Automatic measurement of prosody in behavioral variant FTD

ABSTRACT

Objective: To help understand speech changes in behavioral variant frontotemporal dementia (bvFTD), we developed and implemented automatic methods of speech analysis for quantification of prosody, and evaluated clinical and anatomical correlations.

Methods: We analyzed semi-structured, digitized speech samples from 32 patients with bvFTD (21 male, mean age 63 ± 8.5, mean disease duration 4 ± 3.1 years) and 17 matched healthy controls (HC). We automatically extracted fundamental frequency (f0, the physical property of sound most closely correlating with perceived pitch) and computed pitch range on a logarithmic scale [semitone] that controls for individual and sex differences. We correlated f0 range with neuropsychiatric tests, and related f0 range to gray matter (GM) atrophy using 3T T1 MRI.

Results: We found significantly reduced f0 range in patients with bvFTD (mean 4.3 ± 1.8 ST) compared to HC (5.8 ± 2.1 ST; p = 0.03). Regression related reduced f0 range in bvFTD to GM atrophy in bilateral inferior and dorsomedial frontal as well as left anterior cingulate and anterior insular regions.

Conclusions: Reduced f0 range reflects impaired prosody in bvFTD. This is associated with neuroanatomic networks implicated in language production and social disorders centered in the frontal lobe. These findings support the feasibility of automated speech analysis in frontotemporal dementia and other disorders.

GLOSSARY

ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant of frontotemporal dementia; FTLD = frontotemporal lobar degeneration; GM = gray matter; HC = healthy controls; IFG = inferior frontal gyrus; NPI = Neuropsychiatric Inventory; SAD = speech activity detector; ST = semitones.

We are all expert speakers, yet the speech we produce is the outcome of an extraordinarily complex process. One important suprasegmental attribute of speech is prosody, which reflects a combination of rhythm, pitch, and amplitude characteristics of our speech pattern. Prosody is typically used to convey emotional and linguistic information, and thus is essential to communicating many of our messages in day-to-day speech. In this study, we examined prosodic characteristics of speech in patients with behavioral variant frontotemporal dementia (bvFTD).

Patients with bvFTD have a progressive disorder of personality and social cognition that compromises daily functioning. They have been noted to have subtle linguistic deficits, not qualifying as aphasia: mildly reduced words/min,1 reduced narrative organization manifested as tangential speech,2 limited story comprehension,3 mild difficulty with comprehension of grammatically mediated sentences,4 and impaired comprehension and expression of abstract words5 and propositional speech.6 Prosody has been more difficult to measure directly, thus it is often estimated subjectively7 and qualitatively.8 To characterize prosodic difficulty in bvFTD, we developed and implemented an automated speech analysis algorithm that provides a reliable, objective, and quantitative analysis of speech expression. This is crucial because many of our characterizations of social disorders in bvFTD depend in part on impressions derived from patients’ speech. We implemented this algorithm in a brief, digitized, semi-structured speech...
sample and hypothesized abnormal prosodic expression in patients with bvFTD—specifically, abnormal pitch range and speech segment durations, which are directly measurable with our automated methods—compared to healthy speakers. We emphasize intonation, represented here by pitch range, as the most distinct prosodic impairment in this patient group related to their social and behavioral dysfunction.

We also examined the neuroanatomic basis for impaired prosody in bvFTD. Portions of the neuroanatomic network underlying speech production are atrophic in bvFTD and close to brain regions associated with behavioral symptoms. Thus, we directly related quantitatively analyses of dysprosody to high-resolution MRI. We expected prosodic speech difficulties in bvFTD to be related to bilateral prefrontal disease.

METHODS Participants. We analyzed 32 digitized speech samples from nonaphasic native English speakers who met published criteria for the diagnosis of probable bvFTD and had an MRI scan. These patients had no evidence of other causes of cognitive or speech difficulty such as stroke or head trauma, a primary psychiatric disorder, or a medical or surgical condition. All were assessed between January 2000 and March 2016 by experienced neurologists (M.G., D.J.I.) in the Department of Neurology at the Hospital of the University of Pennsylvania. Five patients had definite frontotemporal lobar degeneration (FTLD) pathology (4 FTLD-tau, 1 FTLD-TDP). From our audio database of 42 bvFTD cases with MRI, we excluded patients with concomitant amyotrophic lateral sclerosis (ALS) symptomatology (n = 2) to minimize potential motor confounds associated with bulbar and respiratory disease, secondary pathologic diagnosis of ALS or Alzheimer disease (n = 3), poor quality sound (n = 3, see below), or poor quality imaging (n = 2). Six cases had a mild semantic impairment as part of the clinical picture but did not meet criteria for semantic variant primary progressive aphasia, and thus were included. We also assessed 17 healthy controls (HC), who were well-matched with the patients (table 1).

