Speech intelligibility decline in individuals with fast and slow rates of ALS progression

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Abstract

Based on the slope of speech intelligibility decline, 54 individuals with amyotrophic lateral sclerosis (ALS) were classified as fast or slow bulbar disease progressors. Following group assignment, the course of speech decline was modeled separately for these two subgroups. Fast progressors were characterized by a three-phase progression pattern with intelligibility declining at a progressively faster rate within each phase. Slow progressors were characterized by a consistent rate of intelligibility decline and thus, a single phase progression pattern. The approach used to identify fast and slow progressors may be useful in the future for stratifying patients enrolled in clinical trials. The subgroup-based models of intelligibility provide an empirical basis for making predictions about the timing of speech loss and the impending need for assistive communication.

Index Terms: speech intelligibility, computational speech modeling, classification, amyotrophic lateral sclerosis

1. Introduction

Amyotrophic lateral sclerosis (ALS) is due to the degeneration of upper and lower motor neurons in the brain, brainstem, and spinal cord [1]. One of the most devastating consequences of ALS is loss of speech intelligibility, which significantly impacts the quality of life among individuals with ALS. Prior studies [2, 3, 19] showed that the decline of speech intelligibility in ALS can roughly be divided into three phases: (1) the normal speech phase (100-97%), (2) the slow decline phase (96-86%), and (3) the rapid decline phase (< 85%). Because these findings were based on a combination of cross-sectional and longitudinal observations from individuals with varying severity, it is unclear whether the changes in intelligibility decline rate during different phases is attributed to different disease progression rates across individuals or variation in progression rate during the disease course of an individual. Distinguishing between- and within-subject effects is important for clinical practice (e.g., stratifying patients for clinical trials; predicting the timing of speech loss) but has proven to be an empirical challenge [4, 5].

To examine the between-subject effect, previous studies assessed the rate of disease progression across individuals using various clinical measures including Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) score, speech intelligibility, speaking rate, and alternate motion rates (AMRs) [3, 4, 6, 7, 8, 9]. It was found that, although all measures showed variability in progression rate across individuals, subgroups of individuals clustered based on factors such as age and initial symptom. In particular, various studies have shown that the site of disease onset (e.g., bulbar/spinal) is associated with different rates of disease progression, that is, individuals with bulbar (speech and swallowing) onsets progress faster than those with spinal (limbs) onsets [10, 11, 12, 13, 14]. The clustering of subgroups has important implications in stratifying patients for clinical trials: given that individuals within a subgroup have less variability, fewer patients are needed to observe drug effects, which will largely reduce the cost of the trials and improve the interpretability of results. Therefore, the first aim of this study is to determine whether individuals with varying severity of ALS can be classified into subgroups based on their rates of speech intelligibility decline relative to speaking rate. We selected speech intelligibility as the basis measure for the classification because loss of intelligibility is one of the most devastating consequences of ALS and because intelligibility is easy to assess in a clinical setting. We selected the rate of intelligibility decline relative to speaking rate instead of the rate of intelligibility decline over time as the classification index because the time course of ALS is not defined consistently (time indices such as "time since diagnosis" and "time since initial symptom" suffer from uncertainty of diagnosis and inconsistency of initial symptoms across individuals). On the other hand, speaking rate serves as a linear indicator of the disease progression [3].

Because speech is produced through the coordinated actions of the respiratory, phonatory, articulatory, and resonatory subsystems, differential timing and ordering of impairments in these subsystems can have a complex effect on intelligibility, resulting in a nonmonotonic pattern of intelligibility decline that corresponds to multiple phases [8, 15, 16]. Yorkston and colleagues [3] found that intelligibility remains relatively high until speaking rate slows to approximately 120 words per minute, after which intelligibility starts to decline relatively rapidly. Determining the phases of intelligibility decline might improve predictions about the timing of speech loss and the impending need for assistive communication. Therefore, the second aim of this study is to model the phasic decline of speech intelligibility as a function of speaking rate.

To achieve the first aim, we developed a classification approach that grouped individuals with ALS into fast or slow bulbar disease progressors, based on their speech profiles. To achieve the second aim, we modeled speech intelligibility decline as (1) a tri-phasic function of speaking rate for fast progressors using a nonlinear mixed effects (NLME) model and (2) a linear function of speaking rate for slow progressors using a linear mixed effects (LME) model.

