

# DETECTION OF BULBAR ALS USING A COMPREHENSIVE SPEECH ASSESSMENT BATTERY

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**Abstract:** The study aimed to develop a predictive method that would aid the diagnosis of the bulbar form of Amyotrophic Lateral Sclerosis (ALS) as early as possible, specifically before the onset of obvious clinical signs (e.g., changes in speech intelligibility and speaking rate). Multiple instrumental physiological measures collected across speech subsystems collected longitudinally from over one hundred patients diagnosed with ALS were subjected to multiple analyses. Variable screening was performed using group comparisons with kernel density estimators and with linear regression. Variables identified as showing sensitivity to bulbar ALS onset and progression were used in a linear classifier, which was able to identify individuals who will develop bulbar form of ALS with 80% accuracy. Although preliminary in nature, these results show that instrumental measures might be able to assist in the clinically important early diagnosis of bulbar ALS.

**Keywords:** Bulbar ALS, speech subsystems, speaking rate, intelligibility

## I. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease with a fast progressing course. There is no biological marker of the condition and the diagnosis is made based on a constellation of clinical observations. As a result, the diagnosis of ALS is significantly delayed. On average, it takes over a year to arrive at the diagnosis [1]. The patients are at risk for multiple referrals to specialists and even for unnecessary surgery [2]. Diagnostic criteria are based on identification of upper and lower motor neuron

signs in three regions (i.e., limb, cervical or bulbar muscles) [3]. The bulbar region, defined as musculature involved in speech and swallowing, becomes crucial for timely diagnosis; yet, subtle changes in speech and swallowing might be difficult to detect. The current assessment methods are either perceptual and, thus, characterized by low sensitivity and reliability, or invasive in nature (i.e., needle electromyography is performed on the tongue musculature). There is a clinical need for an assessment protocol that is objective, reliable, and sensitive to early identification of the bulbar form of ALS.

At present, the clinical diagnosis of bulbar ALS is based on the presence of neurological signs of upper and lower motor neuron damage (e.g., atrophy, fasciculations, aberrant reflexes) as well as the system-level measures such as speech intelligibility and speaking rate. Previous research established that speaking rate is more sensitive to disease onset than intelligibility. Speaking rate begins to decline relatively early in the disease until it reaches approximately 120 words per minute (WPM). This cutoff signifies the point in bulbar disease progression when intelligibility begins to decline precipitously [4]. Physiological measures of each bulbar subsystem performance (i.e., respiratory, laryngeal, velopharyngeal, and articulatory) are suggested to show even more sensitivity to disease-related changes in the bulbar mechanism than speaking rate. In the past, each subsystem has typically been studied individually [5,6,7]. Considering substantial heterogeneity of disease presentation and patterns of progression across muscle groups, subsystems, and individuals, the multi-subsystem approach is essential to improve diagnosis.

In this study, we longitudinally assessed the function of each bulbar subsystem with multiple instrumental measures alongside speech intelligibility, speaking rate and ALS-Functional Rating Scale (ALSFRS-R) [8] for a large number of individuals diagnosed with ALS. Based on this dataset, we asked the following questions:

- (1) Which objective measures within each subsystem distinguish individuals with bulbar ALS from healthy controls?
- (2) Which objective measures are sensitive to disease progression over time?
- (3) Based on these objective physiological measures, can we predict who will and who will not develop bulbar ALS as disease progresses?

## II. METHODS

144 individuals (males=89; females=55) diagnosed with ALS took part in the study. The mean age of these participants was 59.6 years (SD=10.3). 53 healthy controls (males=24, females=29) were recruited as well. The mean age was 57.4 (SD=12.6). 34 patients had bulbar onset ALS at the time of diagnosis, the remaining individuals presented with spinal onset ALS, with or without bulbar signs. The participants in the patient group were recorded every three months for the average duration of 22.11 months (SD=16.74). The control participants were recorded once.

