Towards improving clinical trial design and participant stratification in ALS with digital speech biomarkers

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Background and Objective

- Participant selection based on **eligibility criteria** is crucial in ALS clinical trials to **balance generalizability of the trial and its endpoint heterogeneity**
- **Digital speech biomarkers** can help to optimize clinical trial design because they provide a cost-effective way to **improve participant screening**
- **Canonical timing alignment (CTA)** was shown to be sensitive to ALS progression in prior studies *(Kothare et al., Interspeech 2023)*

We investigate the **inter-relationship between longitudinal change in CTA** and the **time since symptom onset and site of onset** in people with ALS (pALS).

Research Highlights

- Speech biomarkers, particularly CTA, effectively monitor ALS progression and predict disease trajectories
- Potential to effectively stratify fast from slow progressors
- The time since symptom onset is an important factor in modeling disease progression in ALS
- pALS with recent symptom onset and bulbar onset show faster CTA decline

Methods

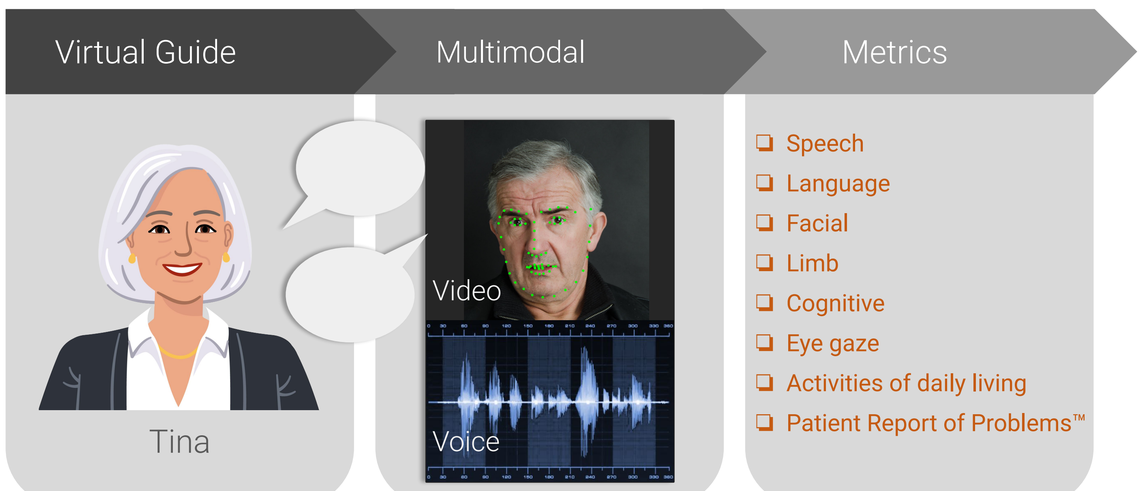


Figure 1. Schematic diagram of the Modality.AI dialogue platform.

- Speech recordings from 116 pALS and 112 healthy controls (HC) from ongoing study in collaboration with EverythingALS were analyzed (6,475 sessions in total)
- pALS stratified into two groups based on date of symptom onset (Fig. 2)
- Canonical timing alignment (CTA) was computed for the Bamboo reading passage
- Growth curve models were applied to model the longitudinal trajectory of CTA measures, with random intercepts and slopes for each participant
- Bayesian hierarchical modeling was used to cluster pALS into slow and fast progressors based on estimated slopes for (a) CTA, and (b) the ALSFRS-R score
- Time series classification (k-nearest neighbors) was applied to predict cluster membership based on the first *n* days since baseline, with varying *n*.

