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Automated Speech Analysis to Differentiate Frontal and Right Anterior Temporal Lobe Atrophy in Frontotemporal Dementia

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Abstract

Background and Objectives

Frontotemporal dementia (FTD) includes behavioral-variant FTD (bvFTD) with predominant frontal atrophy and semantic behavioral-variant FTD (sbvFTD) with predominant right anterior temporal lobe (rATL) atrophy. These variants present diagnostic challenges because of overlapping symptoms and neuroanatomy. Accurate differentiation is crucial for clinical trial inclusion targeting TDP-43 proteinopathies. This study investigated whether automated speech analysis can distinguish between FTD-related rATL and frontal atrophy, potentially offering a noninvasive diagnostic tool.

Methods

This cross-sectional study used data from the University of California, San Francisco Memory and Aging Center. Using stepwise logistic regression and receiver-operating characteristic curve analysis, we analyzed 16 linguistic and acoustic features that were extracted automatically from audio-recorded picture description tasks. Voxel-based morphometry was used to investigate brain-behavior relationships.

Results

We evaluated 62 participants: 16 with FTD-related predominant frontal atrophy, 24 with predominant rATL atrophy, and 22 healthy controls (mean age 68.3 years, SD = 9.2; 53.2% female). Logistic regression identified 3 features (content units, lexical frequency, and familiarity) differentiating the overall FTD group from controls (area under the curve [AUC] = 0.973), adjusted for age. Within the FTD group, 5 features (adpositions/total words ratio, arousal, syllable pause duration, restarts, and words containing "thing") differentiated frontal from rATL atrophy (AUC = 0.943). Neuroimaging analyses showed that semantic features (lexical frequency, content units, and "thing" words) were linked to bilateral inferior temporal lobe structures, speech and lexical features (syllable pause duration, and adpositions/total words ratio) to bilateral inferior frontal gyri, and socioemotional features (arousal) to areas known to mediate social cognition including the right insula and bilateral anterior temporal structures. As a composite score, this set of 5 features was uniquely associated with rATL atrophy.

Discussion

Automated speech analysis demonstrated high accuracy in differentiating FTD subtypes and provided insights into the neural basis of language impairments. Automated speech analysis could enhance early diagnosis and monitoring of FTD, offering a scalable, noninvasive alternative to traditional methods, particularly in resource-limited settings. Future research should focus on

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Glossary

AD = Alzheimer disease; **ATL** = anterior temporal lobe; **AUC** = area under the curve; **bvFTD** = behavioral-variant FTD; **FTD** = frontotemporal dementia; **lATL** = left ATL; **MAC** = Memory and Aging Center; **MMSE** = Mini-Mental State Examination; **NLP** = natural language processing; **OR** = odds ratio; **PPA** = primary progressive aphasia; **rATL** = right ATL; **ROC** = receiver-operating characteristic; **sbvFTD** = semantic behavioral-variant FTD; **svPPA** = semantic variant of PPA; **TDP-C** = TDP-43 proteinopathy type C; **UCSF** = University of California, San Francisco; **VBM** = voxel-based morphometric.

further clinical validation with other neuroimaging or fluid biomarkers and longitudinal cognitive data, as well as external validation in larger and more diverse populations.

Introduction

Frontotemporal dementia (FTD) spectrum disorders encompass various neurodegenerative clinical syndromes, each associated with varying probabilities of a spectrum of pathologic changes called frontotemporal lobar degeneration. Behavioral-variant FTD (bvFTD) is the most prevalent FTD syndrome,[1] clinically characterized by behavioral and personality changes and neuroanatomically by predominant atrophy in the frontal lobes, generally right more than left lateralized.[2,3] Within bvFTD, anterior temporal lobe (ATL) atrophy is variable and, if present, is typically linked to Pick pathology when in conjunction with frontal atrophy, or TDP-43 proteinopathy type C (TDP-C) pathology when atrophy is isolated to the right ATL (rATL).[4,5] Because isolated rATL atrophy is highly predictive of TDP-C pathology, recent studies have highlighted the importance of characterizing and isolating this syndrome from other FTD syndromes.[6] To this end, new criteria have been proposed for a syndrome named semantic behavioral-variant FTD (sbvFTD), characterized by rATL atrophy and nonverbal semantic loss related to socioemotional concepts.[3,7-9] Differential diagnosis of sbvFTD remains challenging because of the clinical overlap in socioemotional functioning with bvFTD and lexical semantic deficits with the left-lateralized semantic variant of primary progressive aphasia (svPPA).[3,7,10] Although distinguishing rATL and svPPA-related left ATL (lATL) atrophy is theoretically interesting, it is less clinically crucial because both syndromes (together classified as semantic dementia) share common pathology. However, accurately differentiating bvFTD and sbvFTD is clinically relevant for selecting participants for trials targeting TDP-43 proteinopathies because predominantly rATL atrophy is specifically linked to TDP-C, while bvFTD-associated frontal atrophy varies in neuropathology.[11]

In the current bvFTD criteria, clinical changes manifest as a wide range of symptoms, including loss of empathy and ability to form social relationships, disinhibition and impulsive behavior, loss of interest in activities and hobbies, decreased motivation and initiative, changes in food preferences and eating habits, apathy and lack of emotion, and/or decline in personal hygiene and grooming.[4,12] SbvFTD with isolated rATL atrophy is instead described as having a more circumscribed set of symptoms related to loss of understanding of socioemotionally relevant, mainly nonverbal semantic concepts, such as person-specific biographical, facial expression, and emotion knowledge.[3] This type of semantic impairment most often results in loss of understanding of people's identity and emotions, manifesting clinically as loss of empathy and difficulties recognizing familiar people. Difficulty interpreting nonverbal concepts (e.g., food-related and taste-related semantics) and extralinguistic social cues (e.g., sarcasm), repetitive behaviors, apathy, and verbal semantic deficits can be present, likely in relation to compromised functional connectivity or atrophy in orbitofrontal regions (linked to behavioral changes) and lATL regions (linked to semantic changes).[3,7,10]

The proposed sbvFTD criteria are in the early stages of development and serve as a starting point to highlight the need for a better understanding of the clinical manifestations of rATL damage, as well as its differentiation from behavioral symptoms caused by mainly frontal atrophy.[3,7] There is a pressing need for new tools that can distinguish between symptoms of frontal atrophy associated with bvFTD and symptoms of predominantly rATL atrophy associated with sbvFTD. Although both bvFTD and sbvFTD share behavioral symptoms, sbvFTD uniquely falls in the semantic dementia spectrum, introducing distinct linguistic and socioemotional impairments that could facilitate clearer differentiation between bvFTD and sbvFTD.