Twenty-one patients had a Neuropsychiatric Inventory (NPI) test performed within 3.3 ± 3.9 months of their analyzed audio, and all except 2 were rated on all individual scores of the test (the remaining speech samples were collected prior to our regular use of the NPI). We calculated 4 composite subscores based on published classification: dysphoria—depression individual score (F × S); social—apathy, disinhibition, irritability, and euphoria (F × S); psychovegetative—sleep, appetite, anxiety, hallucinations, delusions, agitation, and aberrant motor behavior (F × S); sum distress—summarized caregiver distress scores. We examined executive functioning with letter-guided category-naming fluency (available in 30 patients), which were consistent with the diagnosis of bvFTD (table 1).

Speech samples. We used the Cookie Theft picture description task from the Boston Diagnostic Aphasia Examination to elicit semi-structured narrative speech samples. This method has previously shown reliability in speech analysis. Detail on sound collection is provided in the supplemental data at Neurology.org.

Sound processing. We used a speech activity detector (SAD) created at the University of Pennsylvania Linguistic Data Consortium to time-segment the audio files. We manually reviewed the segmented files in Praat to verify accuracy of SAD and excluded segments with interviewer speech or background noises that could confound pitch tracking. To minimize truncation of segments, noise was not labeled out if it was within a silent pause. Segment durations were calculated by subtracting start time from end time of each segment. Silent pauses were excluded from analysis if they were at the beginning or end of the audio or immediately following interviewer prompting.

Pitch tracking was performed with the Praat pitch tracker and an open source script modified by N.N. to extract fundamental frequency (f0) percentile estimates for each participant’s speech segment. f0 is defined as the inverse of the longest period (repeated waveform) in a complex periodic signal. It is the closest physical measure correlating with perceived tone (pitch). Limits for pitch tracking were set at 75–300 Hz. These settings were selected after a preliminary trial using much wider settings and exploring the ranges of both men and women in both patient and HC groups. The goal was to use uniform criteria for processing all participants, regardless of sex, while keeping the margins narrow enough to minimize artefactual pitch estimates.

We extracted f0 estimates for the 10th through the 90th f0 percentiles for each speech segment and then calculated the mean f0 for each 10 percentile bin per participant. We repeated the analysis with larger percentile bins, including 20 and 30 percentile intervals, and found the same statistical results. We chose to report here the results with 10 percentile bins to show the most granular f0 data. We validated our automated f0 range against a blinded subjective assessment of limited vs normal prosody within the patient group. Objective classification as normal was defined by pitch range within the top 33rd percentile. We found no difference in the classification between automated pitch range measurement and subjective judgment (χ² = 1.6, df = 1, p = 0.21).

Table 1. Clinical and demographic characteristics of patients with behavioral variant of frontotemporal dementia (bvFTD) and healthy controls (HCs)

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>bvFTD</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>17</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>66 (6.7)</td>
<td>63 (8.5)</td>
<td>0.235</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>9 (52.9)</td>
<td>21 (65.6)</td>
<td>0.576</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.3 (2.8)</td>
<td>15.7 (2.8)</td>
<td>0.453</td>
</tr>
<tr>
<td>MMSE [max = 30]</td>
<td>29.3 (1)</td>
<td>24.4 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom duration, y</td>
<td>NA</td>
<td>4 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Dysphoria [max = 12] [n = 21]</td>
<td>NA</td>
<td>0.9 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Sum distress [max = 72] [n = 21]</td>
<td>NA</td>
<td>11.3 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Social [max = 48] [n = 20]</td>
<td>NA</td>
<td>10.06 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Psychovegetative [max = 84] [n = 19]</td>
<td>NA</td>
<td>12.2 (9.1)</td>
<td></td>
</tr>
<tr>
<td>F letter fluency [n = 30]</td>
<td>NA</td>
<td>5.7 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Speech rate, wpm</td>
<td>138.5 (39.4)</td>
<td>83 (37.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE = Mini-Mental State Examination; NA = not available; wpm = words per minute.