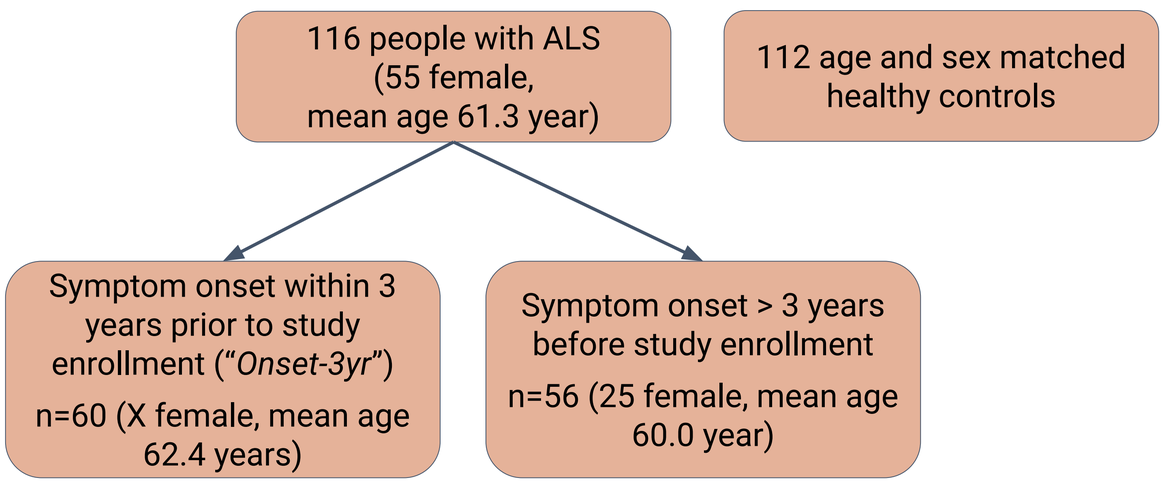
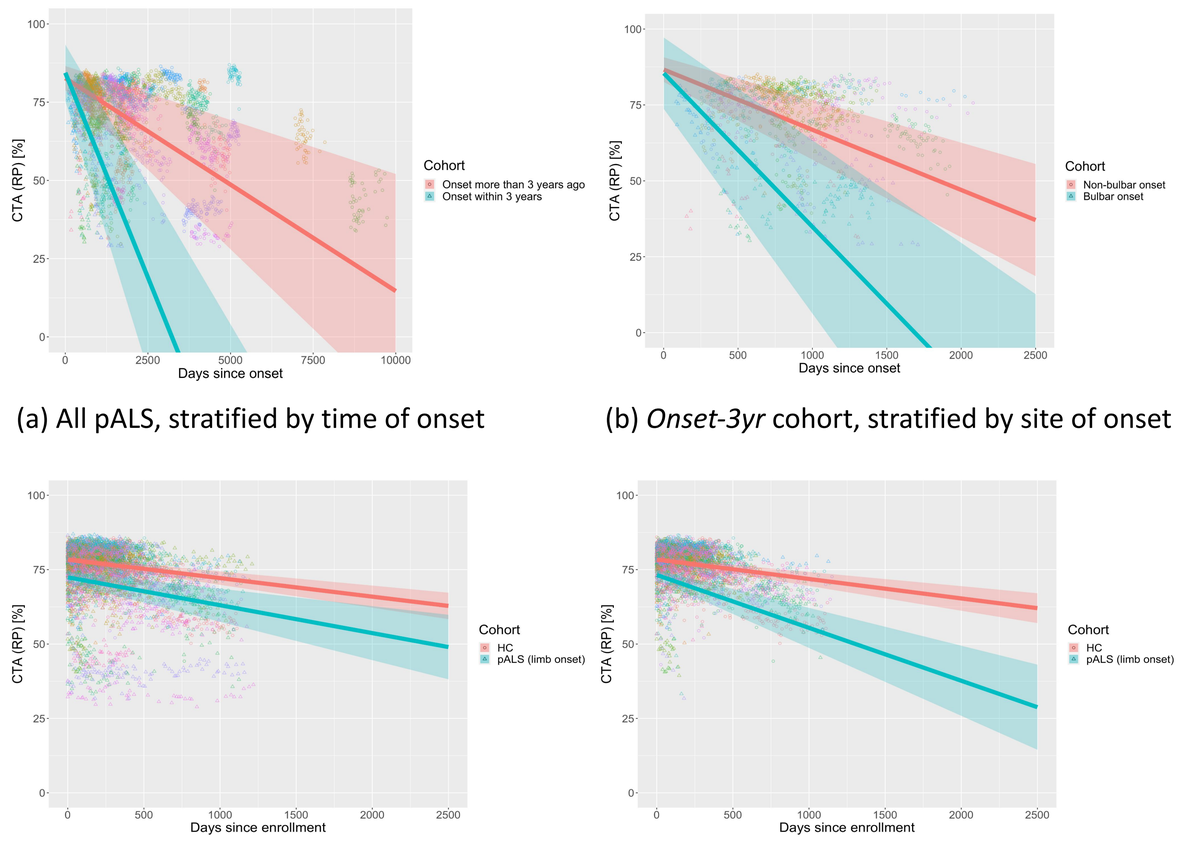


Figure 2. Participant characteristics and stratification.

Results

- **Growth curve models:**
  - pALS with longer symptom duration show slower decline in CTA than those with onset within the last three years (Fig. 3a)
  - *Onset-3yr* pALS with bulbar onset exhibit steeper decline than those with limb onset (Fig. 3b)
  - once bulbar symptoms develop (ALSFRS-R bulbar score < 12), slopes are similar, regardless of the site of onset (in line with findings in *Navar Bingham et al., medRxiv 2024*)
  - HC and pALS with limb onset appear to have similar slopes when including all participants (Fig. 3c), but they show significantly different trajectories when only including *Onset-3yr* pALS (Fig. 3d)



(a) All pALS, stratified by time of onset

(b) *Onset-3yr* cohort, stratified by site of onset

(c) HC vs. all pALS with limb onset

(d) HC vs. *Onset-3yr* pALS with limb onset

Figure 3. Longitudinal trajectory of CTA measures in different cohorts based on growth curve models.

- **Bayesian hierarchical modeling & time-series classification:**
  - Fast and slow progression clusters based on CTA slopes can be predicted with acceptable ROC-AUC (0.76) based data within 45 days since baseline session
  - Clusters based on ALSFRS-R slopes are not well classified (chance level AUC), suggesting that digital biomarkers can be beneficial in patient stratification

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