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A systematic review of the quantitative markers of speech and language of the frontotemporal degeneration spectrum and their potential for cross-linguistic implementation

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ABSTRACT

Frontotemporal dementia (FTD) is a neurodegenerative disease spectrum with an urgent need for reliable biomarkers for early diagnosis and monitoring. Speech and language changes occur in the early stages of FTD and offer a potential non-invasive, early, and accessible diagnostic tool. The use of speech and language markers in this disease spectrum is limited by the fact that most studies investigate English-speaking patients. This systematic review examines the literature on psychoacoustic and linguistic features of speech that occur across the FTD spectrum across as many different languages as possible. 76 papers were identified that investigate psychoacoustic and linguistic markers in discursive speech. 75 % of these papers studied English-speaking patients. The most generalizable features found across different languages, are speech rate, articulation rate, pause frequency, total pause duration, noun-verb ratio, and total number of nouns. While there are clear interlinguistic differences across patient groups, the results show promise for implementation of cross-linguistic markers of speech and language across the FTD spectrum particularly for psychoacoustic features.

1. Introduction

Frontotemporal dementia (FTD) gives rise to a spectrum of clinical phenotypes with variable degrees of speech and language pathology (Moore et al., 2020; Rohrer et al., 2015). All variants of primary progressive aphasia (PPA) by definition present with prominent abnormalities of speech and/or language (Gorno-Tempini et al., 2011), but the FTD spectrum as a whole is strongly associated with such impairments. In behavioral variant FTD (bvFTD), word retrieval, comprehension, reading, writing, verbal and non-verbal semantic knowledge, as well as prosody of speech are impaired, while motor speech and repetition abilities remain generally preserved (Geraudie et al., 2021; Samra et al., 2023). On the other side of the spectrum, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) have been more often associated with motor speech impairments such as apraxia of speech and dysarthria, though more recent research also shows impairment in language abilities, such as confrontation naming, fluency, sentence comprehension and production (Peterson et al., 2019). Meanwhile, FTD combined with amyotrophic lateral sclerosis (FTD-ALS) can occasionally present with agrammatism and/or apraxia of speech, as well as comprehension deficits on the single word and sentence level (Rusina et al., 2021).

While the first clinical trials for genetic FTD are being rolled out

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(Boeve et al., 2022), there is an unmet clinical need for reliable non-invasive markers to monitor disease progression and therapeutic effects. Quantitative analysis of speech and language in FTD could potentially provide objective, low-cost and sensitive markers suitable for this purpose. Specifically, psychoacoustic markers can be used to quantify motor speech disorders such as apraxia of speech and dysarthria, while linguistic markers may quantify single word use or detect sentence construction abnormalities.

One of the important challenges regarding the clinical implementation of psychoacoustic and linguistic markers is to identify which, if any, markers are applicable across different languages. There is a paucity of published research on the speech and language changes that occur in FTD spectrum disorders in non-English speaking patients (García et al., 2023). Therefore, it would be beneficial to determine which changes in speech and language are generalizable across languages and which are language-specific. Research has shown significant interlinguistic differences between patients across the FTD spectrum (García et al., 2023). For instance, significant differences have been found between English and Italian patients with non-fluent variant PPA (nfvPPA) in motor speech and syntactic complexity (Canu et al., 2020).

There are numerous approaches to investigating the changes that occur in speech and language. Connected speech (comprised of consecutive words forming utterances) offers a wealth of information about the cognitive state of a patient, and countless variables can be extracted from a relatively small sample of connected speech. The cookie theft picture description task for instance, one of the most commonly used tasks to generate connected speech (Goodglass and Kaplan, 1972), takes less than two minutes to administer and can be carried out by experts and non-experts alike. There are also numerous alternatives to picture description tasks, for instance, semi-structured interviews (Knibb et al., 2009), narrative tasks (Ash et al., 2006), reading tasks (Baque et al., 2022), and repetition tasks (Bouvier et al., 2021). An advantage of picture description tasks such as the cookie theft picture description task is that large existing databases of speech samples from patients with FTD as well as from controls can be used as comparisons for newly collected data. These large databases will be

