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14. ABSTRACT
Frontotemporal degeneration (FTD) is an understudied form of focal dementia. Its public health impact is immense because clinical FTD is the most common neurodegenerative disease in individuals <65 years old. FTD presents with a specific language deficit (Primary Progressive Aphasia, PPA). A careful analysis of everyday speech can help identify variants of PPA. This proposal fills a major gap by providing an objective, replicable, fully automated approach to discerning speech characteristics of PPA. FTD may co-occur with a motor disorder, including Amyotrophic Lateral Sclerosis (ALS) and Chronic Traumatic Encephalopathy (CTE) which are directly relevant to the military. Detailed analyses of speech in FTD spectrum disorders with associated motor impairments are rare, and we propose to extend our analyses to FTD patients with motor disorders. Finally, longitudinal analyses of speech can play an important role in prognosis and in treatment trials, but longitudinal studies are rare. This study pursues these issues with three Specific Aims: 1. Develop an automated algorithm to analyze lexical semantic word-level content and grammatical category in FTD; 2. Develop automated algorithms to align lexical content with acoustic signal in connected speech samples of FTD speakers; and 3. Develop algorithms to automatically characterize the properties of the complex (acoustic and lexical) signals that are associated with sentence boundaries and syntactic units in FTD speech.

15. SUBJECT TERMS
Frontotemporal dementia, primary progressive aphasia, speech

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1. Introduction

Frontotemporal degeneration (FTD) is an understudied form of focal dementia. Its public health impact is immense because clinical FTD is the most common neurodegenerative disease in individuals <65 years old. FTD presents with a specific language deficit (Primary Progressive Aphasia, PPA). A careful analysis of everyday speech can help identify variants of PPA. This proposal fills a major gap by providing an objective, replicable, fully automated approach to discerning speech characteristics of PPA. FTD may co-occur with a motor disorder, including Amyotrophic Lateral Sclerosis (ALS) and Chronic Traumatic Encephalopathy (CTE) which are directly relevant to the military. Detailed analyses of speech FTD spectrum disorders with associated motor impairments are rare, and we propose to extend our analyses to FTD patients with motor disorders. Finally, longitudinal analyses of speech can play an important role in prognosis and in treatment trials, but longitudinal studies are rare. This study pursues these issues with three Specific Aims: 1. Develop an automated algorithm to analyze lexical semantic word-level content and grammatical category in FTD; 2. Develop automated algorithms to align lexical content with acoustic signal in connected speech samples of FTD speakers; and 3. Develop algorithms to automatically characterize the properties of the complex (acoustic and lexical) signals that are associated with sentence boundaries and syntactic units in FTD speech.

2. Keywords

Frontotemporal dementia, primary progressive aphasia, semantic variant primary progressive aphasia, non-fluent/agrammatic primary progressive aphasia, behavioral variant frontotemporal dementia, speech, natural language processing

3. Accomplishments

Major Goals: Our major goals in the first year included: 1 - exploring, testing and training automated part of speech (POS) tagging algorithms in FTD speech; 2 - testing automated dependency parsing in FTD speech; and 3 - reviewing and correcting aligned output of speech samples from untrained forced alignment (FA).

Accomplishments: Our work was delayed earlier in the reporting period due to delays in HRPO approval as well as ongoing limited campus activity due to the pandemic. Our study team was able to continue some remote work and most recently resumed activity on campus.