Automated connected speech analysis using natural language processing (NLP) offers promising avenues for identifying early cognitive markers of dementia.[13] This method involves automatically extracting various linguistic and acoustic features from audio recordings and transcriptions (e.g., responses to a picture description task or a free prompt). Previous connected speech research has largely focused on Alzheimer disease (AD), mild cognitive impairment, and PPA, with fewer studies focused on behavioral FTD variants.[14-16] Notably, 1 prior study demonstrated the potential of automated connected speech analysis in distinguishing between rATL and lATL atrophy.[17]

The present study focused on investigating the clinically relevant question of whether automated speech analysis can effectively differentiate between rATL atrophy and frontal atrophy in FTD. Language is a multifaceted communication system composed of hundreds of inter-related linguistic and acoustic features that

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work together to convey meaning, structure, tone, emotion, prosody, pragmatics, and speaker intent. The interplay of these elements not only provides the structural and functional framework of spoken language but also encodes social and contextual information, speaker identity, and cognitive states. Our hypotheses about brain-behavior relationships were that behavioral features would link to bilateral frontal brain regions, socioemotional features to the rATL, and semantic features to the lATL. We did not hypothesize specific brain regions for features indicative of less complex language use, beyond anticipating associations with atrophy in the frontal and/or temporal lobes.

Methods

Participants

Participants were part of the University of California, San Francisco (UCSF) Memory and Aging Center (MAC) database. The UCSF MAC database enrolls individuals referred for evaluation because of cognitive, behavioral, or language concerns, and participants undergo comprehensive clinical, neuropsychological, and imaging evaluations. Healthy controls are recruited primarily through the Brain Aging Network for Cognitive Health and are screened for the absence of neurologic or psychiatric conditions. Study sample selection for rATL and frontal atrophy patterns followed procedures as described previously.[3] In short, we identified all individuals meeting a clinical diagnosis of sbvFTD, bvFTD, and/or svPPA based on Neary-FTD, Neary-Semantic, bvFTD, svPPA, and the newly established sbvFTD diagnostic criteria,[6,12,18,19] who had research visits between 1998 and 2023 in the UCSF MAC database. Individuals were excluded in this study if they did not complete a picture description task to elicit connected speech, were not native speakers of English, did not have a brain MRI scan within 1 year of their cognitive evaluation, did not have predominant atrophy in the rATL or frontal lobe, or if did have predominant atrophy in the rATL or frontal lobe but did not have relative preservation of the other area of interest (frontal or rATL, respectively). Based on anatomical criteria using W-score maps to quantify regional atrophy patterns,[3] individuals were included if they had peak atrophy in either the frontal lobe or rATL and if the ratio of temporal to frontal atrophy showed more atrophy in their peak atrophy lobe compared with the contrasting lobe. In addition, a group of cognitively healthy control participants was selected from the MAC database. Figure 1 shows a flowchart of participant selection with a final sample of 62 participants.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants or caregivers provided informed consent following procedures aligned with the Declaration of Helsinki, and the study was approved by the UCSF Institutional Review Board (IRB # 10-03946).

Speech Task and Automated Speech and Language Analysis

Speech samples were collected using the "picnic scene" picture description task of the Western Aphasia Battery.[20] Participants were tested individually in a quiet room at a table with the investigator seated opposite to them and their speech was recorded. Participants were instructed to "Tell me what you see. Talk in sentences." Participants were allowed approximately 3 minutes to complete the task; in our sample, participants completed the picnic picture description task within 1–2 minutes with an average time of 1m20s.

We developed an in-house pipeline for automated connected speech transcription and language analysis, named the Clinical Linguistic Automated Speech Pipeline. Digital audio recordings of participants' picnic descriptions were converted uniformly to .wav files (henceforth acoustic files). Acoustic files were manually diarized by editing out any speech not belonging to the participant using Audacity version 3.5.1 (author B.T.M.). Subsequently, acoustic files were denoised using Adobe Premiere Pro DeNoise at 50% (i.e., the amount of processing applied to the audio signal). In the next step, acoustic files were automatically transcribed using OpenAI's large Whisper model and manually checked for quality in terms of correct wording, punctuation, and grammar (author B.T.M.). Next, the pipeline used various NLP and computational tools to extract acoustic and linguistic features from both the audio recordings and their transcriptions; these tools include spaCy,[21] PRAAT (by MyProsody[22]), PyDub, TAASSC,[23] and custom scripts (Table 1).

For this study, we investigated linguistic and acoustic features based on clinical observations of speech and language in bvFTD, PPA, and semantic dementia.[17,24,25] In particular, we focused on 21 features that may mark elements in speech that capture (1) behavior (e.g., loss of interest and decreased initiative): number of *t*-units (i.e., main clause plus any subordinate clauses that may be attached to it), average *t*-unit length, and number of verb phrases per *t*-unit; (2) socioemotional aspects: valence and arousal; (3) semantic deficits (e.g., word-finding difficulties, coherence, and topic deviation): words containing "thing"/total words ratio, age of acquisition, familiarity, ambiguity, concreteness, lexical frequency, number of content units, informativeness ratio, pause rate, number of silent pauses, average syllable pause duration, and number of restarts; or (4) less complex language use: adpositions/total words ratio, noun/verb ratio, content/function word ratio, and number of content words. Adpositions (i.e., prepositions and postpositions) are words used to express spatial or temporal relations that come before or after a complement such as a noun phrase, for example, in, on, at, under, toward, after, between, about, behind, ago, since, and until.

