models using speech-based digital biomarkers offer more promise and precision than the current clinical standard for predicting individual disease progression trajectories in ALS.

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