

## Investigator's Protocol

**Title:**

DESIPHER Speech Degradation as an Indicator of Physiological Degeneration in ALS

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**Research Site:**

James A. Haley Veterans' Hospital

**Sponsor:**

VA Rehabilitation Research and Development

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**Rationale**

A disease called *Amyotrophic lateral sclerosis* (or ALS), which leads to difficulty swallowing, breathing, and movement, has been found to be higher for those serving in the military than in the general population. There are approximately 4,200 Veterans with ALS and roughly 1,000 new cases each year. When doctors attempt to determine the degree to which an ALS patient is suffering from the disease, they apply tests that are "graded" by experts. However, this approach to testing patients may not be very accurate. Researchers aim to use a system called DESIPHER to "listen" to ALS patients and find speech mistakes related to their condition. Researchers believe that, by detecting different types of errors, DESIPHER serves as a new kind of indicator of medical problems such as difficulty breathing or swallowing, without human "grading". This may also lead to a better electronic system for understanding ALS patients' speech, even with lots of errors.

Hypotheses: Using a longitudinal study of Veterans with recently diagnosed with ALS, we propose to test the following two hypotheses:

H1: Automatic speech recognition can be achieved for ALS patients, whose speech diverges from a baseline, as established from transcribed speech data, using speech-model adaptation.

H2: Divergence of speech from baseline will serve as a marker for disease progression.

Specific Aims: Research questions to be addressed by this study are:

Q1: Is it possible to train a speech recognition system to adapt to increasingly more frequent language/speech errors of particular types, to produce an accurate textual transcript that would be readable by a caregiver or physician?

Q2: Are specific changes in physiological functioning (Forced Vital Capacity, tongue

strength, speech velocity, weight loss, aspiration risk, or psychological distress) associated with different types of language/speech errors?

**Significance:** Results of the proposed study are expected to improve our ability to appropriately identify and intervene when Veterans with ALS are at risk of serious adverse medical issues such as respiratory failure and aspiration. Detection of speech divergence may serve as an additional assessment tool that requires much less effort from the patient than existing clinical measures. A future study may incorporate the divergence voice software into common technology to prolong the Veterans' ability to use their natural voice to control the environment around them. A further study may investigate if monitoring changes in language divergence, which indicate disease progression, could improve timely access when further appropriate interventions might be indicated.

**Relevance:** In 2008, Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease became a presumptively compensable (service connected) disease as the Institute of Medicine (IOM) Committee stated an association between the development of ALS and military service. According to the IOM report, military service increases life risk of ALS by 1.5 fold. There are approximately 4,200 Veterans with ALS and roughly 1,000 new cases each year. At the Tampa VA, since 2007, there has been a consistent rise in the number of Veterans diagnosed and treated with ALS.

## **Background**

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive, neurodegenerative disease that involves upper and lower motor neurons and is the most common form of motor neuron disease. ALS is characterized by muscle atrophy, muscle weakness, muscle spasticity, hyperreflexia, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), and difficulty breathing (dyspnea). A serious healthcare crisis is emerging from the lack of capacity to support ALS sufferers, who typically must rely on a caregiver (often a family member) to manage their daily activities and to assist in relaying information between medical professionals and the patient. Mean survival time is three to five years; however, death may occur within months, or survival may last decades.

There are a number of standardized objective assessments of bulbar function in patients with ALS (Green et al., 2013); for example, breathing patterns, articulatory patterns, and voice loudness. These are generally measured by technologies that record chest wall movements, oral pressures and flows, oral movement and strength, and speech acoustics. However, these measures are focused on the *form* of speech output (e.g., hypernasality) rather than the *content* of the speech output in terms of dialectal variations. Identifying such variations is contextually similar to detecting different accents and dialects in spoken English.

Our speech research focuses on the detection of dialectal variations by identifying spoken language *divergences* along a range of different dimensions. We borrow the notion of divergence from the study of cross-linguistic variations (Dorr, 1993, 1994;

Dorr et al., 2002; Habash and Dorr, 2002), where a language is considered "close" to another language if it shares certain properties (but possibly not others), and "far" (i.e., *divergent*) if very few properties are shared. To illustrate the concept of divergence across languages, consider three properties: vocabulary, pronunciation, and syntactic structure. Table 1 shows the properties that are shared between Spanish and four other languages. The most radically divergent pair in the table is Spanish and Chinese, which do not share vocabulary, syntactic structure, or pronunciation. We note that one could apply the same sort of analysis within a single language, such as English, by examining different dialectal variations. For example, a native U.S. English speaker from Massachusetts is likely to pronounce certain terms like "car" in a way that is more closely aligned to the British English pronunciation (where the "r" is dropped – non-rhotic) than to that of a native U.S. English speaker from Alabama (rhotic).