Neuroimaging Analysis

We performed a voxel-based morphometric (VBM) analysis using the Computational Anatomy Toolbox 12[26] in Statistical Parametric Mapping 12 software[27] through MATLAB R2024b. MRI acquisition T1 images were acquired for all participants with sequences, previously described, on 1.5T (n = 6),[28] 3T (n = 50),[29] or 4T (n = 2).[30] After a visual quality check, the structural images underwent enhancement using

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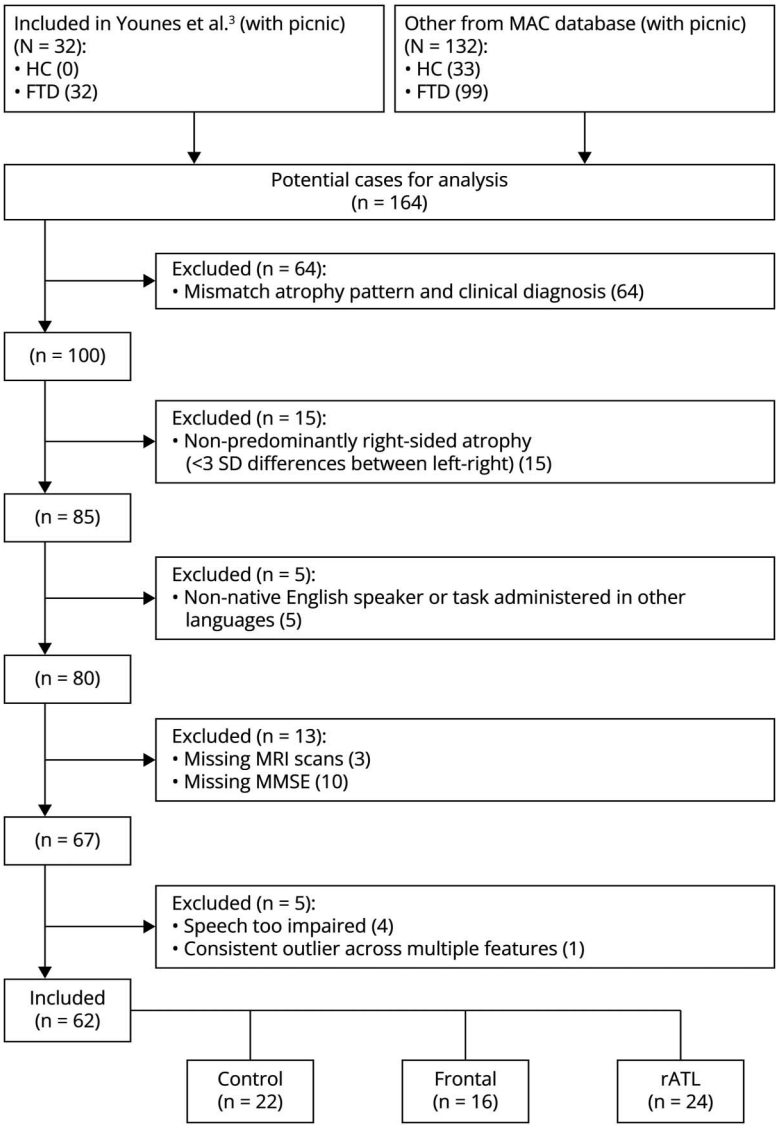
Figure 1 Participant Selection Flowchart



FTD = frontotemporal dementia; HC = healthy control; MAC = Memory and Aging Center; MMSE = Mini-Mental State Examination; rATL = right anterior temporal lobe.

a spatial adaptive nonlocal mean denoising algorithm followed by bias field correction, affine transformation for alignment, and processing using SPM's unified segmentation protocol. The images were then (1) segmented into gray matter, white matter, and CSF and (2) spatially normalized to the Montreal Neurological Institute reference space by an advanced geodesic shooting technique, (3) adjusted by the Jacobian determinants of the deformation field during spatial normalization to maintain the tissue volume integrity, and (4) output with a uniform isotropic voxel resolution of 1.5 × 1.5 × 1.5 mm^3, (5) spatially smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel to compensate for residual anatomical variability.

We examined brain-behavior relationships between linguistic features and gray matter volume loss (atrophy); brain MRI scans were obtained within 1 year of speech sample collection. The search volume included regions of interest based on known distribution of atrophy in FTD variants using an explicit mask created with WFU PickAtlas,[31] including the frontal lobe, temporal lobe, anterior cingulate, frontal-temporal space, precentral gyrus, paracentral lobule, transverse temporal gyrus, and parahippocampal gyrus. Using general linear models across the whole sample (i.e., independent of the diagnostic group), we examined the relationship between gray matter volume and each linguistic feature that was selected in the forward stepwise logistic regression models. In addition, we tested the relationship between gray matter volume and the composite score of the optimal set of features that behaviorally distinguished the rATL and frontal atrophy groups. All models were adjusted for age, sex, scanner (3T vs non-3T), and total intracranial volume. For each computed T-contrast, the corresponding statistical map was evaluated at a peak-level uncorrected

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Table 1 Details of the Linguistic and Acoustic Features Extracted for Speech and Language Analysis