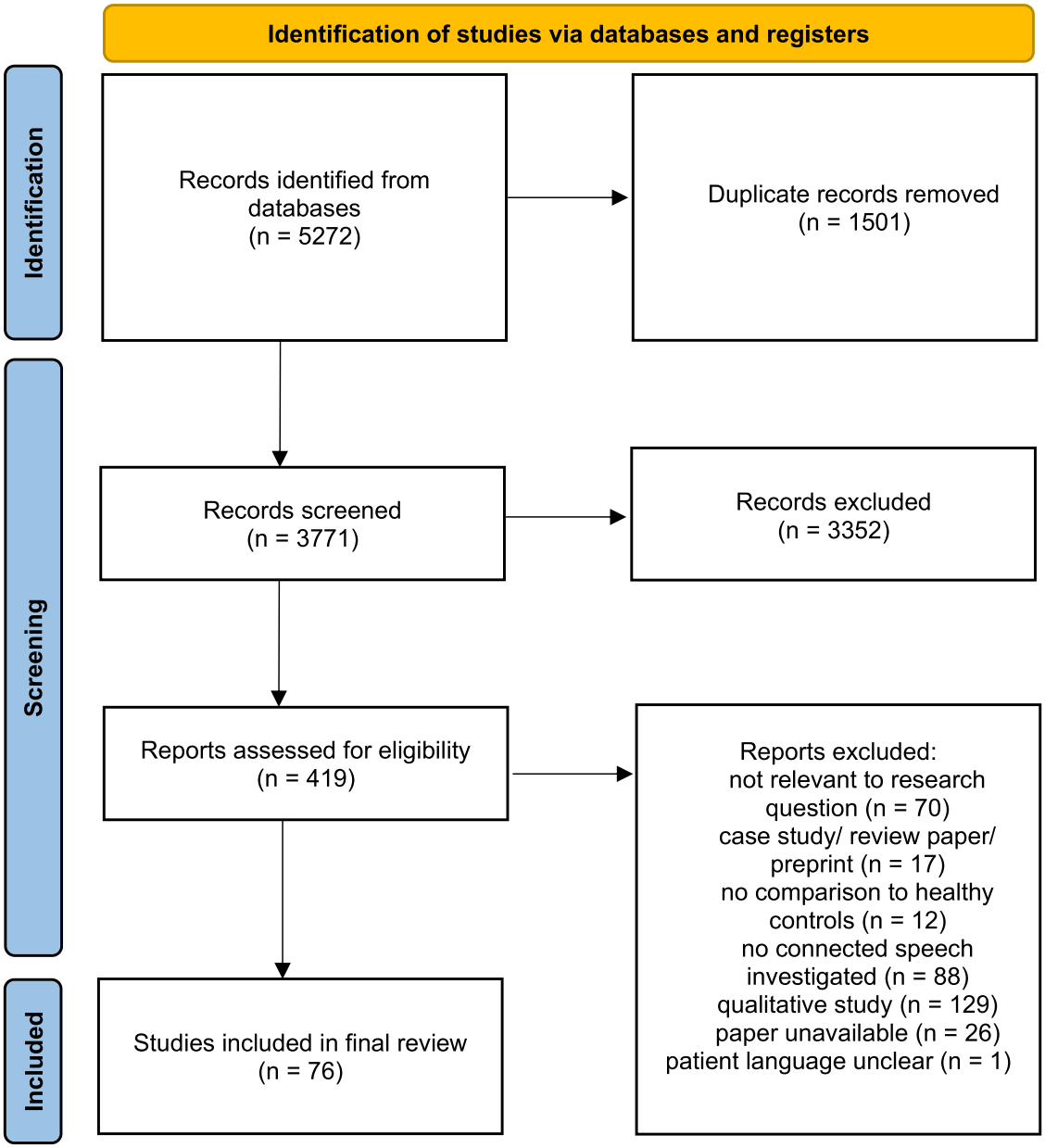

Fig. 1. PRISMA flowchart of methods of systematic literature review.

beneficial in creating machine learning models to diagnose FTD using (semi) automated analysis of speech.

In this paper, we performed a systematic review of the known quantitative psychoacoustic and linguistic markers in connected speech across the FTD spectrum to inform future cross-linguistic research and clinical implementation.

2. Methods

A systematic review of the literature on the quantitative psychoacoustic and linguistic markers of FTD was carried out to determine the most relevant features of speech and language to analyze in discursive speech samples and to determine which features were the most generalizable across different languages. Using the databases SCOPUS and Web of Science the relevant literature was identified and screened on the 1st of March 2023. The search terms used were "FTLD", "primary progressive aphasia", "frontotemporal dementia", "semantic dementia", "non-fluent primary progressive aphasia", "progressive supranuclear palsy", "corticobasal degeneration", "ALSFTD", "speech", and "language". The disorders were grouped by an 'OR' operator and combined with the speech and language search terms with the 'AND' operator, which were also grouped with the 'OR' operator. All words are MeSH terms.

This search yielded 5272 results in total including duplicates, which were manually removed, leaving 3771 peer-reviewed papers (see Fig. 1). Using Rayyan, a literature search tool (Ouzzani et al., 2016), the titles and abstracts were triaged to filter for the relevant papers. Papers were included if they studied a population of patients with frontotemporal lobar degeneration and obtained results relating to the psychoacoustic or linguistic properties of elicited connected speech or discourse of the patients. Patients with nfvPPA, primary progressive apraxia of speech (PPAOS), logopenic variant PPA (lvPPA), semantic variant PPA (svPPA), semantic dementia (SD), mixed PPA (mxPPA), bvFTD, CBS, PSP, and ALS-FTD were included. Only patient groups that were diagnosed according to international consensus criteria were included. Papers were excluded if there was no control group, or if they were case studies or review papers. Only peer-reviewed papers were included.

With the inclusion and exclusion criteria stated in Fig. 1, a total of 419 papers were selected for further reading. The following data was extracted from these 419 papers: (i) the sample size, (ii) the language of the patients, (iii) the methods used to obtain the speech and language features, (iv) the psychoacoustic and linguistic features investigated, and (v) the relevant findings.

Papers published in all languages were considered. Five of the 419 papers were only available in Spanish, one only available in German and the rest were written in English (though not all about English-speaking patients).

Upon further reading and data extraction, 76 papers were selected for inclusion in the final paper. The date range of these papers was from May 1997 to October 2022.

Based on the 76 papers, there were a total of 342 features of speech compared in the patient groups and healthy controls in discourse. 44 of these features were studied in more than one language.

In four papers the PPA patients consisted of a mixed group of several subtypes, or the subtype was not specified. The results that were relevant to this review were considered separately from the other PPA variants.

76 papers studying discourse in patients with FTD were included in the final review. 57 of these papers (75 % of all papers) studied English-speaking patients and the remaining 19 papers studied patients speaking Spanish (Baque et al., 2022; Matias-Guiu et al., 2020, 2022), Czech (Daoudi et al., 2022; Rusz et al., 2015; Skrabal et al., 2020), Italian (Catricala et al., 2019; Silveri et al., 2014), French (Bouvier et al., 2021; Macoir et al., 2021), German (Hohlbaum et al., 2018; Staiger et al., 2017), Dutch (Bruffaerts et al., 2022), Greek (Karpathiou and Kambanaros, 2022; Koukoulioti et al., 2018, 2020; Potagas et al., 2022), Hindi (Sachin et al., 2008), and Korean (Suh et al., 2010) (Table 1). Fig. 2 shows the geographical representation of the published papers, with a paucity of languages from South America, Asia, and Africa. As Fig. 2B shows, the language distribution of the literature is in no way representative of the total population of each language, with English being drastically overrepresented relative its total population of native speakers. The vast majority of these papers describe patients with sporadic FTD (99 %).