**Table 1: Linguistic divergence across languages**

Spanish	Portuguese	French	English	Chinese
Vocabulary	X	X	X	
Syntactic structure	X	X		
Pronunciation	X			

We propose to apply this same notion of *divergence* to the problem of "speech functioning," constraining our language pair to asymptomatic English speech compared to impaired English speech. In this case, the properties to be studied are finer grained than the ones shown in Table 1, in that they are aligned with articulatory patterns in speech. Although we expect speech divergences to develop independently of language accent and dialect, we expect that prior work on dialect adaptation (Lehr et al., 2014) will be relevant for tracking speech divergences even within a single language. Research on modeling non-native or dialectal speech (Livescu and Glass, 2000) is a close approximation to what we propose for recognition of speech changes over time, though the focus of dialectal modeling is on detecting divergent content, not on discerning characteristics of the speech signal. In order to test our hypothesis that divergence from a baseline serves as a marker for disease progression (and that, in fact, specific speech properties vary systematically in impaired speech), the current proposed pilot is for native speakers only; this allows for variability in dialect, but not variability regarding the level of knowledge of the language, thus retaining only one variable: the level of progression of the disease over time. However, an important follow-up study is that of speech recognition of accented (non-native) speech, once the properties that vary systematically with disease progression have been carefully identified in this current pilot study.

A significant aspect of the proposed work is the identification of possible speech-related biomarkers to be examined for correlations with other aspects of physiological function. Some that have been published in the literature (e.g., Duffy, 2012; Rudzicz et al., 2014) that are relevant to dialectal variations, but have not heretofore been measured objectively through dialectal analysis, are those listed below:

- Imprecise consonants
- Distorted vowels
- Slow rate
- Short phrases
- Hypernasality
- Continuous voicing
- Distorted substitutions or additions

Table 2 is a notional table illustrating a range of articulatory properties for "baseline" English (as determined for a native English speaker who has no speech impairment, i.e. pre-symptomatic) compared to those exhibited during different stages of ALS—early, mid, late—thus providing a framework for capturing the degree of divergence. The final column has the highest level of divergence from the baseline: imprecise consonants, distorted vowels, and continuous bilabials.

**Table 2: Articulatory divergence across stages of ALS**

"Baseline" English	ALS English (early)	ALS English (mid)	ALS English (late)
consonants	imprecise	imprecise	imprecise
vowels	~baseline	distorted	distorted
bilabials (b,m)	~baseline	~baseline	hypernasal

Biadsy et al. (2011) conducted a speech processing study similar to our divergence approach, investigating the variation of speech properties under intoxicated and sober conditions. Rudzicz et al. (2014) employed another approach for recognizing impaired speech for detection of Alzheimer's, and Little (2012) developed an analogous application for detection of Parkinson's, as reported by Kepes (2014). These approaches measured the voice signal to answer a yes/no question (presence or absence of impairment), rather than analyzing the signal to determine the degree of divergence from a baseline. Nevertheless, the incidental but significant discovery from these studies, as well as related work of Beukelman et al. (2011), Green et al. (2013), and Orimaye et al. (2014)—that *pronunciation varies systematically within categories of speech impairment*—is a critical finding that can be leveraged for correlating the divergence from baseline English to different stages of ALS (i.e., the degree of biophysical degradation).

A large part of our investigation will involve the characterization of divergence types, most notably: pronunciation divergences (articulatory and acoustic distinctions) and discourse divergences (word choice, duration of utterances, and disfluencies). Table 3 illustrates these distinctions using examples of divergent speech characteristics that have been reported by Duffy (2012). In our proposed pilot study, we would expect to parameterize some—but perhaps not all—of these characteristics, as we have reports from clinician partners conducting a pilot study on ALS patients that phenomena such as these are common in the data they have collected so far (which will form our initial dataset, as described in Data Collection Protocol).