2. Method

2.1. Participants & Data collection

Fifty four participants (32 males and 22 females) aged from 41 to 82 years old ($M = 60$ years, $SD = 10$ years) were stud-
ied. All participants were diagnosed with ALS that varied in presentation, overall disease severity and severity of speech impairment, as measured by the ALSFRS-R and Sentence Intelligibility Test (SIT). Among all participants, 26 had bulbar onsets and 28 had spinal onsets. Each participant was recorded longitudinally during multiple visits; the duration between the first and last visits ranged from 14 days to 1358 days (\(M = 534\) days, \(SD = 330\) days). Different numbers of sessions were recorded between participants (\(M = 7\) sessions, \(SD = 5\) sessions), depending on the schedule of clinical follow up. A total of 441 observations were obtained across all participants from all visits.

At each visit, the following measures were obtained: ALSFRS-R score, speech intelligibility, speaking rate, and AMRs. The ALSFRS-R score was obtained from 12 survey questions that assess the degree of functional impairment [6]. During the SIT, participants were asked to read a list of 10 sentences of varying length (5-15 words) randomly generated by the SIT software. Speech intelligibility (percentage of words correctly transcribed by a native listener out of the total words produced) and speaking rate (words produced per minute [WPM]) were obtained based on the SIT [17]. AMR was measured as the number of syllables per second in repetitions of /ba/ on one breath.

### 2.2. Modeling of the phasic nature of speech intelligibility decline as a function of speaking rate

Following the three-phase bulbar progression pattern in Green et al. [2] and Yorkston et al. [3, 19], we modeled intelligibility decline as a tri-phasic function of speaking rate using an NLME model (nlme, MATLAB R2013b), accounting for subject-dependent random effects on all model parameters. Figure 1 shows a schematic diagram of the tri-phasic function.

![Schematic diagram of the tri-phasic NLME model of speech intelligibility using speaking rate as a predictor](image)

**Figure 1:** Schematic diagram of the tri-phasic NLME model of speech intelligibility using speaking rate as a predictor. On the x-axis is speaking rate; on the y-axis is intelligibility. There are six parameters \((s_1, s_2, x_1, x_2, y_1, y_2)\) in the NLME model. The slopes of the early and late phases are \(s_1\) and \(s_2\), respectively. The transitional points of speaking rate and intelligibility between the early and intermediate phases are \(x_1\) and \(y_1\), respectively. The transitional points of speaking rate and intelligibility between the intermediate and late phases are \(x_2\) and \(y_2\), respectively. The slope of the intermediate phase is determined by \(x_1, x_2, y_1, y_2\) and, thus, not assigned an independent parameter.

The NLME model converged on a solution with subject-dependent \(x_1, x_2, y_1, y_2, s_1\) and a constant \(s_2\) across all subjects. The variation of slope during the late phase (i.e., \(s_2\)) confirmed differences in bulbar progression rate across participants. In the following, we determined whether cross-participant differences in intelligibility decline slope can be used to classify the participants into fast and slow bulbar disease progressors.

### 2.3. Speech intelligibility decline in fast and slow progressors

#### 2.3.1. Classification of fast and slow progressors

A classification was developed to group 54 participants into fast or slow bulbar disease progressors. First, we estimated the average slope of intelligibility decline relative to speaking rate over the disease course by fitting an LME model (fitlme, MATLAB R2013b) that predicted intelligibility based on speaking rate while accounting for subject-dependent random effects on both intercept and slope. Comparisons of the estimated slope for each participant with respect to the baseline (i.e., the mean of slopes across all participants) resulted in an initial classification of two subgroups: those with slopes shallower than the mean were classified as slow progressors; and those with slopes steeper than the mean were classified as fast progressors.