As previously stated, only papers using tasks which elicited connected speech were included. The tasks chosen were varied, but the most commonly used were picture description, interviews, narrative, and reading tasks. The cookie theft picture description task was the most widely used task, in a total of 23 papers with patients speaking English, Spanish, Dutch, Italian, and Greek. Sentence repetition tasks were only used in papers studying non-English-speaking patients. Conversely, conversation as a task was not used by any papers studying non-English-speaking patients, and was only used by two papers studying English-speaking patients (Fig. 3).

The psychoacoustic and linguistic features of speech across the FTD spectrum were extracted, resulting in 342 features. The features were grouped based on the categorization method of Boschi et. al. (2017) for connected speech in neurodegenerative disorders (2017), comprised of the following five categories: phonetic-phonological, lexico-semantic, morpho-syntactic, syntactic, and discourse-pragmatic. The phonetic and phonological category includes features at the level of the speech sound such as pausing behavior, and the time taken to produce components of speech including words, phonemes, and syllables. Lexico-semantic features include features at the word and content level, such as number of nouns, verbs, adjectives, and pronouns, obtained through techniques like part-of-speech tagging (Jarrold et al., 2020). The morphosyntactic-syntactic category includes features relating to inflectional morphology, while the syntactic category includes features purely related to syntax, such as the number of words per clause, utterance, and sentence. Finally the discourse and pragmatic category was comprised of features that contribute to the continuation of conversation, such as cohesion, coherence, and correct use of conjunctions. (Boschi et al., 2017). An additional category for error typing was added, as recent research has demonstrated the importance of these features in FTD (Bruffaerts et al., 2020; Catricalà et al., 2015). This additional category involved features relating to the number or rate of any type of any errors (e.g. phonological errors, semantic errors etc.).

44 of these features of speech and language were studied in more than one language and we focused on these features (see Table 1 for definitions). Within these, the most widely studied features were speech rate and articulation rate. The 18 features with the same main finding in more than one language are shown in Table 2. Six of the features were found to have the same main finding in both *more than one language* and in *more than one clinical variant of FTD*. For these features, the quantitative values of the papers were extracted where possible and plotted for interlinguistic comparison in Fig. 4. Quantitative value comparisons aim

Table 1
The number of studies investigating connected speech in FTD in different languages.

Language	Number of Studies
English	57
Greek	4
Spanish	3
Czech	3
Italian	2
French	2
German	2
Korean	1
Hindi	1
Dutch	1
Total	76

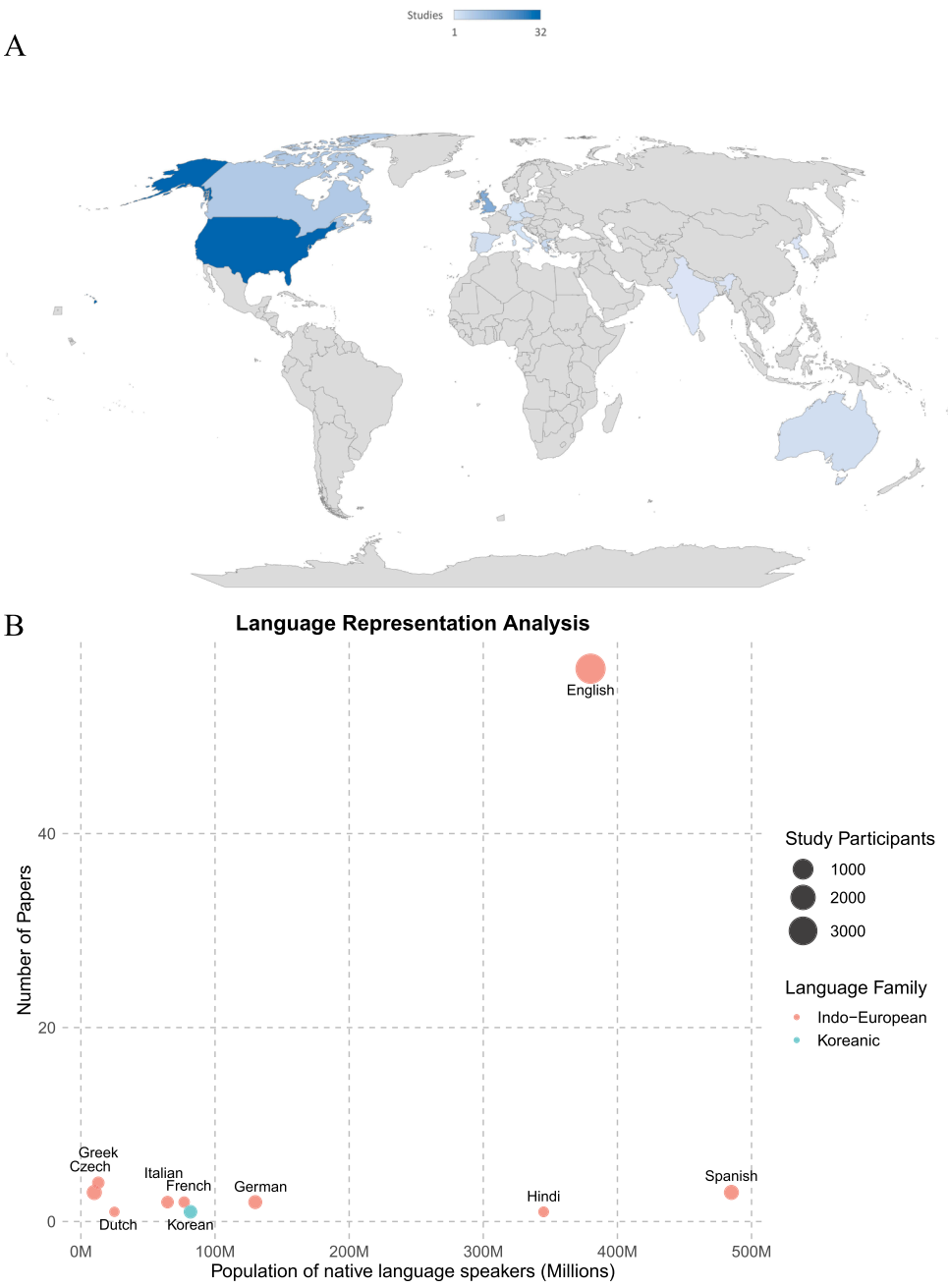

Fig. 2. The (A) geographical locations and (B) language representation analysis of the 76 included papers.