Feature	Description	Interpretation	Extraction tool
Pause rate	Ratio of the number of silent pauses (threshold >750 milliseconds) to the speech sample's total duration	Reflecting the relative frequency with which the speaker takes a long pause indicating difficulties with word retrieval and sentence planning[51]	Adapted code from the Python library MyProsody[22]
Average syllable pause duration	The mean length of filled pauses ("uhm"s), that is, long stable syllables pronounced at a low pitch, measured in milliseconds	Reflecting interruptions in speech flow; longer filled pauses indicate more disfluency in speech	Adapted code from the Python library MyProsody[22]
Number of restarts	The instances where a speaker starts a word or phrase, stops, and then restarts, often to repair the sentence or choose a different word	Reflecting hesitations or corrections; more restarts indicate more disfluency in speech	Custom script based on Transcription Guidelines of the Linguistic Data Consortium[52]
Noun/verb ratio	The ratio of nouns to verbs used	Reflecting the richness and complexity of language use; a lower ratio indicates difficulty with retrieving nouns and a stronger reliance on verbs in simpler sentence structures	Parts of speech extracted using the Python library spaCy[21]; ratios calculated with custom script
Adpositions/total words ratio	The ratio of adpositions (prepositions and postpositions; e.g., in, on, at, under, towards, behind, ago) to the total number of words	Reflecting the use of grammatical structures that show relationships between words; a lower ratio indicates a shift toward simpler, less complex language	Parts of speech extracted using the Python library spaCy[21]; ratios calculated with custom script
Content/function word ratio	The ratio of content words (nouns, verbs, adjectives, adverbs) to function words (pronouns, prepositions, conjunctions, auxiliary verbs)	Reflecting the balance between meaning-carrying words and grammatical words; a lower ratio suggests a reliance on function words that carry less semantic weight	Parts of speech extracted using the Python library spaCy[21]; ratios calculated with custom script
Thing words ratio	The ratio of nonspecific "thing" words (i.e., thing, something, anything) to the total number of words	Reflecting word-finding difficulties; a higher ratio suggests issues with semantic memory to access specific knowledge about objects, people, and events, leading to reliance on nonspecific terms	Custom script based on Clarke et al. (2021)[16]
Age of acquisition	The mean age at which the words used are typically learned	Reflecting lexical richness; the use of words with an earlier age of acquisition indicates a preference for simpler, more easily accessible vocabulary	Custom script based on linguistic database by Kuperman et al. (2012)[53]
Familiarity	The average rating of how familiar the words are to the general population	Reflecting lexical richness; the use of words with higher familiarity indicates a preference for simpler, more easily accessible vocabulary	Custom script based on linguistic database by Brysbaert et al. (2019)[54]
Lexical frequency	The mean lexical frequency of the words used, that is, how often these words are generally used in daily language	Reflecting lexical richness; the use of words with higher lexical frequency indicates a preference for simpler, more easily accessible vocabulary	Custom script based on linguistic database by Brysbaert et al. (2009)[55]
Arousal	The average level of emotional intensity of the words used	Reflecting the overall level of emotional intensity of the words used; a deviation of neutral arousal in a description task indicates emotional alterations	Custom script based on linguistic database by Warriner et al. (2013)[56]
Valence	The mean emotional value (positive or negative) of the words used	Reflecting the overall sentiment of the words used; a deviation of neutral valence in a description task indicates emotional alterations	Custom script based on linguistic database by Warriner et al. (2013)[56]
Number of T-units	The total number of T-units (shortest grammatically allowable sentence), that is, a main clause and any subordinate clause(s)	Reflecting syntactic complexity; a lower number of T-units indicate an overall decrease in speech output	Tool for the Automatic Analysis of Syntactic Sophistication and Complexity (TAASSC 1.3.8)[23]
Average T-unit length	The mean length of T-units in terms of words	Reflecting syntactic complexity; shorter T-units indicate simpler sentences	Tool for the Automatic Analysis of Syntactic Sophistication and Complexity (TAASSC 1.3.8)[23]
Number of content units	The total count of expected key information units for the Western Aphasia Battery Picnic Description Task	Reflecting the completeness and informativeness of the picture description; a lower number of content units indicates a less complete description	Custom script based on Josephy-Hernandez et al. (2023)[57]
Informativeness ratio	The ratio of relevant content units to the total number of words	Reflecting the efficiency and focus of the description in conveying important information; a lower ratio indicates less efficiency	Custom script based on Josephy-Hernandez et al. (2023)[57]

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threshold of $p < 0.001$ and a cluster-level threshold of $p < 0.05$ family-wise error corrected for clusters with a minimum size of 100 voxels. Visualization of peak locations of brain-behavior associations between features and atrophy was performed using MRIcroGL.[32]

Statistical Analysis

Sample characteristics and feature distributions were analyzed with descriptive statistics, general linear models, χ^2 tests, and Pearson correlation coefficients. The distributions of each feature were examined for outliers by diagnostic group (defined as values ≥2.5 SDs from the feature's group mean) for data entry or measurement errors; we did not remove individual outlier values. We closely examined participants with outliers on multiple features and removed 1 participant who was an outlier on 4 features (all other participants had outliers on at most 2 features). We also excluded 4 participants too impaired to complete the task, producing fewer than 25 words (Figure 1). A logarithmic transformation was applied to 10 features to render skewed distributions more normal and diminish effects of outliers. To assess the linearity assumption of continuous predictors in a logistic regression model, we ran Box-Tidwell tests; all variables passed for both outcomes (controls vs FTD or frontal vs rATL atrophy). There were no missing data on the linguistic and acoustic features.

We examined multicollinearity among the 21 features (see Introduction) with a Pearson correlation table; based on a high correlation of $r > |0.7|$, we removed 5 features from further consideration, including number of verb phrases per *t*-unit, number of content words, number of silent pauses, ambiguity, and concreteness. Thus, we included 16 linguistic and acoustic features extracted with our in-house pipeline to measure various aspects of participants' speech and language use (Table 1).

We performed stepwise logistic regression to automatically select a reduced number of linguistic and acoustic features for building the best performing classification model per binary outcome. Both models included age as a covariate, and the model of frontal vs rATL atrophy additionally covaried for Mini-Mental State Examination (MMSE) score as a proxy of disease severity.[33] Sex and education were not included as covariates because there were no significant group differences. The predicted probabilities of the optimal set of features were saved as a new variable and entered into a receiver-operating characteristic (ROC) curve analysis to evaluate the area under the curve (AUC). We combined the feature values of the optimal set to distinguish frontal and rATL atrophy into a composite score using z-scores and tested this composite score in an multiple linear regression model adjusted for age and MMSE score to understand how FTD group membership (frontal vs rATL atrophy; independent variable) is associated with changes in the composite score of features (dependent variable). To put the classification performance of the set of linguistic and acoustic features into context, we also performed an ROC-AUC analysis on the Boston Naming Test,[34] an established neuropsychological task to detect lexical-semantic difficulties.

All statistical analyses were performed in SPSS version 28.0.1.0. Tables and figures for these analyses were generated using R version 4.3.0 with packages: dplyr, ggplot2, furniture, summarytools, pROC, Hmisc, and corrplot. A power analysis in G*Power[35] indicated that based on an alpha level of 0.05, a logistic regression model with 40 participants yields 80% power to detect a moderate effect size (odds ratio [OR] 3.1) and 96% power to detect a large effect size (OR 5). All analysis codes are available online.[36]

Data Availability

The conditions of our ethics approval do not permit public archiving of anonymized study data. Data generated by the UCSF MAC are available upon request. Data requests can be submitted through the online UCSF MAC Resource Request form.[37] Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. All requests will undergo a UCSF-regulated procedure, thus requiring submission of a Material Transfer Agreement, which can be found online.[38] No commercial use would be approved.

Results

Participants

The sample size in this study was primarily determined by the availability of participants meeting the inclusion criteria for frontal and rATL atrophy patterns in a rare disease cohort. The final selection of participants for the behavioral analyses included 16 with predominant frontal atrophy, 24 with predominant rATL atrophy, and 22 control participants (n = 62; Figure 1). Participant characteristics are summarized in Table 2; the 3 groups did not differ in mean years of education, nor their distribution of sex/gender, race/ethnicity, or handedness. The frontal and rATL atrophy groups did not differ in mean age, while the control group was on average slightly older. Four participants' MRI scans, 2 control and 2 rATL, were excluded for neuroimaging analyses because of poor image quality (i.e., n = 58 for neuroimaging analyses).

