Received: 19 July 2022 | Accepted: 29 July 2022

DOI: 10.1111/ene.15518

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Distinct disease trajectories in frontotemporal dementia–motor neuron disease and behavioural variant frontotemporal dementia: A longitudinal study

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Funding information
Australian Research Council (ARC) Future Fellowship, Grant/Award Number: FT160100096; Australian Research Council Centre of Excellence in Cognition and its Disorders, Grant/Award Number: CE110001021; National Health and Medical Research Council of Australia (NHMRC), Grant/Award Number: #1037746, #1072451 and APP1103258

Abstract

Background and purpose: The heterogeneity of cognitive and behavioural disturbances in frontotemporal dementia–motor neuron disease (FTD-MND), and clinical differences between FTD-MND and FTD subtypes, have been illustrated cross-sectionally. This study aimed to examine the FTD-MND disease trajectory by comparing clinical features of FTD-MND and the behavioural variant FTD (bvFTD) longitudinally.

Methods: Neuropsychological and disease severity assessments were conducted in a cohort of FTD-MND (baseline, $n = 42$; follow-up, $n = 18$) and bvFTD (baseline, $n = 116$; follow-up, $n = 111$) using a longitudinal, case–control design. Age-, sex-, and education-matched controls ($n = 52$) were recruited. Predictors of clinical progression were analyzed. Voxel-based morphometry analysis was undertaken to investigate the progression of brain atrophy.

Results: At baseline, FTD-MND was characterized by semantic and general cognition deficits, whereas bvFTD had greater behavioural disturbances. General cognition and language deteriorated in FTD-MND when followed longitudinally. Language deficits at baseline predicted cognitive deterioration and disease progression and correlated with progressive atrophy of language regions. Further deterioration in behaviour was evident in bvFTD over time. The rate of disease progression (i.e., general cognition, semantic association, and disease severity) was significantly faster in FTD-MND than in bvFTD.

Conclusions: FTD-MND and bvFTD appear to have distinct disease trajectories, with more rapid progression in FTD-MND. Language impairments should be closely monitored in FTD-MND as potential predictors of cognitive deterioration and disease progression.

KEYWORDS
behaviour, cognition, FTD, FTD-MND, progression pattern

INTRODUCTION

Frontotemporal dementia–motor neuron disease (FTD-MND) has been considered part of a disease spectrum that places FTD at one extreme and MND at the other [1]. Recent studies [2, 3], including our own [4, 5], have shown that FTD-MND is clinically heterogeneous, indicating that it may constitute a distinct clinicopathological entity within the range of FTD syndromes [5, 6]. Little is known about the progression of FTD-MND over time; no study has systematically explored disease progression in FTD-MND, either because of small case numbers or because of the aggregation of FTD-MND and MND into a single disease cohort.

Motor neuron disease and FTD phenotypes have distinct disease trajectories. MND patients experience progressive cognitive decline over time, independent of behavioural changes [7], but only in those who present with cognitive deficits at baseline [8]. In contrast, disease progression in behavioural variant FTD (bvFTD) is associated with worsening of negative behavioural symptoms (e.g., apathy and loss of empathy) as the disease progresses, and a reduction of positive behavioural symptoms (e.g., stereotyped behaviour and hyperorality) [9, 10]. Cognitively, executive, attention, language, and memory deficits become more prominent in this population, although visuospatial skills tend to remain relatively intact [11]. Whether similar disease progression trajectories occur in FTD-MND is currently unknown.

In this study, we aimed to explore the following questions: (i) How does the clinical (cognitive, behavioural) profile evolve with disease progression in FTD-MND? (ii) Does the pattern of progression in FTD-MND differ from that observed in bvFTD? (iii) Which variables, if any, predict cognitive decline and disease progression in FTD-MND? and (iv) How do cortical changes progress in FTD-MND?