Values are mean (SD) unless noted otherwise.

* Subscore from Neuropsychiatric Inventory.
The f0 data were converted from Hz to semitones (ST) with the following formula: ST = 12 × log2(f0/X), where X is each participant’s own 10th f0 percentile. As an absolute measure of audio frequency, Hz is subject to individual confounds (see below). ST express pitch intervals in relation to an arbitrary baseline frequency, and thus more closely resemble human pitch perception, and are commonly used in music and speech analysis. We used ST in this analysis, centering on each participant’s own 10th f0 percentile to control for individual pitch differences. This optimized examination of the f0 range since all first 10th percentiles were zeroed and the 90th percentiles in ST represent the range.

We identified 2 outliers in the bvFTD group and 1 in HC who had an f0 range differing from their group by >1.5 SD (spanning over 1 octave, or 12 ST). We inspected these 3 recordings and confirmed that the participants’ voices had a creaky quality (a phenomenon sometimes referred to as vocal fry) throughout the recording. This led us to question the reliability of the pitch tracker in these cases, and so they were excluded from further analysis.

**Statistical analysis.** Statistical tests were performed for between-group comparisons and within male and female subpopulations. Comparison of demographic data was performed with analysis of variance for continuous variables and χ² test for categorical variables. Kernel density and Q-Q plots revealed that some of the speech variables diverged from normal distribution, thus we utilized the nonparametric Mann-Whitney test for group comparisons. Correlations of each of the social and executive scores with f0 range used Spearman method. All calculations were conducted in R (version 3.2.3) and RStudio (version 0.99.879).

**Gray matter density analysis.** High-resolution structural brain MRIs were obtained on average within 2.6 ± 3.6 months of the speech sample. We used a previously published MRI acquisition and preprocessing algorithm to obtain an imaging dataset corresponding to the speech samples (see supplemental data). Gray matter (GM) atrophy mask was created by voxel-wise comparisons of the study cohort (HC vs bvFTD) with familywise error correction and threshold-free cluster enhancement at p < 0.05 and cluster size k ≥200 voxels using Randomise in FSL. Regression analysis was performed with 10,000 permutations to control for type I errors. We associated f0 range, expressed as the 90th percentile in ST, to GM density using a p < 0.05 and cluster size threshold at k = 10 voxels. No covariates were included in the regression as none had a significant confounding effect.

**Standard protocol approvals, registrations, and patient consents.** The study was approved by the local ethics committee (institutional review board) of the Hospital of the University of Pennsylvania. Written informed consent was obtained from all participants.

**RESULTS Speech analysis.** The f0 range was shallower on average in patients with bvFTD (mean 4.3 ± 1.8 ST) compared with HC (mean 5.8 ± 2.1 ST, U = 170, p = 0.03), as illustrated in figure 1. Subset analysis by sex revealed a reduction in f0 range in patients relative to HC in both sexes, but this phenomenon was more pronounced for male patients (figure 2).

A density plot of f0 range (figure 3A) showed that HC are much more variable in their chosen pitch range, with 3 distinct subpopulations around 2, 6, and 9 ST. Patients with bvFTD exhibited only one subpopulation with a single broad peak (around 2–4 ST).

Mean speech segment duration differed significantly between HC (2.15 ± 0.64 seconds) and patients with bvFTD (1.33 ± 0.33 seconds, U = 476, p < 0.005) (figure 3B). However, there was no correlation between f0 range and mean speech duration within the bvFTD group (r = −.019, p = 0.3) or the HC (r = 0.17, p = 0.5). Mean pause duration (figure 3C) also differed between HC (0.94 ± 0.54 seconds) and patients with bvFTD (1.73 ± 0.86 seconds, U = 101, p = 0.0002). Total speech-to-pause ratio was

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**Figure 1**  
Fundamental frequency percentiles per group

**Figure 2**  
Fundamental frequency percentiles by group and sex

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**TABLE 1**  
Fundamental frequency (f0) estimates in 10th percentile bins for healthy controls (HC) (n = 17) and behavioral variant of frontotemporal dementia (bvFTD) patient group (n = 32) with standard error bars. The f0 range is represented by the 90th percentile and is limited to 4.3 ± 1.8 semitones (ST) for the patient group compared to HC (5.8 ± 2.1 ST). *p = 0.03.