**Table 3: Examples of Divergent Speech Characteristics**

Level	Speech Characteristics	Example	Comparable ALS Utterance	Divergence Dimensions
Pronunciation	Vowel	I wrote to the owner	I wr[aw]t to the	Substitution of back vowels

	<b>distortion</b>		[ooh]ner (oh/aw, oh/ooh) for front vowels
	<b>Involuntary Repetition</b>	The best part of the movie was the surprise ending.	[The bbbbest thing] * <u>the best thing</u> I wanted to tell you is...
	<b>Imprecise consonants</b>	The blue shirt didn't feel comfortable.	I wasn't comforful in that shirt. Deletion of soft alveolar stop ([t]/[d])
<b>Discourse</b>	<b>Short phrases</b>	I don't feel like a very accomplished chef, although I've made eggplant parmesan.	So how do you make this soup? Well I'm not so sure. See I don't know if I'd go that far. Short discourse words (so, well, see), small number of words per sentence, omission of large content words
	<b>Slow rate</b>	I take pride in being able to cook myself.	Um I do uh some uh cooking myself. Number of words per minute, frequency and pattern of unfilled or filled pauses (um, uh).
	<b>Disfluencies</b>	I walked the dog to the store.	I saw [the dog] * I mean <u>the cat</u> . Substitutions, possibly edited, e.g., I mean, sorry, excuse me, rather

By understanding how speech deterioration correlates with other physiological degradation, it may be possible to apply a new, non-invasive measure for assessing the functionality of an ALS patient. In addition, the features associated with speech deterioration enable the adaptation of existing speech recognition software to a patient's speech as it evolves over time, so that the quality of life for patients may be improved through conversation with a computer.

### **Work accomplished by PI**

*Reducing Barriers to living at home for the rural Veteran with Amyotrophic Lateral Sclerosis* (ORH N08-FY14Q4-S0-P01503, PI: Phillips). This project consists of interviews with caregivers and Veterans with ALS about the challenges of living and the barriers to maintaining living at home. This study is currently ongoing, but preliminary results point to timely and appropriate access to care as an important feature. Communication and transportation issues also present as consistent themes.

*Increasing Access to pulmonary function testing for rural veterans with ALS through at home testing* (ORH FY 2015, PI: Phillips). Begun in Oct 2014, this program provides in-home testing for forced vital capacity (FVC). FVC is an important measure in this study. Additionally, telehealth appointments will be available while the respiratory therapist is in the home to consult with other members of the ALS team. This program may provide important access to the population in this study.

"Machine Translation Divergences: A Formal Description and Proposed Solution," *Computational Linguistics*, 20:4, 1994. Dr. Bonnie J. Dorr was a NSF Presidential Faculty Fellow Awardee in 1997 for her seminal work on the problem of translating from one language into another in the face of *language divergences* (i.e., cross-linguistic distinctions). Her work resulted in a systematic solution to the divergence

problem based on the formalization of linguistically-motivated classes that facilitate the design and implementation of a language processing system that is general enough to be applied to problems in text processing, speech processing, and language translation.

Her subsequent research on cross-language divergence analysis for statistical word-level alignment (Dorr et al., 2002) was successful for analysis of both minimally divergent language pairs (Spanish and English) and maximally divergent language pairs (Spanish and Chinese). Her experience in studying divergent speech patterns will be extremely valuable in leading data analysis efforts of ALS patient speech at Florida IHMC.

### **Research Plan**

Population: Participants with ALS receiving medical services at James A. Haley Veterans' Hospital. According to the National VA ALS registry, one of the highest concentrations of Veterans with ALS is in Mid-Florida. In FY13, 136 Veterans with ALS were served by the Tampa VA. All veterans who meet inclusion criteria will be approached about the study.

Inclusion criteria: Veterans have been diagnosed with ALS, are native monolingual speakers of American English, have bulbar involvement identified during initial ALS inpatient evaluation, a forced vital capacity (FVC) of greater than 50% of the expected value for age, and an ALSFRS-R score of 40 or greater.

Exclusion criteria: a diagnosis of dementia, FVC less than 50%, inability to speak, or inability to follow directions.