The average ALSFRS-R score at the first session was 37.32 (SD=6.32) across all participants. The presence of bulbar ALS was determined by bulbar subscore on ALSFRS-R. At first recording session, the average subscore was 10.42 (SD=1.90). Bulbar performance was also assessed by means of Sentence Intelligibility Test [9] during which individuals were asked to read a series of semantically unpredictable sentences. Speech intelligibility (% words transcribed correctly) and speaking rate (number of words per minute) were determined by a single transcriber unfamiliar with the patients.

The instrumental protocol and measurements are described in detail elsewhere [10, 11]. Briefly, a series of instruments were used to assess the functions of respiratory, laryngeal, velopharyngeal and articulatory subsystems. These instruments included the Phonatory Aerodynamic System (PAS) and Nasometer (KayPentax, MA, USA), acoustic recording equipment (i.e., high fidelity microphone and digital recorder), as well as facial motion (e.g., Optotrak Certus) and tongue motion (Wave) systems (NDI, ON, Canada). Speech tasks included phonation, readings of syllables (e.g., /pa, ma/), words, phrases and paragraphs at normal comfortable speaking rate and loudness.

A large number of measurements per speech subsystem were performed, as those most sensitive to disease onset and progression have not yet been established in the literature. Mean values of multiple repetitions computed by subject/ session composed the final set. The measurements included:

1. Respiratory subsystem – maximum phonation time, minimum and maximum SLP during soft and loud phonation, percent speech and percent pause time, average pause duration, and coefficient of variation of pause duration during paragraph reading, performed using Speech Pause Analysis software (SPA) [12].
2. Laryngeal subsystem – mean fundamental frequency (F0), F0 standard deviation, percent jitter, percent shimmer, F0 maximum, and noise-to-harmonic ratio for a phonated /a/, and laryngeal resistance.
3. Velopharyngeal subsystem – median nasalance scores for a nasal and oral sentence as well as nasalance distance and maximum oral pressure and nasal flow during /pa/ and /ma/.
4. Articulatory subsystem – volume, range, maximum speed and duration of movements of the jaw, lips, and tongue.

For the participants with ALS, all the sessions were subdivided based on the bulbar subscore of ALSFRS-R, speech intelligibility and speaking rate values. The cutoff scores were determined based on the existing literature [4] and the relationship between rate and intelligibility in our sample that showed that the active decline of functional speech was modeled by a linear pattern after speaking rate dropped to 157 and speech intelligibility dropped to 93.

- a. The “No-Bulbar” group was composed of sessions without any bulbar signs based on the clinical assessment; they showed ALSFRS-R score =12, rate  $\geq 157$ , and intelligibility  $\geq 97$ .
- b. The “Bulbar” group was composed of sessions with ALSFRS-R score  $\leq 9$ , rate  $\leq 120$ , or intelligibility  $\leq 93$ .
- c. The “Early-Bulbar” group was composed of patients with early clinical bulbar signs with criteria outside of those identified in a. and b.

The following analyses were performed. First, each variable was assessed for its sensitivity to the presence of clinically confirmed bulbar disease using kernel density estimators. The kernel density estimators were computed using Gaussian kernel functions, using bandwidths chosen according to Scott's Rule [13]. Such estimators are robust to assumptions about the data such as independence of observations, normality of distribution, etc. [14]. The overlap between density functions served as a metric of similarity between distributions, where the probability of correct guess among observations is equal to one minus half the overlap. We declared the amount of overlap to be significant if it was less than 0.6, corresponding to being able to guess correctly more than 70% of the time.

Second, we examined which variables are sensitive to disease progression using a linear regression of the number of days elapsed from the initial session against the change in each variable. The  $p$  values were used to measure the significance of that variable as the bulbar ALS progressed.

Third, a linear classifier was used to derive a predictive score which can be used to determine who will develop bulbar disease over time and who will not, among patients who do not present with the disease initially. Specifically, we used linear regression to find a linear combination of relevant variables which came closest to assigning +1 to patients who will develop bulbar disease, and -1 to patients who will not. This linear combination then gives a predictive score to each new patient, so if their score is positive then we predict that they will develop bulbar disease, while if it is negative then we predict that they will not. Only variables that passed the screening procedures of the two first analyses were used in the classifier.