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2.84 ± 1.51 seconds and 1.02 ± 0.58 seconds for HC and patients with bvFTD, respectively ($U = 477, p < 0.0001$). Correlation of f0 range with behavioral measures, including NPI composite scores listed in table 1 and each of the individual NPI subscores, speech rate (words/min), and executive (F-letters fluency) scores, was performed within the bvFTD group. We found no correlation of these scores with f0 range (all $p$ values $>0.4$).

**Neuroimaging.** Patients with bvFTD showed significant bilateral frontotemporal atrophy (figure 4, blue). Figure 4 (heat map) also shows regression analysis of f0 range with GM atrophy involving left prefrontal, inferior frontal, orbital frontal, anterior cingulate, insula, and left fusiform and right inferior frontal gyri. Peak atrophy and regressions are summarized in table e-1.

**DISCUSSION** We found a limited range of f0 expression in a semi-structured speech sample from a large cohort of patients with bvFTD. The neuroanatomic basis for their deficit was centered in inferior frontal cortex bilaterally. These findings are consistent with the hypothesis that bvFTD may be associated with impaired prosodic expression, which can limit communicative efficacy in these patients. Moreover, since many social judgments of professionals and caregivers are based on vocal quality, this is a potentially important confound in assessments of bvFTD. We discuss each of these issues below.

Prosody is often associated with emotional expression, and also contributes to linguistic expression.
Linguistic prosody is used to mark the end of declarative sentences with a lowering of pitch, for example, or the end of yes/no questions by a rising pitch. The picture description task used to elicit our speech samples has some emotional as well as propositional characteristics. Although most previous work assessing disorders of prosody has focused on emotional and receptive prosody, some investigations have noted expressive dysprosody for linguistic forms as well.

Previous reports have described linguistic and acoustic analyses of spontaneous speech samples in patients with various neurodegenerative conditions. To our knowledge, the current study uniquely uses a novel, automated, and objective approach to demonstrate a reduction in pitch range, measured acoustically directly from digitized audio, in patients with bvFTD. We hypothesized that patients with bvFTD would be impaired in their ability to regulate their expressive prosody, coinciding with informal clinical observations of monotone speech in these patients. Speech characterized by a limited prosodic range may be interpreted by the listener as an indifferent or apathetic voice. Indeed, apathy has been reported to be a prominent symptom in this patient population, observed in over 80% of cases.

Apathy in bvFTD has been associated with a social disorder and limited executive functioning in non-verbal behavior. In fact, f0 range did not correlate with any NPI subscore. One possibility is that dysprosody is at least in part independent of the rated neuropsychiatric symptoms, and a disorder of prosody may not necessarily reflect only a behavioral disorder. Our suprasegmental prosodic measurements may reflect in part subtle grammatical deficits previously described in bvFTD. However, we did not find a correlation between prosodic range and language measures. Our findings thus may be consistent with the hypothesis that prosodic control is a partially independent function that neither exclusively reflects commonly associated social–emotional changes such as apathy, depression, or vegetative dysfunction nor language limitations found in bvFTD. Additional work is needed to assess the basis of limited prosodic range in FTD using more specific linguistic and emotional materials.

Other explanations for limited f0 range in bvFTD may be related to potential physiologic confounds. The fundamental frequency is produced primarily by subglottal air pressure vibrating the vocal folds. A physiologic effect on f0 stems from the duration of the speech segment. These natural speech segments are often referred to by phoneticians as breath groups, since breathing is the strongest constraint on speech duration. Subglottal air pressure decreases throughout the breath group. This may cause a physiologic decrease in pitch, often used to explain the f0 declination phenomenon in phonetics research. More recent phonetic publications suggest a linguistic effect on f0 declination. We excluded patients with concomitant ALS to avoid the confound of respiratory weakness, and examined the correlation between f0 range and speech segment durations in our samples. The lack of correlation is inconsistent with the hypothesis that limited f0 range depends on a breathing or oral musculoskeletal mechanism.