We then used an optimization approach to refine the initial classification through iterative adjustments of baseline slope to maximize the variance accounted for by the model of each subgroup. Specifically, during each iteration, the baseline slope was increased from its original value for fast progressors and decreased from the original value for slow progressors; and the classification was updated accordingly. For the updated subgroup of slow progressors, an LME model with a fixed slope (i.e., \(s_1\), see Section 2.2) and a subject-dependent random intercept was fitted. For the updated subgroup of fast progressors, a tri-phasic NLME model with fixed slopes (e.g., slope for the early phase was fixed as \(s_1\); slope for the late phase was also fixed but was to be determined by the model) and subject-dependent breakpoints was fitted. Among all iterations, the one that resulted in a model with the largest \(R^2\) was selected as the optimal classification of each subgroup.

#### 2.3.2. Verification of classification

To verify the classification, we assessed the disease progression rates between the fast and slow progressors as determined above, based on the declines of four functional measures (i.e., ALSFRS-R score, speech intelligibility, speaking rate, AMR) over time. For each subgroup, we applied an LME model with a fixed slope and a subject-dependent random intercept to predict the decline of each measure as a function of time, where time was specified as the days since speaking rate dropped below 150 WPM, which was identified as the landmark that indicated the onset of precipitous decline in speech performance [18]. The rate of decline over time in each measure was compared between the fast and slow progressors.

#### 2.3.3. Modeling speech intelligibility decline as a function of speaking rate for fast and slow progressors

Because the slope of intelligibility decline relative to speaking rate was found to be constant (i.e., \(s_1\)) across all participants during the early phase (see Section 2.2), we kept this slope while modeling intelligibility decline for subgroups. To model intelligibility decline as a function of speaking rate for the fast progressors, we applied a tri-phasic NLME model with a fixed slope of \(s_1\) during the early phase. For the slow progressors, because the tri-phasic NLME model did not converge, we applied an LME model with a fixed slope of \(s_1\) to model intelligibility decline as a function of speaking rate.
3. Results

3.1. Modeling of the phasic nature of speech intelligibility decline as a function of speaking rate

Figure 2 shows intelligibility in relation to speaking rate in the form of a tri-phasic function. The estimated mean of slopes for the early, intermediate, and late phases are 0.02%/WPM, 0.30%/WPM, 1.24%/WPM, respectively. The estimated mean of breakpoints are 143 WPM for $x_1$, 98% for $y_1$, 103 WPM for $x_2$, and 85% for $y_2$. The $R^2$ based on population estimates (i.e., based on fixed effects) is 0.55; and the $R^2$ based on individual estimates (i.e., based on both fixed and random effects) is 0.92.

3.2. Speech intelligibility decline in fast and slow progressors

3.2.1. Classification of fast and slow progressors

The severity of ALS was evaluated by the ALSFRS-R score, which ranged from 26 to 46 ($M = 38, SD = 5$) across participants at the first visit. The impairment of speech was evaluated by intelligibility that ranged from 35.46% to 100% ($M = 95.32\%, SD = 10.68\%$) and speaking rate that ranged from 56 WPM to 241 WPM ($M = 165$ WPM, $SD = 39$ WPM) across all participants at the first visit.

Among 54 participants, 26 were classified as fast progressors (11 had bulbar onsets, 15 had spinal onsets), 25 were classified as slow progressors (12 had bulbar onsets, 13 had spinal onsets), and 3 had intermediate progression rates that did not fit into either fast or slow subgroup (all had bulbar onsets). According to Figures 3-6, all measures (centered at the mean of the intercept of the LME model) showed different rates of decline over time between the two subgroups.

3.2.2. Modeling of speech intelligibility decline as a function of speaking rate for fast and slow progressors

With the participants classified into two subgroups, the tri-phasic NLME model showed a slope of 0.02%/WPM during the early phase, a slope of 0.42%/WPM during the intermediate phase, and a slope of 1.65%/WPM during the late phase. The NLME model accounted for 89.39% of the total variance in the fast progressors. The LME model with a slope of 0.02%/WPM accounted for 23.46% of the variance in the slow progressors.