MATERIALS AND METHODS

Participants

In total, 210 participants with baseline assessments were recruited for this study; 42 patients had FTD-MND, 116 patients had bvFTD, and 52 participants were healthy controls. The bvFTD and control groups were matched to the FTD-MND group for age, education, and sex distribution. Controls were recruited randomly matched for age, gender, and education in years to bvFTD and FTD-MND patients. The number of matched controls was chosen to lie between the number of FTD-MND and bvFTD patients to minimize the potential for statistical bias. Follow-up assessment data were available for 18 patients with FTD-MND and 111 patients with bvFTD. The progression interval (i.e., time from baseline to follow-up assessment) varied between FTD-MND and bvFTD across tasks, with 12.8–16.7 months in bvFTD and 7–12 months in FTD-MND (details in Table S2). Survival duration was defined as the time in months between symptoms onset and death; it was treated as a missing variable for patients who were living at the time of data analysis. Diagnoses of probable bvFTD and of MND were established in accordance with current consensus diagnostic criteria [12–14]. Patients were diagnosed with FTD-MND when they met both FTD and MND diagnostic criteria [15]. For the patients who were diagnosed with FTD-MND after presenting with either FTD or MND, only the data that followed the reclassification were included in the study.

Exclusion criteria included prior lifelong history of mental illness, significant head injury, extensive cerebrovascular disease, movement disorders (e.g., clear-cut Parkinson disease), alcohol, and other drug abuse. Patients with a diagnosis of possible bvFTD (as opposed to probable), which covers a range of clinical presentations, patterns, and rates of disease progression [16], were excluded. Patients diagnosed with the right temporal variant of FTD were excluded from the study to avoid bias of voxel-based morphometry (VBM) analyses due to severe right anterior temporal atrophy characteristic of that phenotype. The presence of extrapyramidal symptoms and/or signs in patients who met the diagnostic criteria for FTD-MND or bvFTD were not treated as exclusion criteria.

Ethical approval was granted by the ethics committees of the University of New South Wales and South Eastern Sydney Local Health District. Written informed consent was provided from all participants or their carers in accordance with the Declaration of Helsinki.

Cognition, disease stage and severity, and behavioural and language assessments

The Addenbrooke Cognitive Examination–version III (ACE-III) total score and attention and orientation, memory, verbal fluency, language, and visuospatial subscores [17] were used to determine the cognitive profile of all participants. Disease stage and severity were assessed using the Clinical Dementia Rating–Frontotemporal Lobar Degeneration (CDR-FTLD) [18] and Frontotemporal Dementia Rating Scale (FRS) [19]. Specifically, the CDR-FTLD was used for general dementia staging and the FRS for staging of behaviour and functional ability.

Behavioural changes were assessed using the Cambridge Behavioural Inventory–Revised (CBI-R) [20]. Language abilities such as confrontation naming, single word comprehension, single word repetition, and semantic association were measured using the Sydney Language Battery (SYDBAT) [21]. The single word repetition component of the SYDBAT was excluded from the total score to avoid the potential confounding effects of dysarthria. Syntactic (i.e., sentence) comprehension was evaluated using the Test for Reception of Grammar (TROG) [22].

Statistical analysis

Categorical variables (e.g., sex) were examined using chi-squared tests. Due to the unequal sample size across groups, groupwise comparisons were performed using the Kruskal–Wallis test,

whereas the Mann–Whitney *U*-test was used for post hoc pairwise comparisons. A *p*-value <0.05 was considered statistically significant. Analysis of covariance (ANCOVA) was used to control for the potential confounding effect of onset duration between FTD-MND and bvFTD at baseline. To avoid potential confounding effect of sample size, a permutational ANCOVA (permANCOVA) was conducted. This approach randomly selects the least number of cases, based on the smallest sample size at baseline (i.e., $n = 42$ in FTD-MND) across all groups, and runs each permutation 1000 times. permANCOVA results remained consistent with ANCOVA (Table S1). For simplicity, the original ANCOVA results are therefore presented. To rule out potential confounding effects of a variable progression interval, limited statistical power, and uneven sample size between bvFTD and FTD-MND, the rate of decline on cognitive and behavioural measures from baseline to follow-up assessment was calculated for individual patients with Mann–Whitney *U*-test [23] for pairwise comparison, following an approach used in previous studies of MND [24] and bvFTD [25]. Specifically:

$$\Delta\text{ACE} - \text{III total} = \frac{(\text{ACE} - \text{III score at follow} - \text{up}) - (\text{ACE} - \text{III score at baseline})}{\text{Time interval in months}}$$

To illustrate the pattern of progression in each disease group on a spider chart, the rates of progression were normalized as a percentage of the maximum score for each measure.

To examine predictors of cognition dysfunction and disease progression in each disease group, bivariate correlation analysis using Pearson *r* was conducted. Variables exhibiting a correlation with ΔACE-III total or ΔCDR-FTLD at a threshold of $p < 0.1$ were considered candidate predictors of disease progression. Candidate predictors were then used in a linear regression analysis using an "enter" model to identify predictors of cognitive dysfunction and disease progression.