Automated Speech and Language Analysis

From the list of 16 linguistic and acoustic features (Table 1), the forward stepwise logistic regression model selected an optimal set of 3 features to classify controls vs participants with FTD: content units, lexical frequency, and familiarity. The model demonstrated a good fit as indicated by the Omnibus test of model coefficients (unadjusted: $\chi^2 = 54.385$, $df = 3$, $p < 0.001$; adjusted: $\chi^2 = 54.826$, $df = 4$, $p < 0.001$); this test evaluates whether the model significantly improves fit over a baseline intercept-only model indicating that at least one of the included variables has a significant impact on the outcome variable. Moreover, the model explained a large proportion of the variance with a Nagelkerke R^2 of 0.803 unadjusted and 0.807 adjusted. The model achieved an

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Table 2 Participant Characteristics

Demographic measures	Controls (n = 22)	Frontal atrophy (n = 16)	rATL atrophy (n = 24)	*p* Value
Age, y	72.82 (7.47, 53–88)	64.38 (10.01, 48–77)	66.83 (8.7, 47–87)	0.010
Sex (male)	9 (40.9%)	6 (37.5%)	14 (58.3%)	0.342
Years of education	17.45 (2.09, 12–20)	15.69 (2.87, 9–20)	15.92 (2.7, 12–21)	0.060
Race				0.627
Black/African American	1 (4.5%)	0 (0%)	0 (0%)	
Hispanic	0 (0%)	0 (0%)	0 (0%)	
Mixed	1 (4.5%)	0 (0%)	1 (4.2%)	
Non-Hispanic White	20 (90.9%)	16 (100%)	23 (95.8%)	
Handedness				0.167
Ambidextrous	0 (0%)	0 (0%)	2 (8.3%)	
Left	4 (18.2%)	0 (0%)	3 (12.5%)	
Right	18 (81.8%)	16 (100%)	19 (79.2%)	
MMSE	29.45 (0.67, 28–30)	23 (5.73, 8–29)	25.62 (4.34, 12–30)	<0.001
CDR Box Score	0.03 (0.11, 0–0.5)	3.78 (2.78, 0–9)	4.5 (2.55, 1.5–10)	<0.001
Boston Naming Test (15-item)	14.76 (0.56, 13–15)	10.44 (3.98, 3–15)	8 (3.58, 2–15)	<0.001
CVLT Short Delay	12.15 (2.98, 6–16)	4.33 (2.61, 0–9)	4.75 (2.17, 0–8)	<0.001
CVLT Long Delay	11.45 (3.35, 5–15)	3 (3.32, 0–9)	3.25 (2.64, 0–8)	<0.001

Abbreviations: CDR = Clinical Dementia Rating; CVLT = California Verbal Learning Test; MMSE = Mini-Mental State Examination; rATL = right anterior temporal lobe.

accuracy (i.e., number of correct predictions/total number of predictions) of 90.3% unadjusted and 91.9% adjusted. The predicted probabilities from the logistic regression were used to generate a ROC curve with an AUC of 0.969 (95% CI 0.933–1.00) for the linguistic features alone (Figure 2A). When age was included as a covariate, the AUC increased to 0.975 (95% CI 0.943–1.00).

The forward stepwise logistic regression model to distinguish between frontal and rATL atrophy selected from the list of 16 features an optimal set of 5 features: adpositions/total words ratio, arousal, syllable pause duration, restarts, and words containing "thing" (henceforth "thing words"). The model demonstrated a good fit (Omnibus test unadjusted: χ^2 = 24.682, df = 5, p < 0.001; adjusted: χ^2 = 29.669, df = 7, p < 0.001), explained a substantial proportion of the variance (Nagelkerke R^2 unadjusted = 0.622; adjusted = 0.708), and achieved an accuracy of 80.0% unadjusted and 85.0% adjusted. The AUC was 0.924 (95% CI 0.847–1.00) for the linguistic features alone (Figure 2B); when age and MMSE scores were included as covariates, the AUC increased to 0.943 (95% CI 0.873–1.00). In comparison, an unadjusted model of the Boston Naming Test showed a moderate fit (Omnibus test: χ^2 = 3.953, df = 1, p = 0.047), explained a small proportion of the variance (Nagelkerke R^2 = 0.130), and achieved an accuracy of 74.4% and AUC = 0.688 (95% CI 0.507–0.868). When adjusted for age and MMSE scores, these metrics improved to Omnibus test χ^2 = 12.832, df = 3, p = 0.005; Nagelkerke R^2 = 0.378; accuracy = 79.5%; and AUC = 0.813 (95% CI 0.670–0.955).

We created a composite score from this optimal set of 5 features that distinguish between frontal and rATL atrophy: adpositions/total words ratio, arousal, syllable pause duration, restarts, and thing words. Within the 40 participants with FTD, this composite score ranged from −0.59 to 1.07 (mean = 0.087, SD = 0.388). Multiple linear regression showed that the unstandardized coefficient B was 0.557 (SE = 0.97; 95% CI 0.360–0.754) units higher in the rATL group than the frontal group, holding covariates constant (standardized β = 0.712, p < 0.001; indicating a large effect size). Boxplots of performance on the selected features and the composite score per diagnostic group are shown in Figure 3.

Brain-Behavior Associations

Table 3 summarizes the VBM results for the neural correlates of the speech and language features selected in the logistic regression models. Across all participants, the adpositions/total word ratio was positively associated with cortical atrophy in the right orbitofrontal cortex and left inferior frontal and precentral gyri. Arousal was negatively associated with