Relatedly, individual physical attributes such as height and sex can have an effect on the mean f0 produced by a speaker. We observed a limited prosodic range in bvFTD, and this was more prominent in male patients (figure 2). Sex has a major effect on estimated f0: women typically have higher fundamental frequencies than men, and as a result may also seem to have a wider pitch range if measured in absolute frequency units, i.e., Hz. Our method of conversion to a relative ST scale minimizes this sex confound, and suggests that our f0 range is a genuine representation of limited prosody in patients from both sexes. Our sex analysis suggests a sex effect, making female patients’ prosodic performance closer to sex-matched HC. This sex effect must be interpreted cautiously because of the small sample size and because 36% (4/11) of female patients had a limited f0 range (beyond 1 SD of HC). Evidence for a sex predominance in bvFTD is mixed. Nevertheless, a similar sex effect was recently observed in a dysfluency study of autism spectrum disorders. Additional work is needed to clarify the existence of sex effects in bvFTD.

We found that dysprosody in bvFTD is related to bilateral inferior frontal regions. Previously published anatomic correlates of dysprosody focused on linguistic dysprosody in left frontal and opercular injuries. Linguistic and emotional receptive prosody also was investigated in FTD presenting as primary progressive aphasia, and intonation discrimination difficulty was associated with left frontotemporal regions and the fusiform gyrus. The left inferior frontal gyrus (IFG) has been shown in a functional MRI study to be associated with processing of linguistic prosody tasks. Others suggested involvement of the right IFG in descriptions of impaired emotional prosody. Our findings coincide with these descriptions, as both hemispheres were associated with decreased prosody in our bvFTD cohort. While our work examines these frontal regions in the context of prosodic aspects of speech production, these same areas are also implicated in the social and behavioral disorders found in bvFTD. Additional work is needed to help us specify the role of these anatomic regions in the linguistic and social basis for dysprosody.
Strengths of our study include the large cohort of nonaphasic patients with bvFTD we examined, and the objective, automated method of speech analysis. Thus, we are introducing a novel analytic approach to speech production that may be useful in examination of naturalistic endpoints in therapeutic trials. This automated method is independent of the human labor of transcription and biases inherent in informal analyses, and produces robust markers for identifying pathologic prosody in bvFTD. Further study of psycholinguistic-acoustic measures will be valuable to the development of prosodic biomarkers.

Nevertheless, several limitations should be kept in mind when interpreting our findings. First, even though the group size is much larger than most previously reported in FTD studies, it is still statistically small. Second, we used a uniform source for speech sample production to control the topic of narrative expression, and it would be valuable to assess prosody using other samples including conversational and emotional speech. Third, several technical issues that limited data analysis and interpretation should be addressed. Some recordings were collected prior to development of the automated analysis, and thus were not controlled in terms of sound quality and acoustic properties such as sampling rate and bandwidth settings. Recording specifications did not allow for accurate comparison of speech intensity between participants. In addition, the properties of the SAD do not allow matching of acoustic data to subsegmental lexical elements such as syllables and words. Fourth, pitch trackers can only estimate the lowest periodicity per window, and are subject to many potential confounds resulting from background noise, specific vocal features (e.g., soft, creaky), and octave jumps in pitch. Some inaccuracy in f0 estimation can be avoided by applying optimal settings for pitch tracking. We tested the pitch settings by applying different settings for men (60–260 Hz) and women (90–400 Hz). The results were similar to the ones reported here.

With these caveats in mind, our findings suggest that prosodic regulation is impaired in patients with bvFTD. The disorder of prosody we observed is associated with specific cortical regions that are in turn linked to neural networks implicated in language production and social disorders.

AUTHOR CONTRIBUTIONS
Naomi Nevler drafted/revised the manuscript for content, contributed to study concept/design, performed analysis/interpretation of the data, and performed statistical analysis. Sharon Ash contributed to acquisition of the data and revised the manuscript for content. Marc Liberman contributed to analysis/interpretation of the data. Murray Grossman drafted/revised the manuscript for content, contributed to study concept/design, contributed to acquisition and analysis/interpretation of the data, obtained funding, and provided supervision.

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