Neuroimaging acquisition and analysis

At baseline, 32 FTD-MND patients, 36 bvFTD patients, and 37 age- and sex-matched control participants had available magnetic resonance imaging (MRI) data; these patients were included in the VBM analysis. The FTD-MND and bvFTD groups were matched for onset duration (time from symptom onset to baseline assessment). At follow-up, 11 FTD-MND and 11 bvFTD patients, matched for scan interval (i.e., time interval between baseline and follow-up scans), had available MRI data and were included for VBM analyses. The mean scan interval was 0.87 ± 0.39 years in FTD-MND and 0.85 ± 0.19 years in bvFTD ($p = 0.87$). Participants underwent whole brain T1-weighted imaging on a 3-T Philips MRI scanner using the following sequences: coronal orientation, matrix = 256×256, 200 slices, 1-mm slice thickness, 1-mm^2 in-plane resolution, echo time/repetition time = 2.6/5.8 ms, flip angle $\alpha = 8°$. VBM analysis was conducted using the FSL package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Brain extraction of structural images was conducted using the FSL Brain Extraction Tool [26], followed by tissue segmentation with automatic segmentation FMRIB's Automated Segmentation Tool (FAST) [27]. Grey matter volume maps were then registered to Montreal Neurological Institute standard space (MNI152) using nonlinear registration FMRIB's Nonlinear Registration Tool (FNIRT) [28], with a b-spline representation of the registration warp field [29]. Baseline scans were used to generate a study-specific template. Age was used as a nuisance variable for VBM comparisons with controls at baseline, and comparisons between baseline and follow-up in disease groups (e.g., FTD-MND baseline vs. FTD-MND follow-up). In addition, age together with onset duration, and age together with scan interval, were applied as nuisance variables for comparisons between FTD-MND and bvFTD at baseline and follow-up, respectively.

A whole brain general linear model was used to examine progression patterns of grey matter atrophy in patients with FTD-MND and bvFTD. Nonparametric permutation *t*-tests were conducted with 5000 permutations per contrast [30] for both VBM analyses. All clusters were extracted voxelwise at $p < 0.01$ corrected for false discovery rate with a cluster extent threshold of 100 contiguous voxels. The anatomical distribution of statistically significant results was overlaid on MNI standard space. The Harvard-Oxford Cortical Structure and Subcortical Structure atlases were used as references for grey matter labels.

RESULTS

Demographics and baseline profiles

Onset duration (i.e., time from symptom onset to baseline assessment) and progression interval (i.e., time from baseline to follow-up assessment) were found to differ between FTD-MND and bvFTD groups on multiple tasks. Details are presented in Table S2.

Group demographics and profiles of cognition and disease stage at baseline are presented in Table 1. The FTD-MND group did not differ from the bvFTD group in terms of age at symptom onset but did have a significantly shorter survival duration from symptom onset ($p < 0.001$). More severe behavioural disturbance and functional ability, reflected in a reduced FRS logit score, was found in bvFTD ($p = 0.05$). There was no significant difference in the CDR-FTLD Sum of Boxes (SoB) or subdomains between disease groups.

Both FTD-MND and bvFTD groups displayed significant overall cognitive impairment compared to controls, reflected in lower scores across all components of the ACE-III (all *p*-values <0.001). The FTD-MND group performed worse on the ACE-III total and ACE-III language compared to bvFTD (both *p*-values <0.05), even after controlling for the potential confounding effects of duration of symptoms from onset to baseline assessment.

Language impairments were also present in both FTD-MND and bvFTD groups compared to controls, reflected by poorer performance on the SYDBAT and TROG (all *p*-values <0.01; Table 2).

TABLE 1 Demographic and baseline profiles of cognition and disease staging in study sample