to identify potential variances in baseline measures among healthy controls across distinct languages, which may be important for determining differences in cut-off points for what should be considered normal values of different features within each language. Tables 3a 3b

3. Results

As is shown in Fig. 4A, the **speech rate** of patients was reduced compared to controls in more than half the papers for all patient groups. Lines in Fig. 4 connect groups reported in the same study and asterisks denotate which languages showed significant differences. However, a Greek patient population showed a reduced speech rate in nfvPPA while lvPPA and svPPA had no significant reduction in speech rate (Potagas et al., 2022). A second paper investigating Greek patients with PPA also found no significant reduction in speech rate, though they did not differentiate between the variants (Karpathiou and Kambanaros, 2022). The majority of English patient populations with lvPPA, svPPA, and bvFTD showed significant reductions in speech rate. Aside from Greek, all other non-English languages (Spanish, Italian, Hindi, and Czech) studying the FTD spectrum had a significant reduction in speech rate although not every patient group has been studied (Catricala et al., 2019; Daoudi et al., 2022; Matias-Guiu et al., 2022; Sachin et al., 2008; Silveri et al., 2012; Potagas et al., 2022). The values of healthy controls did not visibly differ based on language. However, considerable variability within the English-speaking controls was observed.

Fig. 4B shows that the **articulation rate** was reduced compared to controls in more than half of papers investigating nfvPPA, lvPPA, and PSP. As is visible in Fig. 4B, there was an overall trend of Spanish patients and controls to exhibit the highest values for articulation rate and Greek patient and control samples to exhibit the lowest values (Baque et al., 2022; Potagas et al., 2022). A study investigating Greek PPA patients also found a significant reduction in articulation rate, though

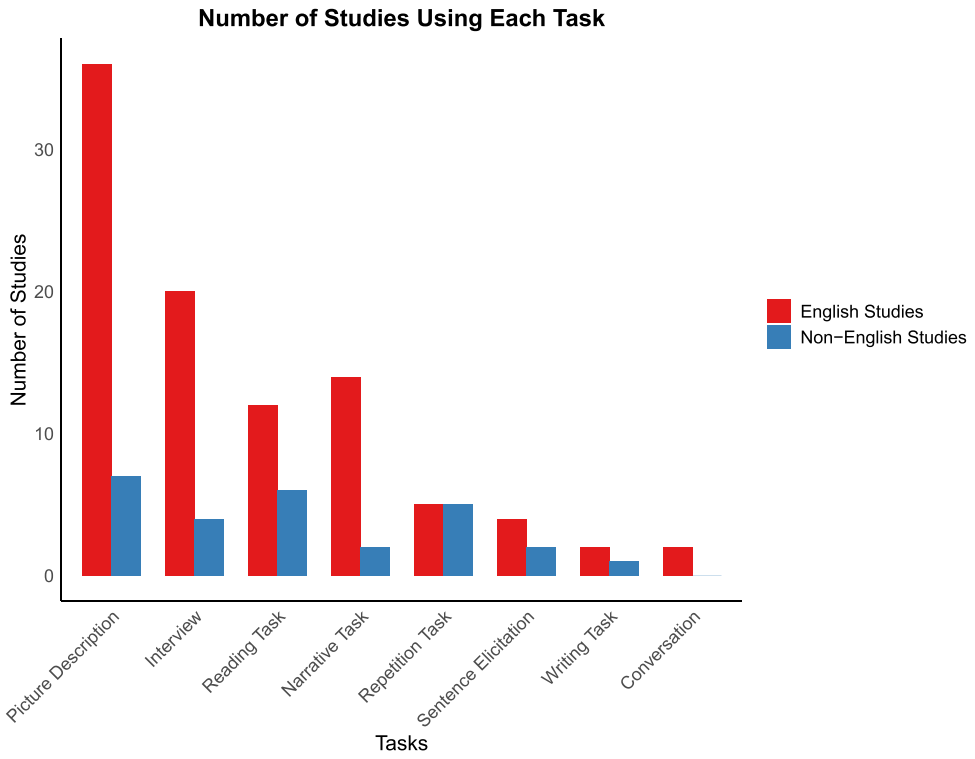

Fig. 3. The tasks used by the papers in the review in English and non-English speakers.

again the authors did not differentiate between the variants (Karpathiou and Kambanaros, 2022). On the other hand, the lvPPA Spanish and Greek patient samples did not exhibit a significant difference compared to healthy controls from the same language group, while the English patient samples had a significantly reduced articulation rate (Cho et al., 2022; Cordella et al., 2019, 2017). PSP patients had a significantly reduced articulation rate in both Czech and German patient samples (Rusz et al., 2015; Skrabal et al., 2020; Staiger et al., 2017). ALS-FTD also had a significantly reduced articulation rate in English patients (Yunusova et al., 2016); however there was no significant difference in the Spanish patient sample (Baque et al., 2022). Finally, the bvFTD patient samples did not have a significant difference in articulation rate compared to controls for both the English and Spanish patient groups (Baque et al., 2022; Yunusova et al., 2016). The values of healthy controls do not noticeably differ based on language.

As can be seen in Fig. 4C, the **pause frequency** was increased in nfvPPA in English-speaking patient samples as well as Greek (Cordella et al., 2017; Nevler et al., 2019; Parjane et al., 2021; Potagas et al., 2022). For lvPPA, svPPA, and ALS-FTD patient groups, the difference was not significant in most papers in both Greek and English-speaking patient samples (Cordella et al., 2017; Potagas et al., 2022; Yunusova et al., 2016). For PSP and CBS, the pause frequency was also increased in one English patient sample (Parjane et al., 2021). As shown in Fig. 4D, the **total pause duration** was significantly increased in nfvPPA, lvPPA, bvFTD, PSP, CBS, and ALS-FTD in all English, Spanish, and Greek-speaking patient samples (Matias-Guiu et al., 2020; Parjane et al., 2021; Potagas et al., 2022; Yunusova et al., 2016). In one relatively small Greek svPPA sample there was an increase in pause duration (visible in Fig. 4D). However this difference was not found to be significant (Potagas et al., 2022). The values of healthy controls do not appear to differ based on language for total pause duration.