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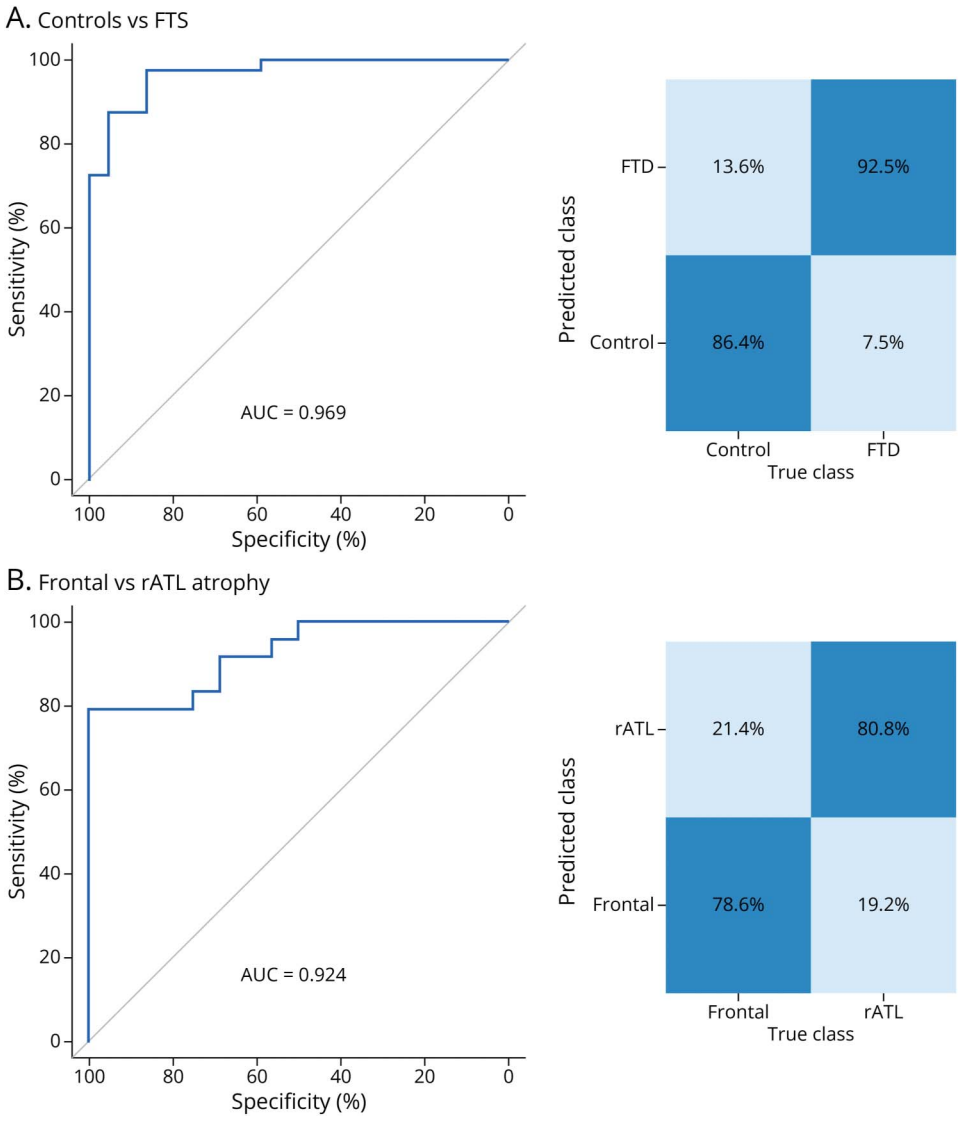
Figure 2 ROC Curves and Confusion Matrices



AUC = area under the curve; FTD = frontotemporal dementia; rATL = right anterior temporal lobe; ROC = receiver operating characteristic.

atrophy in the right insula, middle temporal gyrus, and anterior cingulate, as well as left inferior temporal structures. Content units was positively associated with atrophy in left inferior temporal structures and a right-sided cluster that stretched from the amygdala to the orbitofrontal cortex. Lexical frequency was negatively associated with the left inferior temporal gyrus and left middle frontal gyrus. Syllable pause duration was negatively associated with atrophy in the left pars triangularis, and thing words was negatively associated with atrophy in the right fusiform, middle temporal, and inferior temporal gyri. We did not find associations of familiarity (a priori tested direction: negative) or number of restarts (a priori tested direction: negative) with cortical atrophy in our sample. The composite score of the optimal set of features that distinguished frontal from rATL atrophy (adpositions/total words ratio, arousal, syllable pause duration, restarts, and thing words) was negatively associated with focal atrophy in the rATL, with peaks in the right fusiform gyrus, right middle temporal gyrus, and right temporal pole; Figure 4 displays a visual representation.

Discussion

This study investigated the utility of automated speech and language analysis in differentiating between healthy controls and participants with FTD, focusing on 2 atrophy patterns: participants with frontal atrophy (typically associated with bvFTD) and rATL atrophy (typically associated with sbvFTD). The results revealed a set of 3 linguistic and acoustic features that distinguished FTD from healthy controls and 5 features that discriminated frontal and rATL atrophy. This study addressed a crucial gap in diagnosis, given the challenges in differentiating between bvFTD and sbvFTD,[3,7] which has traditionally relied heavily on clinical judgment and neuroimaging. Moreover, distinguishing

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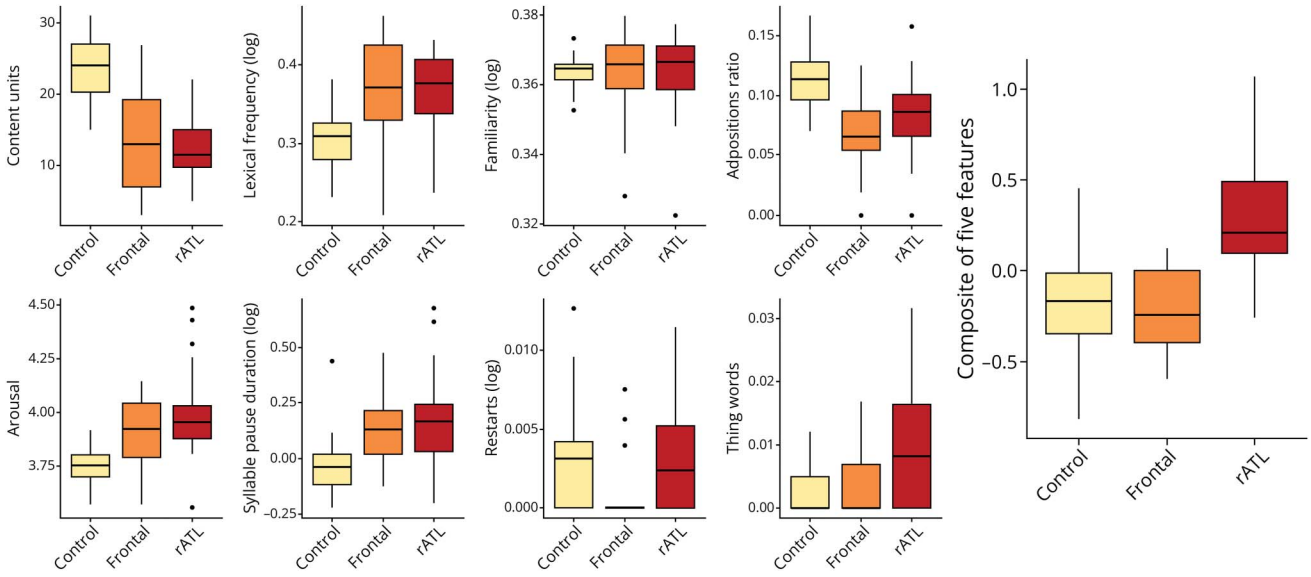
Figure 3 Performance on Selected Speech and Language Features Across Diagnostic Groups