	FTD-MND, $n = 42$	bvFTD, $n = 116$	Controls, $n = 52$	Overall p
Age, years	66.14 ± 7.97	67.72 ± 8.55	68.29 ± 7.74	NS
Education, years	12.46 ± 3.20	11.88 ± 2.84	12.38 ± 2.06	NS
Sex, male, *n* (%)	31 (73.8%)	73 (62.9%)	34 (65.4%)	NS
Age at onset, years	60.9 ± 7.81	58.31 ± 8.22	N/A	NS
Survival duration, months	57.61 ± 39.43	105.7 ± 47.66	N/A	**
ACE-III				
Attention (18)	14.76 ± 3.46[a]	14.88 ± 3.09[a]	17.3 ± 0.57[b,c]	**
Memory (26)	17.26 ± 5.88[a]	17.94 ± 5.51[a]	24.42 ± 1.85[b,c]	**
Fluency (14)	4.29 ± 3.74[a]	6.12 ± 3.86[a]	11.71 ± 1.46[b,c]	**
Language (26)	18.31 ± 5.14[a,b]	21.41 ± 4.76[a,c]	25.3 ± 0.95[b,c]	**
Visuospatial (16)	13.11 ± 2.9[a]	13.91 ± 2.4[a]	15.45 ± 0.9[b,c]	**
Total (100)	67.37 ± 17.01[a,b]	74.09 ± 15.83[a,c]	94.16 ± 3.1[b,c]	**
FRS logit score (5.39)	0.1 ± 1.67[b]	−0.55 ± 1.44[c]	N/A	N/A
FRS stage, *n*				
Very mild	2	0	0	
Mild	1	3	0	
Moderate	19	55	0	
Severe	10	49	0	
Very severe	1	7	0	
Profound	0	0	0	
CDR-FTLD				
Memory (3)	0.59 ± 0.5[a]	0.94 ± 0.71[a]	0.12 ± 0.22[b,c]	**
Orientation (3)	0.48 ± 0.52[a]	0.93 ± 0.69[a]	0 ± 0[b,c]	**
Judgement (3)	0.84 ± 0.68[a]	1.45 ± 0.92[a]	0 ± 0[b,c]	**
Community (3)	0.75 ± 0.53[a]	1.14 ± 0.83[a]	0 ± 0[b,c]	**
Home hobbies (3)	0.84 ± 0.59[a]	1.35 ± 0.87[a]	0 ± 0[b,c]	**
Personal care (3)	0.45 ± 0.67[a]	0.93 ± 1.03[a]	0 ± 0[b,c]	**
Behaviour (3)	0.73 ± 0.78[a]	1.34 ± 0.88[a]	0 ± 0[b,c]	**
Language (3)	1.2 ± 0.73[a]	1.04 ± 0.96[a]	0.05 ± 0.15[b,c]	**
CDR-FTLD sum of box	5.89 ± 3.28[a]	9 ± 5.3[a]	0.17 ± 0.33[b,c]	**

Note: Data are displayed as mean ± SD except as indicated. Overall *p* indicates the significance of overall group differences. Where relevant, parentheses indicate the possible maximum score. Analyses of covariance were conducted to control the potential confounding effects of onset duration.

Abbreviations: ACE-III, Addenbrooke Cognitive Examination–version III; bvFTD, behavioural variant FTD; CDR-FTLD, Clinical Dementia Rating–Frontotemporal Lobar Degeneration; FRS, Frontotemporal Dementia Rating Scale; FTD-MND, frontotemporal dementia–motor neuron disease; N/A, not applicable; NS, nonsignificant.

[a]Post hoc test vs. controls ($p < 0.05$).

[b]Post hoc test vs. bvFTD ($p < 0.05$).

[c]Post hoc test vs. FTD-MND ($p < 0.05$).

**$p < 0.01$.

The FTD-MND group was more impaired than the bvFTD group on the SYDBAT total and confrontation naming subtest (both *p*-values <0.05), with a trend for greater impairment in single word comprehension ($p = 0.065$) and single word repetition ($p = 0.08$) subsets, even after controlling for the duration of symptoms at baseline assessment. No significant difference was found between FTD-MND and bvFTD on TROG total score. In contrast, behavioural changes on the CBI-R were more pronounced in bvFTD relative to FTD-MND, predominantly on CBI-R subdomains of abnormal behaviours, eating habits, and motivation (all *p*-values <0.05; CBI-R total: $p = 0.057$; Table 2).

Progression in disease groups

Rates of progression in cognitive and behavioural disturbances across disease groups are presented in Table 3. The rates of change in overall cognition (ΔACE-III total) and disease severity (ΔCDR-FTLD SoB) were significantly faster in FTD-MND than in bvFTD (both *p*-values <0.05), as was the decline on the semantic association subtest of the SYDBAT ($p < 0.05$; Figure 1). In contrast, the rate of progression in terms of behavioural disturbances (i.e., ΔCBI-R) was comparable in FTD-MND and bvFTD ($p = 0.173$).