As is shown in Fig. 4E, the **noun-verb ratio** was significantly reduced in the majority of the English patient groups with svPPA (Fraser et al., 2014; Garrard and Forsyth, 2010; Mack et al., 2015; Thompson et al., 2012). However, in one Spanish patient sample there was no significant difference in this ratio (Matias-Guiu et al., 2022). For the English, Spanish, and Italian patients with nfvPPA, lvPPA, and PSP there were no significant differences in the noun-verb ratio (Catricala et al., 2019; Fraser et al., 2014; Graham et al., 2004; Knibb et al., 2009; Mack et al., 2015; Marcotte et al., 2017; Matias-Guiu et al., 2022; Thompson et al., 1997, 2012). Some variability was observed for noun-verb ratio in the English-speaking control group (the highest having a ratio of 1.55 (Fraser et al., 2014) and the lowest a ratio of 0.9 (Garrard and Forsyth, 2010)). The Italian-speaking control group had the highest noun-verb ratio. Fig. 4F reports the values for noun tokens and combines the number of noun tokens per total words, per 100 words, and the total count. As is shown in Fig. 4F, the **number of noun tokens** was significantly decreased in nfvPPA, lvPPA, and svPPA, in both Spanish (for total number of tokens) (Matias-Guiu et al., 2022) and English-speaking patients (for nouns per 100 words, per total words, total noun count, and for nouns per utterance – which is not plotted because of the difference in units) (Ash et al., 2009; Cho et al., 2022; Cupit et al., 2017; Fraser et al., 2014; Graham et al., 2004; Mack et al., 2015). In contrast, the number of noun tokens per 100 words was significantly increased in PSP and CBS in one English patient sample (Parjane et al., 2021). There was no significant difference in the number of noun tokens per utterance in bvFTD in one English-speaking patient sample (Ash et al., 2009), which is not plotted because of the difference in measured units. The values of healthy controls do not appear to differ based on language for the number of noun tokens.

Further information about the speech and language alterations found in FTD can be found in supplementary Table 1, which includes the sample sizes, languages, speech and language features studied, and relevant findings of all included papers.

3.1. Exploratory meta-analysis

An exploratory meta-analysis was attempted on the six features which were found to be the most generalizable based on the systematic literature review. For the meta-analysis, the following variables were extracted from 45 papers studying the relevant features: mean values, standard deviation, sample size, language, and task. Hedge's g and

Table 2
The definitions of the 44 linguistic and psychoacoustic features studied in more than one language in the FTD spectrum. References to the papers can be found in the supplementary materials.

Linguistic Feature	Definition of Feature	Languages studying Feature
Phonetic and Phonological		
false starts	the number of partial words spoken	English, Spanish
F0 standard deviation	the degree of variability of the fundamental frequency of speech	English, Czech
PVI strong-weak	the pairwise variability index of length of syllables words	English, Dutch
PVI weak-strong	the pairwise variability index of length of syllables words with a weak-strong timing, includes median and mean	English, Dutch
intensity level	the intensity level of speech	English, Czech
pause frequency	the frequency that filled pauses occur	English, Greek
mean pause duration	the average of the pause durations in speech	English, Greek
total pause duration	the total pausing time throughout speech	English, Spanish, Greek
number of pauses	the total number of pauses that occur in speech	English, Spanish, Greek, Italian
pause duration variability	the standard deviation of pausing during speech	English, Spanish
speech rate	the number of speech units per time. Included in this feature are - words per minute, syllables per second and content units per second	English, Spanish, Greek, Italian, Czech
articulation rate	the number of syllables per total speech time. Included in this feature are - words per second and syllables per second	English, Spanish, Greek, German, Czech
total speaking time	the total response time taken to speak on a topic	English, Spanish, Italian
median silence length	the median length of silent pauses with no filler words.	English, Spanish
percentage of speech	the percentage of speech in the total response	English, Spanish
Lexico Semantic		
pronoun ratio	the total pronouns divided by the total words	English, Italian
#nouns/#words	the total number of nouns divided by the total number of words	English, Italian
nouns (token)	the total number of nouns spoken	English, Spanish
verbs (token)	the total number of verbs spoken	English, Spanish
#verbs/#words	the total number of verbs divided by the total number of words	English, Italian
no. closed-class words	the total number of closed-class words	English, Spanish
noun-verb ratio	the total number of nouns divided by the total number of verbs	English, Spanish
verb frequency	the frequency of the verbs spoken based on occurrence in speech corpus	English, Spanish
noun frequency	the frequency of the nouns spoken based on occurrence in speech corpus	English, Spanish
nouns per 100 words	the total number of nouns divided by the number of hundred words spoken	English, Spanish
inaccurate/irrelevant information	the total number utterances that are unrelated to the question or task at hand	English, Italian
conduites d'approche	the repetition of a response several times in succession with or without improvement	Spanish, Italian
content units	the number of speech units that contain information	English, Italian
Morphosyntactic Syntactic		
total dependent clauses	the total number of dependent clauses	English, Italian
total words/total time	the total number of words divided by the total time spent speaking	English, Spanish, Italian
syllable duration	the average duration of syllables	English, German
total words	the total number of words spoken	English, Spanish, Greek, Italian
MLU	the mean length utterance in speech	English, Spanish, Italian
number of sentences	the total number of sentences spoken	English, Italian
total utterances	the total number of utterances spoken	English, Italian
mean length of sentence	the mean length of sentences in speech	English, Greek
Errors		
number of errors	the total number of errors in speech	English, Spanish
number of errors/ number of words	the total number of errors divided by the total number of words	English, Spanish
word omissions	the total number of word omissions	English, French
word repetitions	the total number of word repetitions	English, French
phonological	the total number of phonological errors	English, Spanish
semantic	the total number of semantic errors	English, Italian
phonetic errors	the total number of phonetic errors	English, Italian
phonemic	the total number of phonemic errors	English, Italian

variance were calculated for each study. A random effects model with a restricted maximum likelihood (REML) was selected due to the range of tasks, languages, and patient groups that were studied. The analyses were performed using the "rma" function from the metafor package in R (Viechtbauer, 2010). An insufficient number of studies investigated individual variants of FTD and different tasks or languages (other than English). For this reason, a moderator analysis was not included for variant, task, or language.