### III. RESULTS

#### A. Bulbar ALS versus Healthy Controls

In this analysis, we compared healthy controls to ALS data in sessions specified as Bulbar in order to identify measures that are associated with the clinical presentation of bulbar ALS. Fig.1 shows the results of kernel density analysis on the variable Pause Duration. Other physiological measures sensitive to the presence of clinically confirmed bulbar disease included % pause time and number of pauses during paragraph reading, nasal flow during /pi/, laryngeal resistance, maximum speed and duration of opening/ closing cycles of the tongue movement (overlaps ranging between 0.42 and 0.55).

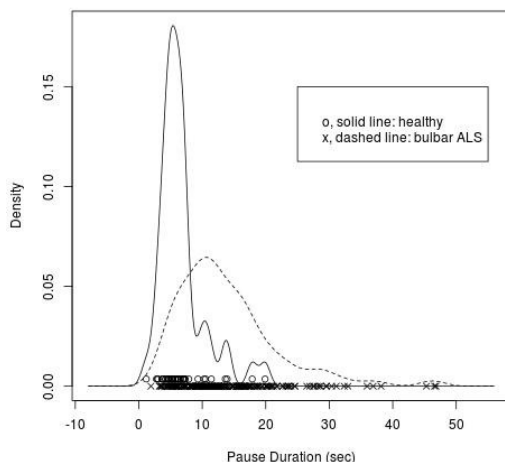


Fig. 1 Kernel density functions for healthy and ALS groups for Pause Duration (overlap=0.46).

#### B. Change over time

All variables were assessed for their sensitivity to disease progression. For this analysis, only those patients who showed change over time in clinical scores (ALSFRS-R, speaking rate and intelligibility) from the No-Bulbar to either Early-Bulbar or Bulbar groups were selected. 36 out of 67 variables were found to show a statistically significant change with disease progression ( $p < 0.05$ ), including those identified in Step A above.

#### C. Classification

The five variables with the smallest overlap in step B were selected for the linear classifier to predict who will develop bulbar ALS and who will not, among patients who do not present with the disease. The classifier derived a predictive score given by the following linear combination of the five measures:

$$1.16 + 0.039*PauseDuration - 22.01*NasalFlowPi + 0.00316*LarResistance + 0.00721*TongueMaxSp - 20.39*DurationOpenJaw \quad (1)$$

The predictive rule can then be described as follows: Given a new ALS patient who does not currently show clinical bulbar symptoms, if their score of the above linear combination is positive, then we predict that they will develop bulbar symptoms in the future; if it is negative, then we predict that they will not. This predictive rule gives the correct prediction in 80% of the 20 patients for whom we have complete records of all of the required variables.

### IV. DISCUSSION

Diagnosing bulbar ALS and predicting disease progression is essential for patient recruitment into clinical trials as well as patient management in a multidisciplinary clinic setting. Approximately 70% of individuals diagnosed with ALS present with spinal signs only (i.e., symptoms associated with arm/ hand/ leg) function. We are exploring the possibility of subclinical bulbar presentation that might be assessed using sensitive instrumental measures of bulbar function. As a result of our preliminary analyses, five variables play an important role in identifying potential early changes associated with bulbar ALS. They include Pause Duration, Nasal Flow during syllable /pi/, laryngeal Resistance, Tongue Maximum Speed and the duration of the Opening-Closing Jaw movement cycle. These variables identified based on their sensitivity to presence of bulbar disease

and progression of the disease over time classified individuals into those who will and will not develop bulbar ALS with 80% accuracy.

We are currently continuing to explore other classification approaches (e.g., kernel density, support vector machine [15]) to achieve higher classification accuracy and cross-validating our results on a different data set.

#### V. CONCLUSION

Further work is necessary to improve our data reduction and prediction methods, yet current findings provide preliminary indication that we can develop an accurate method for predicting future bulbar symptoms among ALS patients who do not display clinical bulbar signs by virtue of clinical instrumental monitoring.

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