Predictors for clinical progression

Candidate predictors for cognitive decline and disease progression were determined for each disease group using correlation analyses. The results of correlation analyses are presented in Table S3 for FTD-MND and Table S4 for bvFTD. Candidate predictors were entered into separate linear regression analyses for each disease group.

Performance on tests of language were found to be predictors of both cognitive decline and disease progression in FTD-MND. Specifically, SYDBAT semantic association predicted decline in general cognition as reflected by ΔACE-III total ($p < 0.05$, $\beta = 0.899$,

TABLE 2 Baseline profiles of behaviour and language in study sample

	FTD-MND, $n = 42$	bvFTD, $n = 116$	Controls, $n = 52$	Overall *p*
CBI-R				
Memory and orientation	39.81 ± 22.57[a]	44.21 ± 21.88[a]	8.91 ± 9.21[b,c]	**
Everyday skills	28.02 ± 23.29[a]	29.64 ± 24.78[a]	0.75 ± 2.13[b,c]	**
Self-care	10.94 ± 17.61[a]	12.81 ± 22.16[a]	0 ± 0[b,c]	**
Abnormal behaviours	22.19 ± 19.89[a,b]	35.75 ± 24.01[a,c]	3.13 ± 5.06[b,c]	**
Mood	24.06 ± 22.76[a]	30.35 ± 22.7[a]	3.75 ± 5.26[b,c]	**
Beliefs	5.42 ± 13.15[a]	9.49 ± 17.41[a]	0.42 ± 2.64[b,c]	**
Eating habits	28.28 ± 27.66[a,b]	42.46 ± 29.26[a,c]	4.22 ± 8.88[b,c]	**
Sleep	33.75 ± 28.76[a]	42.46 ± 31.49[a]	13.44 ± 16.6[b,c]	**
Stereotypic and motor behaviours	40.94 ± 29.07[a]	44.83 ± 28.66[a]	8.91 ± 17.21[b,c]	**
Motivation	42.88 ± 31.07[a,b]	60.83 ± 31.22[a,c]	4.25 ± 6.36[b,c]	**
Total	29.11 ± 16.42[a]	36.9 ± 16.66[a]	4.68 ± 4.67[b,c]	**
SYDBAT				
Naming (30)	16.91 ± 7.46[a,b]	20.44 ± 5.89[a,c]	27.05 ± 1.7[b,c]	**
Repetition (30)	25.61 ± 5.46[a]	28.35 ± 4.08[a]	29.83 ± 0.44[b,c]	**
Comprehension (30)	23.68 ± 4.87[a]	25.17 ± 4.8[a]	29.33 ± 1.24[b,c]	**
Semantic association (30)	22.48 ± 5.42[a]	23.33 ± 5.09[a]	28.23 ± 1.46[b,c]	**
Total (90, no repetition)	64.07 ± 15.4[a,b]	70.49 ± 12.16[a,c]	84.65 ± 3.75[b,c]	**
TROG				
Total corrected (40)	27.4 ± 10.08[a]	29.38 ± 7.69[a]	39.09 ± 0.61[b,c]	**

Note: Data are displayed as mean ± SD. Overall *p* indicates the significance of overall group differences. Where relevant, parentheses indicate the possible maximum score. Analyses of covariance were conducted to control the potential confounding effects of onset duration.

Abbreviations: bvFTD, behavioural variant FTD; CBI-R, Cambridge Behavioural Inventory–Revised; FTD-MND, frontotemporal dementia–motor neuron disease; SYDBAT, Sydney Language Battery; TROG, Test for Reception of Grammar.

[a]Post hoc test vs. controls ($p < 0.05$).

[b]Post hoc test vs. bvFTD ($p < 0.05$).

[c]Post hoc test vs. FTD-MND ($p < 0.05$).

**$p < 0.01$.

TABLE 3 Rate of progression in FTD-MND and bvFTD

	FTD-MND, $n = 18$	bvFTD, $n = 111$	p
ΔACE-III total	−1.92 ± 1.74	−0.65 ± 1.21	*
ΔFRS logit score	−0.08 ± 0.22	−0.09 ± 0.12	NS
ΔCDR-FTLD SoB[a]	0.47 ± 0.39	0.22 ± 0.4	*
ΔCBI-R[a]			
Abnormal behaviour	0.41 ± 16.79	0.41 ± 2.12	NS
Eating habits	−8.79 ± 26.42	0.65 ± 2.92	NS
Stereotypic and motor behaviours	4.06 ± 16.65	0.4 ± 2.25	NS
Motivation	2.75 ± 28.27	0.62 ± 3.86	NS
Total	1.41 ± 9.79	0.64 ± 1.4	NS
ΔSYDBAT			
Naming	−0.06 ± 0.46	−0.09 ± 0.34	NS
Comprehension	−0.17 ± 0.38	−0.16 ± 0.45	NS
Semantic association	−0.54 ± 0.48	−0.12 ± 0.46	*
Total	−0.42 ± 1.11	−0.4 ± 1.17	NS
ΔTROG			
Total corrected	−0.56 ± 0.62	N/A[b]	N/A