The composite score includes the optimal set of 5 features to distinguish between frontal and rATL atrophy: adpositions/total words ratio, arousal, syllable pause duration, restarts, and thing words. rATL = right anterior temporal lobe.

controls from FTD based on speech and language features presents a promising screening tool, offering quick and scalable assessments. By distinguishing among FTD-related frontal vs rATL atrophy, this approach could help identify patients with rATL atrophy for inclusion in molecule-targeted pharmacologic clinical trials.

Previous work using automated speech analyses has often compared individual features, overlooking that the complex shape of communication emerges from how these features interact and are tuned together in a multidimensional context. Our analytic approach using stepwise logistic regression centered on selecting a combined set of features for discrimination, highlighting the importance of synergistic combinations for predictive accuracy. This set of features outperformed the Boston Naming Test, an established task for detecting lexical-semantic difficulties. The composite score was uniquely associated with rATL atrophy, with individual features aligning with expected language impairment patterns. For example, the rATL atrophy group used words with on average higher arousal ratings compared with the frontal atrophy and control groups: previous work showed that atrophy in left-lateralized emotion-relevant systems in the temporal lobe relates to enhanced positive emotions in FTD,[39] corresponding to the asymmetrical yet bilateral temporal atrophy in rATL. Moreover, the increased syllable pause duration, use of restarts, and thing words are indicators of word-finding problems, characteristic of semantic difficulties similar to svPPA.[19] Thus, the combined set of features differentiating frontal and rATL atrophy includes both aspects of emotional alterations and semantic impairment that together mark the sbvFTD syndrome.

The clinical presentations of bvFTD and sbvFTD have been linked to specific focal atrophy patterns. Neuroanatomically, bvFTD is associated with atrophy particularly in the bilateral medial frontal cortex, its adjacent frontal cortex, anterior insula, and striatum.[2,3] These areas are considered to play a role in social cognition, emotion alterations, motivation, and decision making.[40,41] SbvFTD is associated with bilateral right-more-than-left and medial-more-than-lateral neurodegeneration of the ATLs, right-more-than-left insula, right caudate, and right anterior cingulate cortex.[3,8,28] The bilateral ATLs have been linked extensively to their role in semantic processing[42]; the lATL has been largely associated with verbal semantics, whereas the rATL has been largely associated with nonverbal semantics, particularly regarding visual and socioemotional knowledge.[8,43] Our neuroimaging results show associations of linguistic and acoustic features with both left and right cortical structures, reflecting the bilateral atrophy patterns of both groups as well as the role of the left hemisphere in language and the right hemisphere in emotional processing. For example, we showed that the average arousal value of the generated words was associated with the right insular cortex. The insula is known for its role in moderating social cognition.[44] Moreover, the right insula in particular has been linked to moderating physiologic arousal such as heart rate.[45] Importantly, we observed that both patient groups produced on average words with a higher arousal rating than controls, in line with previous reports showing that left-lateralized atrophy in the temporal and frontal lobes in FTD can impair the ability to suppress positive emotions.[39,44]

Lexical frequency, content units, and thing words share a common semantic focus. We found that these linguistic features

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Table 3 Voxel-Based Morphometry: Neural Correlates of Selected Speech and Language Features

				Peak MNI coordinates			Peak-level inference		Cluster-level inference	
Feature	**Hemisphere**	**Lobe**	**Brain region**	**x**	**y**	**z**	***t* Value**	***p* Value (uncorrected)**	**Cluster size[a]**	***p* Value (FWE)**
Adpositions	Right	Frontal	Gyrus rectus	3	65	−17	5.395	<0.001	27,517	<0.001
	Left	Frontal	Pars orbitalis (IFG)	−41	24	−5	5.158	<0.001		
	Left	Frontal	Pars triangularis (IFG)	−45	38	0	4.999	<0.001		
	Left	Frontal	Precentral	−44	−3	58	4.518	<0.001	852	0.031
Arousal	Right	Temporal	Insula	45	5	−6	5.089	<0.001	23,464	<0.001
	Right	Frontal	Anterior cingulate	8	12	−21	5.033	<0.001		
	Right	Temporal	Middle temporal gyrus	57	6	−21	4.978	<0.001		
	Left	Temporal	Temporal pole	−33	11	−48	4.796	<0.001	7,915	<0.001
	Left	Temporal	Fusiform gyrus	−30	−18	−32	4.788	<0.001		
Content units	Left	Temporal	Inferior temporal gyrus	−45	−6	−32	6.875	<0.001	71,888	<0.001
	Right	Temporal/frontal	Amygdala; gyrus rectus	21	5	−14	6.760	<0.001		
	Left	Temporal	Temporal pole	−29	8	−29	6.724	<0.001		
Frequency	Left	Temporal	Inferior temporal gyrus	−50	−8	−26	6.664	<0.001	71,618	<0.001
	Left	Frontal	Middle frontal gyrus	−33	36	21	4.726	<0.001	771	0.041
Syllable pause duration	Left	Frontal	pars triangularis (IFG)	−38	21	17	5.046	<0.001	1,212	0.010
	Right	Frontal	Pars triangularis (IFG)	34	26	12	4.392	<0.001	1,506	0.004
Thing words	Right	Temporal	Fusiform gyrus	38	−36	−20	4.758	<0.001	4,097	<0.001
	Right	Temporal	Middle temporal gyrus	58	−46	−3	4.005	<0.001	1,467	0.005
	Right	Temporal	Inferior temporal gyrus	66	−39	−18	3.672	<0.001		
Composite score	Right	Temporal	Fusiform gyrus	40	−32	−28	5.20	<0.001	13,226	<0.001
	Right	Temporal	Middle temporal gyrus	48	2	−22	4.95	<0.001		
	Right	Temporal	Temporal pole	57	9	−9	4.58	<0.001		

Abbreviations: FWE = family-wise error; IFG = inferior frontal gyrus; MNI = Montreal Neurological Institute.
[a] Using a cluster-forming voxelwise threshold of $p < 0.001$ uncorrected; results displayed with a cluster size of minimum 100 voxels at peak-level $p < 0.001$ uncorrected that survived FWE correction at cluster level at $p < 0.05$.

were related to inferior temporal lobe structures, which are known to be a critical neural substrate for semantic processing.[46] Notably, the association of the left inferior temporal gyrus with lexical frequency derived from automated speech analysis in an FTD population replicates the findings by Cho et al.[24] Average syllable pause duration, which detects filled pauses ("uhm"), was associated with the pars triangularis of the inferior frontal gyrus—part of the Broca area—supporting its role in speech production and articulation.[47] These findings underscore the importance of both temporal and frontal regions in different aspects of speech production and semantic processing, highlighting the neural basis of language impairments in FTD.