For all 6 features, we observed very high heterogeneity (I^2: between 79.31 % and 97.16 %) and significant p-values for Cochran's Q Test ($P < 0.001$). Given the very high heterogeneity, we concluded that insufficient data was available to pursue a further meta-analysis.

4. Discussion

This review shows that the most generalizable speech and language features of FTD across languages are speech rate, articulation rate, pause frequency, total pause duration, noun-verb ratio, and number of noun tokens. Four out of the six features are in the phonetic and phonological category and the remaining two are in the lexico-semantic category. Phonetic and phonological features were useful in the detection of nfvPPA and PSP. In contrast, lexico-semantic features were more able to detect svPPA. Our results suggest that connected speech analyses on relatively short samples can be used across multiple diverse languages to detect emerging neurodegenerative diseases in the FTD-spectrum. Our findings also promote the use of not just one single feature but advocate for the creation of an individualized speech and language profile for each phenotype combining both phonological and lexico-semantic features.

With regard to the phonetic and phonological features, one aspect that should be considered is the fact that nfvPPA is the most widely studied of the variants, both in number of papers and number of languages. NfvPPA tends to have more alterations at the speech sound level, in the phonetic and phonological category, which is reflected in the fact

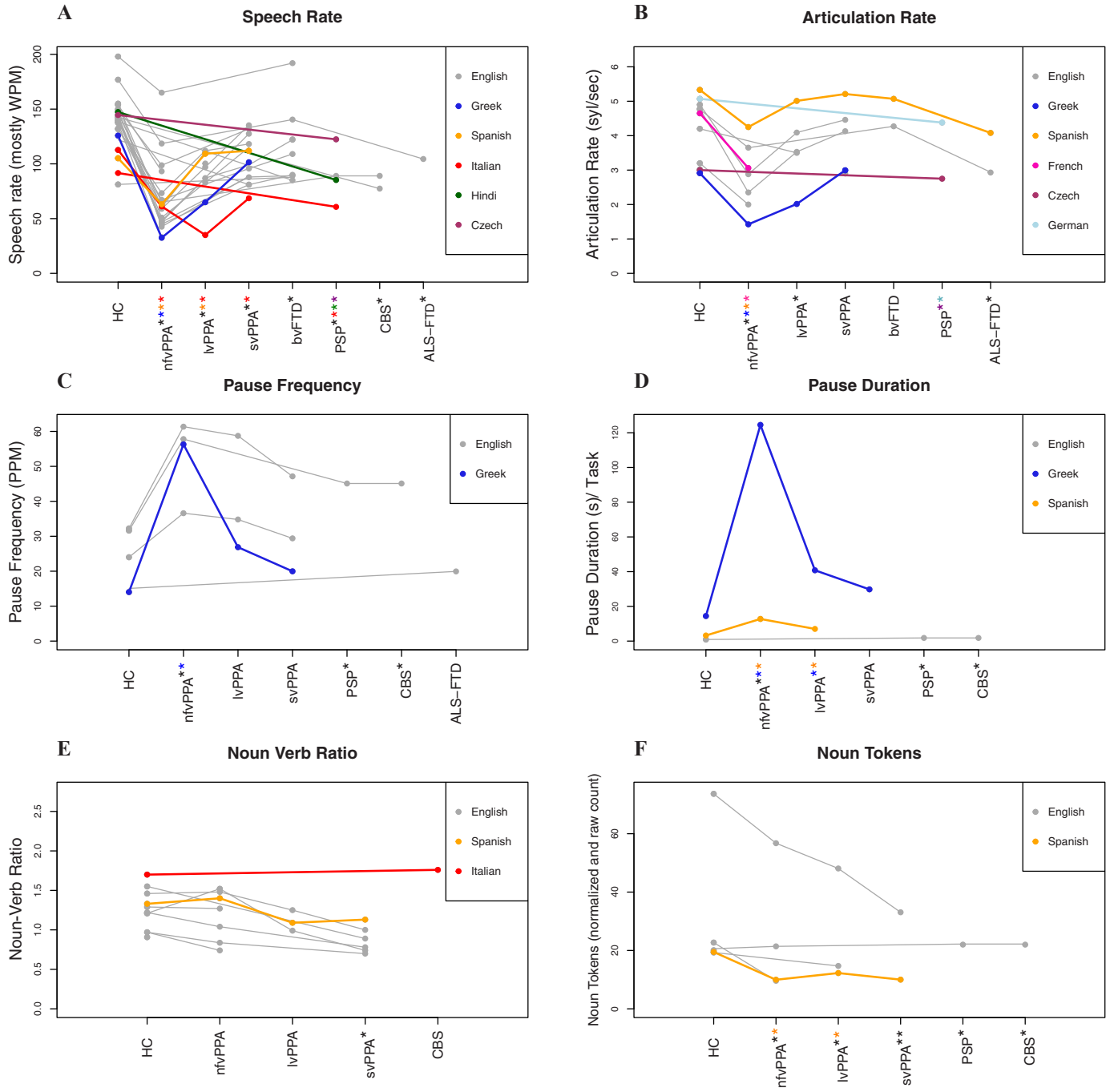

Fig. 4. The quantitative values of each paper studying the 6 most generalizable features. Lines in the plot connect groups from the same study. A) Speech rate: the papers investigating syllables per second were combined with papers investigating words per minute (after being multiplied by 60). This does not appear to have affected the results, as the highest values for speech rate do not measure syllables per second, but words per minute. B) Articulation rate: for the papers using syllables per minute or words per minute, the values were divided by 60 to compare to the values of the papers using syllables per second. C) Pause frequency: certain papers used different units of measurement, for instance, some papers used pauses per second (PPS) while others used pauses per minute (PPM). In these instances, the PPS values were multiplied by 60 to compare them to the PPM values. D) Pause duration per task (s), task duration of 1-2 minutes. E) Noun-verb ratio. F) Number of nouns shows the number of noun tokens per total words (Catricala et al., 2019; Fraser et al., 2014; Graham et al., 2004; Matias-Guiu et al., 2022; Thompson et al., 1997), per 100 words (Ash et al., 2013, 2016; Cho et al., 2022; Parjane et al., 2021), and the total count (Mack et al., 2015). Despite the variation in the units used, the values were found to be comparable on the same scale, ranging from 0 to 70 and were therefore plotted and displayed within the same graph to allow a rough comparison across studies in English and Spanish. Studies based on nouns per utterance were excluded (Ash et al., 2009) because it was not possible to compare these results with the other three metrics. See Supplemental Table 2 for full list of studies included in Fig. 4. WPM = words per minute, PPM = pauses per minute. Different languages are represented by different colors. * Shows which groups were significantly different to controls (in at least half of papers). Color of * shows which language was significantly different for which group.

Table 3a)
features with the same finding in more than one language in PPA.

Linguistic Feature	PPA/ mxPPA		Languages	nfvPPA		Languages	lvPPA		Languages	svPPA/SD		
Phonetic and Phonological												
PVI strong-weak				nfvPPA<HC**	G	EN, DU	-			-		
Pause frequency				nfvPPA>HC**	G	EN, GR	-	g	EN, GR	-	n	EN, GR