Note: Data are presented as mean ± SD and calculated as points/month; p indicates the significance of disease groups differences. CBI-R subdomains of abnormal behaviour, eating habits, stereotypic and motor behaviours, and motivation are previously reported to be sensitive to FTD patients [47]. Mann–Whitney *U*-tests were used to compare progression rate between FTD-MND and bvFTD.

Abbreviations: ACE-III, Addenbrooke Cognitive Examination–version III; bvFTD, behavioural variant FTD; CBI-R, Cambridge Behavioural Inventory–Revised; CDR-FTLD, Clinical Dementia Rating–Frontotemporal Lobar Degeneration; FRS, Frontotemporal Dementia Rating Scale; FTD-MND, frontotemporal dementia–motor neuron disease; N/A, not applicable; NS: nonsignificant; SoB, Sum of Boxes; SYDBAT, Sydney Language Battery; TROG, Test for Reception of Grammar.

[a]Higher score indicates more impaired.

[b]Only one bvFTD patient had TROG assessment at follow-up.

*$p < 0.05$.

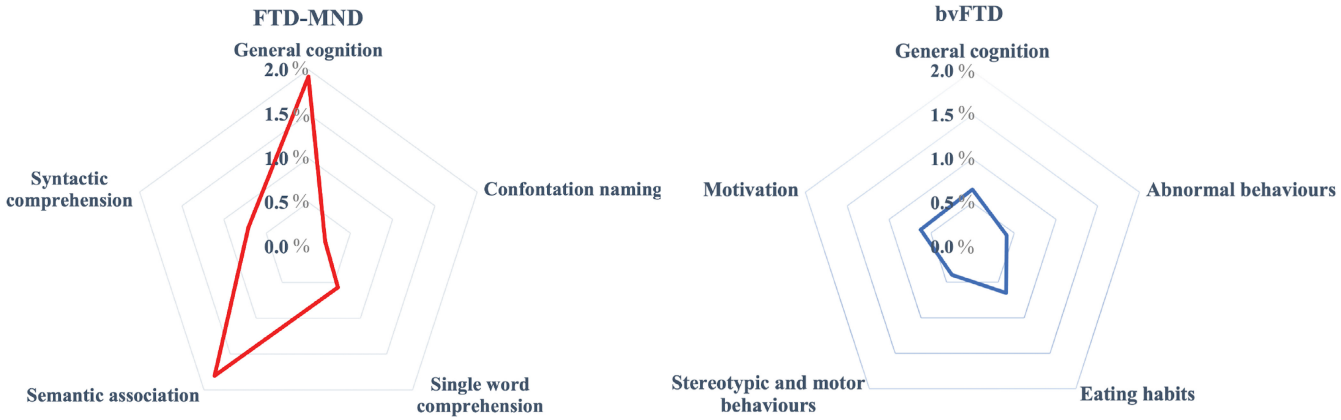

FIGURE 1 The rate of progression on dominant domains in each disease group. The number labels are the normalized percentage of progression rate (see Materials and Methods). As the progression on behavioural changes is highly variable in frontotemporal dementia–motor neuron disease (FTD-MND), as reflected by the high values of SD for difference in Cambridge Behavioural Inventory–Revised score, mean values of progression rate on general cognition and language progression pattern are illustrated here. bvFTD, behavioural variant FTD [Colour figure can be viewed at wileyonlinelibrary.com]

95% confidence interval [CI] = 0.044–0.480), whereas TROG total predicted disease progression as reflected by ΔCDR-FTLD SoB ($p < 0.05$, $\beta = -0.632$, 95% CI = −0.044 to −0.002). The regression models explained 58.2% and 39.9% of the variance in progression of cognitive deficits and overall disease progression, respectively (Table 4).