1) <u>Major activities</u>:

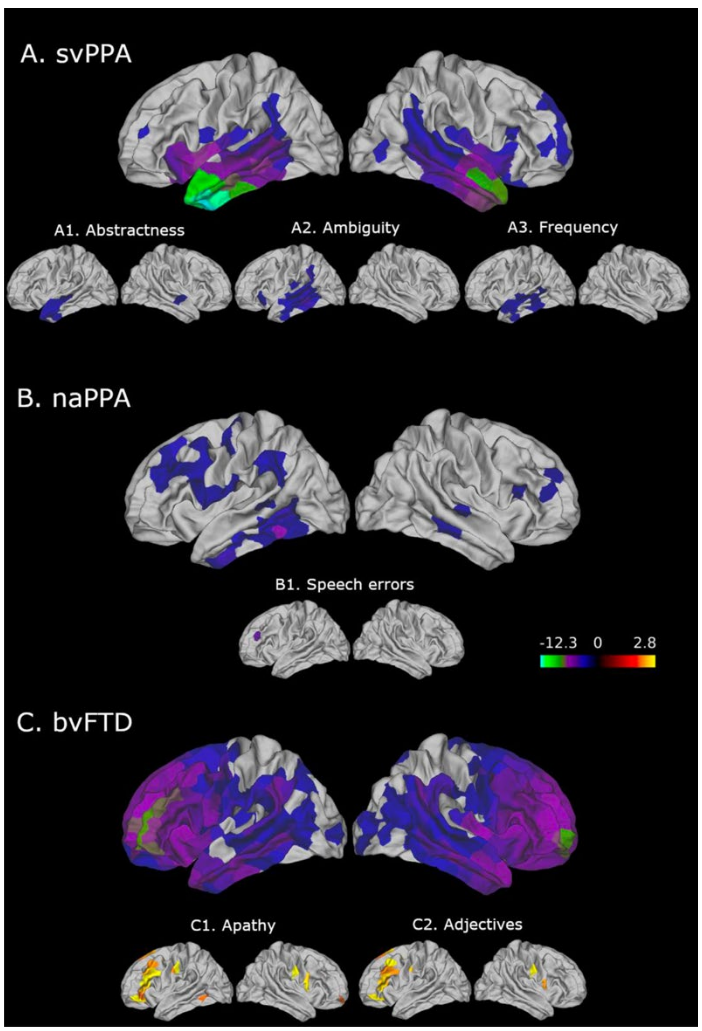
(a) Tested and trained automated part of speech (POS) tagger on FTD speech corpus, (b) Trained and reviewed English dependency parser analyzing FTD speech samples.

2) <u>Specific objectives</u>:

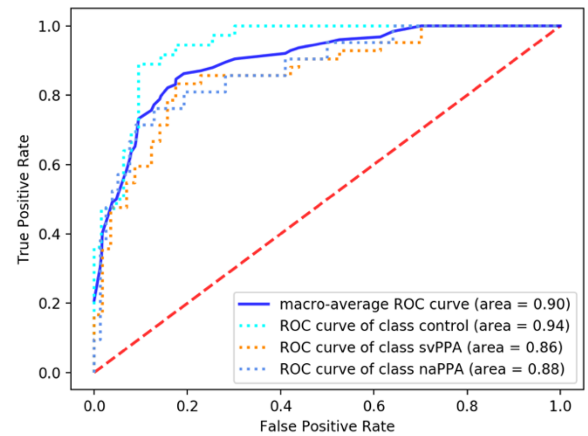
(a) Perform Exploratory Data Analysis (EDA) on untrained POS tags; (b) Characterize speech of different FTD phenotypes; (c) Validate characteristic speech features of FTD phenotypes with clinical measures; (d) use machine learning algorithms to train POS classifiers for FTD syndromes; (e) evaluate accuracy of automated POS tagger; (f) review and correct dependency parser analysis of FTD speech samples; (g) Review and correct aligned files from untrained forced alignment (FA).