A major strength of this study lies in its innovative use of automated methods to analyze connected speech, providing a scalable and quantitative alternative to time-consuming manual transcription. Although a manual quality check is currently included, future research should determine whether this step can be omitted without significantly affecting classification accuracy, enabling full automation. Another strength is the inclusion of a relatively large group with rATL atrophy, despite the low prevalence of this disease,[48] made possible by data collection over many years at the specialized UCSF MAC. However, focusing on a single database may limit generalizability to more diverse populations. This proof-of-concept study requires replication in larger, more diverse data sets to confirm findings, including AUC-ROC classifications. Because sbvFTD and bvFTD are rare diseases, our moderate sample sizes, while comparable with other studies,[9,33,49] allow for detecting moderate-to-large effects but limit small-effect

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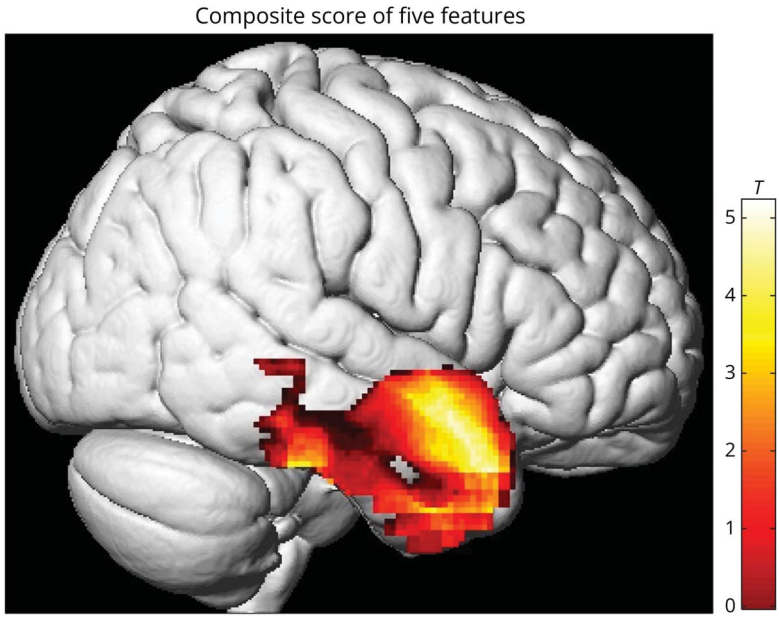
Figure 4 Render View of Brain-Behavior Association Between Composite Score and Gray Matter Atrophy at $p < 0.001$ Uncorrected



detection. Larger cohorts would enable testing for overfitting using k-fold cross-validation and allow the use of more complex machine learning approaches for improved precision in pattern recognition. Moreover, the moderate sample size may have made the results vulnerable to potential biases inherent in speech sample collection, such as participants' mood or environment during recording. Finally, brain-behavior relationships identified by MRI are limited to regions affected by atrophy, potentially missing associations in unaffected areas.

Future research should aim to replicate these findings in larger and more diverse populations and focus on external validation efforts. In addition, future work should focus on developing these measures into an easy-to-use tool with a friendly user interface to assist health care providers in overcoming any barriers to using these techniques. Moreover, exploring the integration of speech analysis in a multimodel approach with other biomarkers and diagnostic methods, such as cognitive, neuropathologic, and genetic data, could enhance the accuracy and utility of these findings. Longitudinal studies may also provide insights into the progression of FTD and the potential of speech analysis in monitoring disease progression and response to treatment. The methods and findings of this study also have broader implications for research in other neurodegenerative diseases. In addition to AD and FTD, the application of automated speech and language analysis could be extended to conditions such as Parkinson disease and multiple sclerosis, where language and cognitive impairments are also prevalent.

Our findings support the growing evidence of language and speech impairments as early indicators of neurologic decline.[13] While most connected speech studies in dementia have focused on AD,[14,16] this study further expands the field to FTD,[24,25,50] showcasing the potential of connected speech analysis in differentiating its nonlanguage dominant subtypes. Theoretically, these findings elucidate relationships between language dysfunction and brain atrophy patterns, particularly in FTD. Practically, they could aid in participant selection for clinical trials targeting TDP-43 proteinopathies. Clinically, connected speech analysis can complement established methods by capturing nuanced interactions between language and behavior often missed in standard neuropsychological testing and serve as a noninvasive, cost-effective, scalable, and remote screening tool particularly valuable in settings with limited neuroimaging access. These digital innovations enhance diagnostic capabilities and support longitudinal studies, where objective measures of cognitive function are needed to evaluate therapeutic interventions, opening new avenues for understanding and addressing FTD.

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Author Contributions

J.M.J. Vonk: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. B.T. Morin: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Pillai: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D. Rosado Rolon: drafting/revision of

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the manuscript for content, including medical writing for content. R. Bogley: drafting/revision of the manuscript for content, including medical writing for content. D.P. Baquirin: drafting/revision of the manuscript for content, including medical writing for content. Z. Ezzes: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B.L. Tee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. de Leon: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Wauters: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Lukic: drafting/revision of the manuscript for content, including medical writing for content. M. Montembeault: drafting/revision of the manuscript for content, including medical writing for content. K. Younes: drafting/revision of the manuscript for content, including medical writing for content. Z.A. Miller: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.M. García: drafting/revision of the manuscript for content, including medical writing for content. M.L. Mandelli: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B.L. Miller: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H.J. Rosen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.P. Rankin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Sturm: drafting/revision of the manuscript for content, including medical writing for content. M.L. Gorno-Tempini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

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Disclosure

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