Meanwhile, in bvFTD, there was a trend for SYDBAT semantic association as a potential predictor for ΔACE-III total ($p = 0.052$,

$\beta = 0.625$, 95% CI = −0.001 to 0.298), and ACE-III fluency predicted disease progression, as reflected in the ΔCDR-FTLD SoB ($p < 0.05$, $\beta = -0.257$, 95% CI = −0.046 to −0.007). The regression models explained 5.7% and 36.2% of the variance in progression of cognitive deficits and overall disease progression, respectively (Table 4).

Neuroimaging progression profile

At baseline, the FTD-MND and bvFTD groups had widespread brain atrophy compared to controls, involving the frontal and temporal lobes, the peri-insular regions, and the basal ganglia (Table 5). The FTD-MND group had greater atrophy of bilateral anterior temporal lobe and precentral gyrus, compared with the bvFTD group, but less atrophy in the bilateral midposterior cingulate gyrus (Table 5, Figure 2).

Despite a relatively short time period between the initial and follow-up scans, progressive atrophy was detectable in FTD-MND but not bvFTD. Specifically, the FTD-MND group developed atrophy of the bilateral inferior frontal gyrus and precentral gyrus, as well as left temporal pole, at follow-up compared to baseline (Table 6, Figure 2). In contrast, no significant differences in atrophy at baseline and follow-up were observed in the bvFTD group. At follow-up, the FTD-MND group had more left-lateralized atrophy in the inferior frontal gyrus, anterior temporal lobe, and angular gyrus than the bvFTD group (Table 6, Figure 2).

DISCUSSION

To our knowledge, the present study is the first to systematically investigate the progression of cognitive and behavioural deficits in FTD-MND. As expected, cognitive and behavioural deficits, and disease severity, progressed over time, but the rate of deterioration differed across cognitive and behavioural domains. In FTD-MND, deterioration in general cognition and language predominated. Furthermore, language abilities appeared to predict cognitive deterioration and disease progression in FTD-MND; this finding was indirectly supported by the demonstration of progressive atrophy of cortical regions important for language. In contrast, the bvFTD group displayed more pronounced behavioural disturbances over time, in the context of more gradual progression of general cognitive and behavioural disturbances. Notably, general cognition, semantic association, and disease severity appeared to deteriorate at a significantly faster rate in FTD-MND relative to bvFTD. Taken together, our findings support the view that, although related, FTD-MND and bvFTD are distinct clinical entities with divergent clinical profiles over time.

FTD-MND typically starts with variable combinations of behavioural, cognitive, or motor dysfunction [2, 4]. Once the diagnostic criteria for FTD-MND are fulfilled, the clinical presentation is multimodal and heterogeneous, probably reflecting widespread brain atrophy [4]. FTD-MND progresses rapidly, with much shorter survival and worse prognosis than FTD phenotypes [31–33]. The present study demonstrated that general cognition and some aspects of language (semantic association, syntactic comprehension) declined most rapidly in FTD-MND. By contrast, progression of behavioural deficits in FTD-MND was more variable, highlighting clinical heterogeneity.

On the neural level, we found that as the disease progressed in FTD-MND, atrophy extended posteriorly, and involvement of motor areas and language centres became more pronounced. In particular, the left temporal pole and inferior frontal gyrus, the brain regions involved in semantic processing and syntactic comprehension,

TABLE 4 Predictors for general cognition and disease progression in FTD-MND and bvFTD

Predictor	β	p	95% CI for hazard ratio	R^2
FTD-MND				
ΔACE-III total				0.582
SYDBAT comprehension	−0.175	0.618	−0.295 to 0.184	
SYDBAT semantic association	0.899	0.023	0.044 to 0.480	
ΔCDR-FTLD SoB				0.399
TROG corrected total	−0.632	0.037	−0.044 to −0.002	
bvFTD				
ΔACE-III total				0.379
SYDBAT naming	0.182	0.543	−0.091 to 0.166	
SYDBAT comprehension	−0.193	0.572	−0.227 to 0.129	
SYDBAT semantic association	0.625	0.052	−0.001 to 0.298	
ΔCDR-FTLD SoB				0.057
ACE-III attention	−0.074	0.493	−0.033 to 0.016	
ACE-III memory	0.056	0.600	−0.011 to 0.018	
ACE-III fluency	−0.257	0.008	−0.046 to −0.007	

Abbreviations: ACE-III, Addenbrooke Cognitive Examination–version III; bvFTD, behavioural variant FTD; CDR-FTLD, Clinical Dementia Rating–Frontotemporal Lobar Degeneration; CI, confidence interval; FTD-MND, frontotemporal dementia–motor neuron disease; SoB, Sum of Boxes; SYDBAT, Sydney Language Battery.