4. Discussion

4.1. Classification of fast and slow progressors

Due to the heterogeneous genetic and neuromechanical effects of ALS among other factors, affected individuals vary in disease progression rate. Predicting the rate of disease progression in this highly heterogeneous population has proven to be one of the greatest challenges in ALS research and in clinical practice [4, 5]. Focusing on the speech function, our successful classification of 54 participants into fast and slow progressors suggests that the slope of intelligibility decline relative to speaking rate might serve as a useful index for classification of bulbar disease progression rate. This finding has potential clinical implications in recruiting for clinical trials and predicting survival. Our finding of mixed participants with bulbar and spinal onsets in both fast and slow progressors suggests that once bulbar disease develops enough to affect speech intelligibility and rate, the disease progresses rapidly regardless of the initial site of symptom.

We also compared the sensitivity of four commonly-used clinical measures (ALSFRS-R score, intelligibility, speaking rate, and AMR) to disease progression. It was found that, among the four measures, (1) ALSFRS-R score itself did not distinguish the fast and slow progressors, nor did its rate of decline show a sufficient distinction; (2) speech intelligibility and speaking rate were distinct (both the value and the rate of decline) between the two subgroups once speaking rate dropped below 150 WPM; and (3) AMR differed in both the value and the rate of decline between the two subgroups prior to impairment of speech function (i.e., slowing of speaking rate below 150 WPM). The poor sensitivity of ALSFRS-R score to disease progression.
progression suggests that it might be an ineffective diagnostic tool for the early detection of bulbar involvement. Subscores of ALSFRS-R targeted at specific functions (e.g., bulbar subscore) might serve as a better predictor of disease progression, which needs to be evaluated in future studies. AMR, on the other hand, assesses the dynamic capacity of alternate orofacial muscle contractions, which require higher levels of muscle force beyond the range involved in normal speech production, and is thus, potentially affected at earlier stages than other speech measures.

4.2. Modeling of speech intelligibility decline as a function of speaking rate for fast and slow progressors

In this study, we modeled intelligibility decline as a function of speaking rate based on longitudinal data, accounting for individual differences in disease progression. Our model suggested a drop of speaking rate to 143 WPM accompanied by a drop of intelligibility to 98% marked the first transitional change in intelligibility decline rate; and a drop of speaking rate to 103 WPM accompanied by a drop of intelligibility to 85% marked the second transitional change in intelligibility decline rate. Our findings are consistent with prior descriptive observations of the phasic nature of intelligibility decline [2, 3].

We further examined the patterns of intelligibility decline among individuals with fast and slow bulbar disease progression rates. Our subgroup-based models suggested that (1) fast and slow progressors had different patterns of intelligibility decline and (2) within each subgroup, all participants showed a consistent pattern, which yielded a linear model that accounted for 23.46% of the variance in the slow progressors and a tri-phasic nonlinear model that accounted for the bulk of the variance (89.39%) in the fast progressors. The fit of the model for the slow progressors was not as good as that for the fast progressors probably because the proportion of disease-related variation relative to the total variation in intelligibility (a combination of disease-related variation and random variation that was not explained by the model) was smaller in slow progressors than in fast progressors. Increasing model complexity (e.g., nonlinear model) for the slow progressors did not improve the goodness of fit. Therefore, we consider it is appropriate to model intelligibility decline in the slow progressors using a linear model.

Because of the progressive nature of ALS, early diagnosis and prognosis is particularly important, especially for fast progressors. The subgroup-based model provides essential information on the timing of speech loss. For fast progressors, intelligibility is expected to decline beyond the normal range when speaking rate drops to about 150 WPM. Precipitous decline in intelligibility occurs as speaking rate slows down to about 100 WPM, resulting in loss of speech communication within a short time span [3, 18]. The intermediate phase, in which speech remains intelligible and speaking rate drops from 150 WPM to 100 WPM in about 17 months, might afford speech-language clinicians the time to successfully transition patients to assistive communication devices, which has proven to be one of the greatest challenges in clinical management of ALS [3, 19].

5. Conclusions

Based on the rate of speech intelligibility decline with respect to speaking rate, 54 participants with ALS were classified as fast or slow bulbar disease progressors. Intelligibility decline was modeled as a linear function of speaking rate for the slow progressors and a tri-phasic function of speaking rate for the fast progressors. The intelligibility model for the fast progressors indicates the timing of speech loss, which has potential implications in planning of assistive communication interventions.

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7. References