Total pause duration	PPA>HC*			nfvPPA>HC**	G	EN, GR, SP	lvPPA>HC**	G	GR, SP	-	g	GR, SP
Number of pauses	PPA>HC*		GR	nfvPPA>HC**	G	EN, SP	lvPPA>HC*					
Speech rate	PPA<HC**	n	EN, GR, SP	nfvPPA<HC**	G	EN, GR, SP, IT	lvPPA<HC**	n	EN, GR, SP, IT	svPPA<HC*	n	EN, SP, GR, IT
Articulation rate	-		GR	nfvPPA<HC**	G	EN, GR, SP, FR	lvPPA<HC**	n	EN, GR, SP	-	n	EN, SP, GR
Total speaking time				nfvPPA<HC**	G	EN, SP	lvPPA<HC*			-		
Lexico Semantic												
Nouns (token)				nfvPPA<HC**	n	EN, SP	lvPPA<HC**	G	EN, SP	svPPA<HC**	G	EN, SP
Verbs (token)				nfvPPA<HC**	n	EN, SP	-	g	EN, SP	-	g	EN, SP
Noun-verb ratio				-	g	EN, SP	-	g	EN, SP	svPPA<HC**	G	EN, SP
Noun frequency				-	g	EN, SP	-			svPPA>HC**	n	EN, SP
Nouns per 100 words				-	g	EN, SP	lvPPA<HC*	n	EN, SP	svPPA<HC**	n	EN, SP
Morphosyntactic Syntactic												
Total words	PPA>HC*			nfvPPA<HC**	G	EN, SP	-			-		
MLU	PPA>HC*			nfvPPA<HC**	G	EN, SP, IT	lvPPA<HC**	n	EN, SP, IT	-	n	EN, IT
Errors												
Number of errors/number of words				nfvPPA>HC**	G	EN, SP	lvPPA>HC*	n	EN, SP	svPPA>HC*	n	EN, SP
Word repetitions							lvPPA>HC*	G	EN, FR			
Incomplete sentences				-		-			-			
Syntactic errors				-		lvPPA>HC*			-			

Table 3b)
features with the same finding in more than one language in bvFTD, PSP, and ALS-FTD.

Linguistic Feature	bvFTD		Languages	PSP		Languages	ALS-FTD		
Phonetic and Phonological									
PVI strong-weak									
Pause frequency							-		
Total pause duration	bvFTD>HC*						ALS-FTD>HC*		
Number of pauses	bvFTD>HC*								
Speech rate	bvFTD<HC**			PSP<HC**	G	EN, CZ, IT, HI	ALS-FTD<HC*		
Articulation rate	-	g	EN, SP	PSP<HC**	G	CZ, GE	ALS-FTD<HC*	n	EN, SP
Total speaking time	-			-					
Lexico Semantic									
Nouns (token)	-			PSP>HC*					
Verbs (token)	-			-					
Number of closed-class words									
Noun:verb ratio				-					
Noun frequency									
Nouns per 100 words	bvFTD<HC*								
Morphosyntactic Syntactic									
Total words	bvFTD<HC**			PSP<HC*					
MLU	-			-					
Errors									
Number of errors/number of words	-								
Word repetitions									
Incomplete sentences	-			-					
Syntactic errors	-			PSP>HC*					

Note: - attested in at least one paper and insignificant in more than half of papers; *attested and significant in one paper and significant in half or more of papers; **attested and significant in two or more papers and significant in half or more of the papers, g: same insignificant result in more than one language, G: same significant result in more than one language, n: different result in more than one language. The features in **bold** are generalizable in more than one variant.

that such features were found to be generalizable. While phonetic and phonological features offer the most potential as interlinguistic markers of nfvPPA, inter-linguistic differences have been described in patients with nfvPPA. For instance, when comparing Italian nfvPPA patients to English nfvPPA patients, Canu et. al., 2020 found significant differences in the number of motor speech errors. In addition, work in Chinese patients with nfvPPA shows an increase in compound word production and in radical dysgraphia (substitution, transposition, omission, or addition of graphical units) relative to English patients (Tee et al., 2022). Despite differences, the findings of this review show generalizable results across language groups for phonetic and phonological features. The literature suggests that phonetic and phonological features may be broadly applicable in the Indo-European languages, in PSP as well as nfvPPA, with Hindi as an Indo-Iranian language (Potagas et al., 2022; Sachin et al., 2008), Greek as a Hellenic language (Potagas et al., 2022), Czech as a Slavic language (Daoudi et al., 2022; Rusz et al., 2015; Skrabal et al., 2020), Italian, French, and Spanish as Romance languages (Baque et al., 2022; Bouvier et al., 2021; Silveri et al., 2014), and English and German as Germanic languages (Hohlbaum et al., 2018; Parjane et al., 2021).