3) <u>Key outcomes</u>:

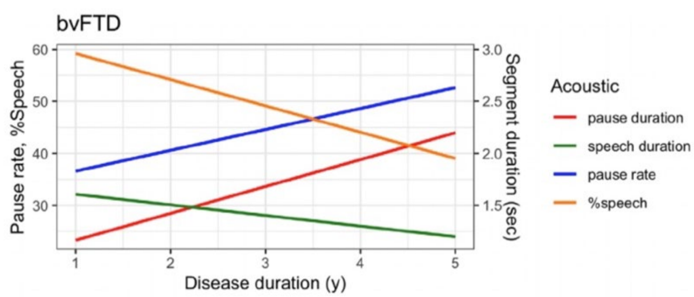
We used an untrained natural language processing (NLP) tool (spaCy) to characterize the speech of different FTD phenotypes in terms of their use of different word categories, or Part-of-Speech (POS) such as nouns, verbs, adjectives, etc. We included additional parameters such as partial word and speech error counts, inflected verb and wh-word counts. Controlling for speech production (/100 words) we found distinct sets of speech features for each FTD phenotype, that were compatible with our a-priori hypotheses for the expected speech characteristics in patients. We then localized and validated some of the more distinct speech features with atrophy in relevant areas of the brain cortex (see figure below). Additional validation of speech features was done by correlating speech features with clinical test scores. For example, we found a strong correlation (r=0.32, p=0.01) between apathy scores and adjective counts in our bvFTD speakers, which suggested that these patients with a behavioral impairment that manifests as increased apathy, use less adjectives to describe the picture in detail.



We successfully applied a Support Vector Machine (SVM) machine learning algorithm to train an automatic POS tagger on our FTD speech samples, resulting in speech classifiers for different types of FTD syndrome as shown in the ROC curve below.



An expert linguist manually reviewed random speech samples from each FTD phenotype to evaluate the accuracy of automated POS tagging and characterize any systematic errors made by the untrained model. We also explored the longitudinal behavior of distinct speech features in FTD phenotypes and found progressive impairment in some features that correlated with disease progression as illustrated in Figure 2 below, where bvFTD speakers showed increased pauses and reduced speech time with overall gradual decline in the production of speech when describing the picture.



4) Other achievements: Nothing to report.

Opportunities for Training and Professional Development: While there was no formal intent to provide opportunities for professional development, there are postdoctoral fellows who benefit greatly from learning about design and execution of multidisciplinary research projects. This includes regular weekly meetings, regular scientific presentations of project progress, and sharing these at scientific conferences.

Dissemination of Results: In addition to peer-reviewed publications (listed below), our team members present our work regularly within our department (Neurology), at other departments at the university of Pennsylvania (Linguistics, Children's Hospital of Philadelphia Autism Research Center) as well as outside of UPenn (Washington University, Miami University CReATe consortium annual meeting). We also have an outreach annual conference for caregivers of FTD patients, where we present our work to the general public.

Next Reporting Period Activities to Accomplish Goals: Our major goals in the next year will include: (a) reviewing and correcting aligned files from an automated forced aligner (FA); (b) defining spoken phrase boundaries by characterizing the lexical and acoustic cues surrounding boundaries and exploring different methods to quantify dependency distance within spoken phrases.

4. Impact

Impact on Principal Discipline: In the past year we saw an increased interest in developing biomarkers from speech to identify cognitive decline and language impairment. Multiple collaborations have begun between our center and other centers that resulted in the initiation of speech data collection from patients with a variety of neurodegenerative disorders, including FTD and ALS. We have been working with our collaborators to standardize data collection and canonizing speech processing. We have also expanded our data collection to include additional speech tasks beyond picture descriptions, such as fluency tasks. These developments will result in greater implementation and applicability of our speech analysis methods in different clinical settings.

Impact on Other Disciplines: Our work can be generalized to other neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. We are collaborating with other teams to study speech in these conditions as well.

Impact on Technology Transfer: Rising collaborations in the field are leading to better standardization of speech data collection and processing and this, in turn, will lead to improved cost-effective outcome measures for multi-center treatment trials for FTD, ALS, AD and other neurodegenerative conditions.

Impact on Society: Because speech is so easily collected with minimal burden to the subject and can even be collected remotely, society as a whole will benefit from widespread standardized speech analysis methods to track cognitive decline and the development of neurodegeration.

5. Changes/Problems

Changes in Approach: No changes.