Number of subjects: We will recruit 20 Veterans with ALS who currently have bulbar involvement into the study. The process of recruitment begins when potential recruits are initially assessed in the ALS clinic. The examining physician will make the potentially subject aware of the study. If the potential subject is interested, they will be referred to the research assistant, who will inform the subject about the study, and begin the consent process if the potential subject is interested in participating. 20 control healthy subjects without a diagnosed ALS will be recruited. A ONETIME recording will be done of the TIMIT and Ba repetition.

Timeline: Veterans will provide data quarterly (every 3 months) for two years for 8 visits total. Each time the Veteran visits the Tampa VA, the research assistant will make a set of voice recordings. If the Veteran is not able to come to the VA within a 3 month time period, the research assistant will make a home visit to make the recording. The control 20 healthy subjects without a diagnosed ALS will be a ONETIME recording of the TIMIT and Ba repetition.

Data Collected: In order to minimize the burden to the subjects, research data collection and clinical data collection is being coordinated. The following data is collected per standard of care each time the Veteran is seen

Potential participants will be screened and evaluated for *Amyotrophic lateral sclerosis* (or ALS) within the Tampa VA systems of care. After screening a letters will be mailed about the study to these potential participants. For those who respond to the letter showing interest in participating in the study and who are eligible, an appointment will be scheduled to meet for the consenting and enrollment process. There will be Waiver of document; for control 20 healthy subjects without a diagnosis of ALS. Script for waiver of Documentation will be used to recruit the 20 healthy subjects.

This information will be extracted by the Research Assistant from participants' medical records on a quarterly basis:

1. Forced Vital Capacity (FVC),
2. Penetration-Aspiration Scale (a paper-pencil screen; Rosenbek, 1996),
3. ALSFRS-R (Cedarbaum, 1999), and
4. Speech Intelligibility Test (SIT; Beukelman et al., 2007).
5. Ba repetition test ( Rong et al., 2015).

If any measurements are missing, the research assistant will confirm collection of clinical measurements and coordinate with the clinical team.

The research assistant will measure tongue strength using the Iowa Oral Performance Instrument (IOPI Medical, Redmond, WA), and speech recordings made of four preselected passages. These passages, selected from the Texas-Instrument/MIT (TIMIT) corpus (Garofolo et al., 1993), combat what would generally lead to unintelligibility in speech recognition by providing a "ground truth"; with the knowledge of what the sentence is in advance, even if the patient is not otherwise able to speak intelligibly, the speech recognition system can be appropriately calibrated to expect certain levels of deviation from a baseline. And, the 'Ba' repetition test ( Rong et al., 2015). The diadochokinetic (DDK) rate test in which the participants were asked to clearly and rapidly repeat /ba/ was used in (Rong et al. 2015), to help with speech intelligibility deterioration as a result neurologic atrophy. While this pilot study focuses on speech recognition that accommodates varying levels of impairment, in later stages of the disease, adaptive speech recognition technology would be most useful in combination with alternative and augmentative communication (AAC) technologies and brain computer interfaces (BCI); this powerful combination would accommodate typing, gaze, and head-mouse input, in addition to speech input (see related discussion in Dorr et al., 2015).

We would expect to follow a patient from enrollment to the end of the study, or end of life. When possible, speech recordings and assessments will be coordinated during the quarterly visits to Tampa VA. If not possible, separate visits will be scheduled. If the patient were unable to come to Tampa VA, home visits would be scheduled. If results are promising, we would seek additional funds to follow this cohort beyond the end of study.

The 20 control speakers will participate in ONETIME only, recording during the rest of the study time of the TIMIT Sentences and Ba repetition.

Participants diagnosed with ALS CPRS notes will be reviewed for the following co-existing conditions to be found on the CPRS Notes:

- I. Parkinson's disease
- II. Multiple Systems Atrophy
- III. Olivopontocerebellar degeneration
- IV. Shy Drager syndrome
- V. Progressive Supra nuclear palsy
- VI. Any kind of laryngeal dystonia

Data Analysis: Data analysis will be conducted at the Florida Institute of Human and Machine Cognition (IHMC) in Ocala, Florida. Data sharing and security will be governed under the IPA agreement between James A. Haley Veterans' Hospital and IHMC. Phonetic annotation of the training data is required in instances where we want to identify speech characteristics in the transcribed text (e.g., hypernasality). The Tampa VA will provide transcribed, annotated speech data (in addition to the audio recordings) to IHMC for setting up the baseline speech recognition system. To perform quality annotation, we will utilize a consistent set of guidelines to ensure that the system can learn patterns to aid in understanding speech with errors. Speech recordings will be separately annotated for speech irregularities by two research assistants using the annotation guidelines, and differences in annotations will be arbitrated by the PI or his designee. The annotated script, along with the original recording, will be de-identified and sent to IHMC using Cradeon, a FIPS 140-2 compliant encryption program. Sample annotations are provided below. It is critical that the degree to which the ALS has progressed be associated with each transcript, so that a different set of speech models can be produced for different degrees of ALS progression.