The lexicosemantic features of speech and language were, as expected, the most studied and generalizable features for svPPA, though they were only studied in Indo-European languages. However, lexicosemantic features also offer the potential to diagnose lvPPA. Due to its underlying pathology, lvPPA is often considered an atypical variant of Alzheimer's Disease (AD), rather than a variant of FTD. This could have constituted a reason to exclude such cases in the present review. However, as lvPPA patients are an integral clinical phenotype within the primary progressive aphasias, and as it is often a necessary challenge to differentiate nfvPPA and lvPPA at an early stage, we chose to include these cases. Moreover, findings of speech and language differences in lvPPA may inform the study of typical AD patients. For instance, the number of nouns is reduced in connected speech in both AD and lvPPA (Fraser et al., 2016; Matias-Guiu et al., 2020). Pronoun use is also increased in both lvPPA and AD (Boschi et al., 2017; Lavoie et al., 2021; Slegers et al., 2018; Wilson et al., 2010). In addition, impaired naming abilities are typically found in both disorders (Brandt et al., 2010; Evrard, 2002; Jebahi et al., 2023).

Morphosyntactic and syntactic features tend to differ across languages so it was expected that these features would be less generalizable, though they are associated with nfvPPA, which was most frequently studied. Discourse and pragmatic features were not widely studied in the reviewed papers, and definitions of cohesiveness and coherence varied greatly. However, with consistent measures, this category may still contain generalizable features of the FTD spectrum.

Defining the variants of PPA poses a challenge in the clinic, as the optimal diagnostic tools and definitions of certain speech and language abnormalities are still subject to debate. It is also likely that the criteria for PPA derived in English-speaking patients do not perfectly map onto those of non-English-speaking PPA patients (Tee et al., 2022). For instance, word repetition tasks with polysyllabic words with consonant clusters, often used in English to detect PPAOS, are not applicable for Chinese patients, as Cantonese is generally monosyllabic (Tee et al., 2022). Even within English, there is some contention regarding aspects such as motor speech, which has variable definitions depending on the authors and clinicians (Duffy et al., 2014; Grossman, 2018).

While the Indo-European languages are relatively well represented in the papers included in this review, data is lacking entirely for some major language groups. At the time of writing there are no known papers studying connected speech in FTD for the Uralic, Altaic, Caucasian, Sino-Tibetan, Tai, Austronesian, Niger-Congo, or Afro-Asiatic language families. The absence of diverse language representation in FTD research hinders tailored characterization and sensitive assessment methods for non-English speaking patients. This gap could result in delayed or misdiagnosis, and ultimately perpetuate healthcare disparities. However, some research is being carried out investigating language in FTD for these language groups. For instance, the Genetic FTD Initiative (GENFI) consortium is starting to investigate Finnish (a Uralic language). Further research is necessary to determine whether the results from Indo-European languages apply to these other major language groups.

Another consideration when investigating speech and language markers is the difference in quantitative values across different languages, as well as the variation seen within languages. It is difficult to discern which differences are due to linguistic differences and which are due to differences in methods and metrics. Differences in task use likely contribute to the observed variation within English controls. Differences in units of measurement presented significant challenges when comparing the quantitative values of features across different studies in Fig. 4. This issue was especially pronounced for "non-normalized" features such as total pause duration (Fig. 4D) and the number of noun tokens (Fig. 4F).

Additionally, FTD is a very heterogeneous group, and disease stage plays a great role. Different studies often include patients with different disease severities, which may also contribute to the observed variation within English patients. Standardization using z-scores based on norms for each language would make comparisons across languages feasible and allow us to apply findings to less-studied language groups. On the other hand, simply translating speech and language tests into another language is not always possible; for every language, linguistically and culturally equivalent tasks are necessary and should be developed to elicit valid responses (Fyndanis et al., 2017).

In alignment with the findings of García et al., (2023) on speech and language research in neurodegenerative diseases, we reiterate the need for cross-linguistic behavioral research in the FTD spectrum. Collection of data in a standardized and transparent way is vital for future comparisons across languages and disorders, in order to determine accurate baseline values to detect different disorders. This requires the adaptation of tasks for the study of connected speech to other languages. We show a clear need for further investigation of speech and language markers of the FTD spectrum in more non-English languages, especially non-Indo-European languages.

5. Limitations

Certain limitations should be taken into consideration when interpreting the findings of this systematic literature review. Firstly, the different tasks and methods used to elicit connected speech in the studies varied widely (see Fig. 2). These variations likely influenced the observed differences, highlighting the need for further research to determine potential interactions between task type, patient language, disease severity, and diagnosis. Related to this, the reviewed papers use variable units of measurement for speech and language features; without standard units of measurement, comparison between values across different papers is limited. Secondly, the sample sizes in many of the included studies were limited. This, combined with the fact that very few studies investigated connected speech in FTD patients in non-English languages, makes extrapolating findings from English-speaking to non-English-speaking populations challenging. Future research should aim to include a more diverse range of languages to improve the generalizability of the results. The high heterogeneity between studies and lack of inclusion of non-English languages also prevented a robust meta-analysis to determine the linguistic effects on effect size.

6. Conclusion

The findings of this systematic review show that while interlinguistic differences in FTD patients exist, there may indeed be features of speech and language that are generalizable across several languages. Certain phonological and lexico-semantic features offer the potential for future implementation as interlinguistic markers of FTD. Further study of these variables in different languages and across the FTD spectrum will determine the applicability of these markers in the clinic.

Competing interests

The authors declare the following competing interests: Jonathan D. Rohrer: received a grant from Bluefield Project Alzheimer's Association and receives consulting fees from Novartis, Wave Life Sciences, Prevail, Alector, Aviado Bio, Takeda, Arkuda therapeutics, and Denali Therapeutics.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105909.

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