Problems or Delays and Actions or Plans for Resolution: Our project was delayed by almost six months due to delays in HRPO approval, which was granted in March 2021. Additionally, the covid pandemic restricted activity on UPenn campus until recently. This affected our ongoing clinical data collection, which is now gradually resuming in-person as well as remotely. We hope to return to pre-pandemic clinical visits capacity, and we maintain contingency plans for remote speech data collection as well.

Changes Impacting Expenditures: Nothing to Report.

Changes in Human Subjects: Nothing to Report.

6. Products

Publications, conference papers, and presentations:

- Cho S, Nevler N, Ash S, Shellikeri S, Irwin DJ, Massimo L, et al. Automated analysis of lexical features in frontotemporal degeneration. Cortex. 2021; 137:215-31.
- Parjane N, Cho S, Ash S, Cousins KA, Shellikeri S, Liberman M, Shaw LM, Irwin DJ, Grossman M, Nevler N. Digital speech analysis in progressive supranuclear palsy and corticobasal syndromes. Journal of Alzheimer's Disease. 2021 Jan 1;82(1):33-45.
- Nevler N, Ash S, Cho S, Shellikeri S, Parjane N, Irwin DJ, Liberman MY, Grossman M. A longitudinal study of automated analysis of acoustic speech markers in FTD and PPA: Biomarkers (non-neuroimaging)/Longitudinal change over time. Alzheimer's & Dementia. 2020 Dec;16:e045315.
- Nevler N, Ash S, Cho S, Shellikeri S, Parjane N, Irwin DJ, Liberman MY, Grossman M. Automated semantic speech analysis in AD and lvPPA: Biomarkers (non-neuroimaging)/novel biomarkers. Alzheimer's & Dementia. 2020 Dec;16:e045300.
- Shellikeri S, Cho S, Ash S, Parjane N, Elman L, McMillan CT, Grossman M, Nevler N. Longitudinal changes of automated speech measures in natural connected speech in ALS: Biomarkers (non-neuroimaging)/Longitudinal change over time. Alzheimer's & Dementia. 2020 Dec;16:e043028.
- Nevler N, Ash S, McMillan C, Elman L, McCluskey L, Irwin DJ, Cho S, Liberman M, Grossman M. Automated analysis of natural speech in amyotrophic lateral sclerosis spectrum disorders. Neurology 2020 Sept; 95(12): e1629-e1639.

Websites: Nothing to Report.

Technologies: Nothing to Report.

Inventions: Nothing to Report.

Other Products: Nothing to Report.

7. Participants & Other Collaborating Organizations

Participants:

NAME	PROJECT ROLE	PERSON-MONTHS WORKED	CONTRIBUTIONS	FUNDING SUPPORT
M. Grossman	PI	1	Scientific design and report	NIH
M. Liberman	Co-I	1	Scientific design and report	NSF
N. Nevler	Postdoc	12	Digitized acoustic analysis	
S. Cho	Postdoc	12	Digitized Lexical analysis	
S. Shellikeri	Postdoc	12	Digitized analysis of motor speech	
G. Agmon	Postdoc	1	Digitized analysis of utterance syntax	
W. Xu	Res. Coord.	1	Research program coordination	NIH
Y. Balgenorth	Res. Coord.	6	Research data collection	
TBN	Res. Coord.	0	Transcription analysis	NSF
S. Ash	Res. Specialist	3	Transcription supervision, expert linguistic assessment of automated lexical tags	NIH
B. Nelson	Res. Specialist	1	Database design and maintenance	NIH
N. Ryant	Res. Specialist	1	Algorithm programming	NSF
S. Kulich	Res. Specialist	1	Algorithm programing	NSF
J. Fiumara	Res. Specialist	1	Project integration	NSF

Change in Other Support: Dr. Grossman's support from AG017586 ended on February 28. Dr. Grossman's new source of support comes from AG066597. Projects NS092089 and AG045390 have been consolidated into a single project AG063911.

Other organizations: Nothing to Report.

8. Special Reporting Requirements

N/A.

9. Appendices

None.