From the audio recordings collected, 90% will be used for training the system. A randomly selected 10% will be used to test the divergence construct.

### **Risk/Benefit Assessment**

There are minimal risks to the subject. The subject could fatigue, in which case they would be allowed to rest until they were ready to continue. Subjects could become frustrated while reading the passage. In that case, subjects would be given a break, and then continue with the protocol. There are no known benefits to participating in this research study.

The etiology of ALS frequently creates other health issues. These anticipated issues that may require medical intervention and hospitalization include, but are not limited to:

- Respiratory Insufficiency
- sleep apnea
- malnutrition
- dehydration
- tracheotomy
- frontotemporal dementia
- falls

### **Data Safety Monitoring Plan**

A data and safety monitoring plan will be implemented to insure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. The PI, Co-PI, and research staff will be responsible for data safety and monitoring. All data obtained in the course of the study will be confidential. All participants will be informed of their confidentiality rights at the time informed consent is administered. Data collection, management and destruction will be conducted in strict accordance with the policies and procedures set forth by the Tampa VA Research & Development Office Research Data Security and Privacy Policy. Data will be stored on the password-protected research server which sits behind the VA firewall. All data will be stored and maintained in a Microsoft SQL Server or Microsoft Access back-end database. The server is managed by VATAM OI&T and data are backed up on a nightly basis. The following staff members will have access to the data once it is saved on the research server: the PI and the project staff. If a staff member leaves the project, an amendment to the IRB will remove their access to identifiable patient information for the study.

Patients and providers will be assigned a number at the time of enrollment in the study and will be identified by that number during the course of the study and data analysis. Identifiable personal information will be stripped from the database so as to protect confidentiality. Monthly meetings of the investigators will include a discussion of issues pertaining to the assurance of patient confidentiality, and any needed changes will be instituted immediately to assure optimal patient protection. Breaches of confidentiality will be brought to the attention of the appropriate persons immediately as will any proposed changes to the data safety and monitoring plan

### **Process for Obtaining Informed Consent and Protecting Patient Privacy**

Eligible participants will be referred to the Research Assistant who will review in detail the consent form and study procedures. After participants have acknowledged complete understanding of the study, they will be asked to sign a consent form. Subjects will also be given a copy of the signed consent and will be advised of their rights to withdraw from the study at any time without penalty.

#### Process for assessing ALS-related dementia:

The cognitive ability of this population is closely followed by the clinical team. The chart will be reviewed for competence to consent. If no assessment score is available, the RA will administer the exam. The Mini-Mental Exam will be used for assessing dementia. The cut score for competence to consent is established in the literature.

### **Documentation of Informed Consent**

The Research Assistant will enter progress notes for study enrollment into the CPRS medical records for each subject after consent forms have been signed. A copy of the consent form will be placed in the participant's CPRS medical record and a copy will be maintained with the study records which will remain locked in a file cabinet in the Research Assistant's office.

### **Payment to Subjects for Their Participation**

Participants will be compensated \$25 in check form or direct deposit per session visit for up to eight study visits.

### **Provisions for Data Storage and Confidentiality**

All electronic data will be stored in

R:\PROJECTS\_CURRENT\Phillips\_DESIPHER\_RR&D\_SPIRE\Secure. All original documents (i.e. consent forms) will be stored in a locked file cabinet in PI's office 147A, Grand Oaks Building.

Each subject will be given a unique subject number. All data will be stored under that subject number. The PI will hold an electronic list with the map between subject number and patient information. All information sent to colleagues at IHMC will be de-identified. There is minimal risk of loss of identifiable information.

### **Dissemination of Research Results**

The PI will be the take the lead in writing up the results of this work.

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