TABLE 5 Profile of grey matter atrophy in FTD-MND and bvFTD at baseline

Contrast name	Regions	Side	Voxels, *n*	Peak MNI coordinates			*t*
				x	y	z	
Controls < FTD-MND	Superior/middle/inferior temporal gyrus, temporal pole, peri-insular regions, superior/middle/inferior frontal gyrus, frontal pole, frontal orbital cortex, frontal medial cortex, subcallosal cortex, precentral/postcentral gyrus, caudate, putamen, thalamus, amygdala, accumbens, hippocampus, parahippocampal gyrus, cingulate gyrus, precuneus cortex, lingual gyrus, angular gyrus, supramarginal gyrus, lateral occipital cortex, occipital pole, cerebellum I–IV, V, VI, VIIb, VIIIa, crus I, II	Bilateral	74,958	−30	−70	−60	3.72
	Cerebellum V, VI, VIIb, crus I, II	Right	3239	34	−66	−62	3.72
	Superior lateral occipital cortex, superior parietal lobule	Right	173	−10	−46	−50	3.72
Controls < bvFTD	Superior/middle/inferior temporal gyrus, temporal pole, peri-insular regions, superior/middle/inferior frontal gyrus, frontal pole, frontal orbital cortex, frontal medial cortex, subcallosal cortex, precentral/postcentral gyrus, caudate, putamen, thalamus, amygdala, accumbens, hippocampus, parahippocampal gyrus, cingulate gyrus, paracingulate gyrus, precuneus cortex, lingual gyrus, angular gyrus, supramarginal gyrus, lateral occipital cortex, occipital pole, cerebellum V, VI, VIIb, VIIIa, crus I, II	Bilateral	88,837	34	−66	−62	3.71
	Superior lateral occipital cortex	Right	130	26	−62	64	3.71
bvFTD < FTD-MND	Anterior superior/middle temporal gyrus, temporal pole, anterior parahippocampal gyrus	Left	1218	−26	−6	−38	3.73
	Precentral gyrus, juxtapositional lobule cortex	Bilateral	539	0	−24	50	3.73
	Temporal pole, anterior parahippocampal gyrus	Right	413	24	0	−34	3.73
FTD-MND < bvFTD	Posterior cingulate gyrus, precuneus cortex	Bilateral	604	−4	−48	12	3.73
	Superior lateral occipital cortex	Right	109	16	−68	48	3.73

Note: Age was used as a covariate in voxel-based morphometry analysis for comparisons with controls. Age and onset duration were used as covariates for comparisons between FTD-MND and bvFTD. Significant clusters were reported voxelwise at $p < 0.01$ corrected for false discovery rate, with a cluster extent threshold of 100 contiguous voxels. Peak MNI coordinates indicate the coordinates of the voxel that had the most grey matter atrophy in each significant cluster.

Abbreviations: bvFTD, behavioural variant FTD; FTD-MND, frontotemporal dementia–motor neuron disease; MNI, Montreal Neurological Institute standard space.

respectively [34–36], showed progression of atrophy in FTD-MND as disease progressed. Our results are broadly consistent with previous findings that reported progressive involvement of the bilateral premotor cortex, primary motor cortex, and parietal lobe (i.e., Brodmann areas 4, 6, and 7) over a mean time period of 5.3 months [37]. The present study confirmed these results, albeit with a larger cohort of patients and a longer period of follow-up (mean = 10.4 months). These patterns of progressive atrophy mesh well with the clinical and cognitive changes observed here.

Both the FTD-MND and bvFTD groups in the present study exhibited behavioural disturbances at initial assessment, although they were less pervasive in FTD-MND. This finding aligns with previous studies [4, 38] that showed more frequent disinhibition, loss of sympathy/empathy, stereotypic behaviours, and changes in eating habits in bvFTD than in FTD-MND [39], and that behavioural disturbance overall is more severe in bvFTD [40]. With disease progression, the nature of behavioural disturbances differed in FTD-MND and bvFTD, even though no statistical significance was identified, as behavioural change is highly variable and fluctuant in FTD-MND. This finding is in keeping with previous studies of bvFTD that showed multimodal dysfunction of behaviour and language with disease progression [41]. Importantly,

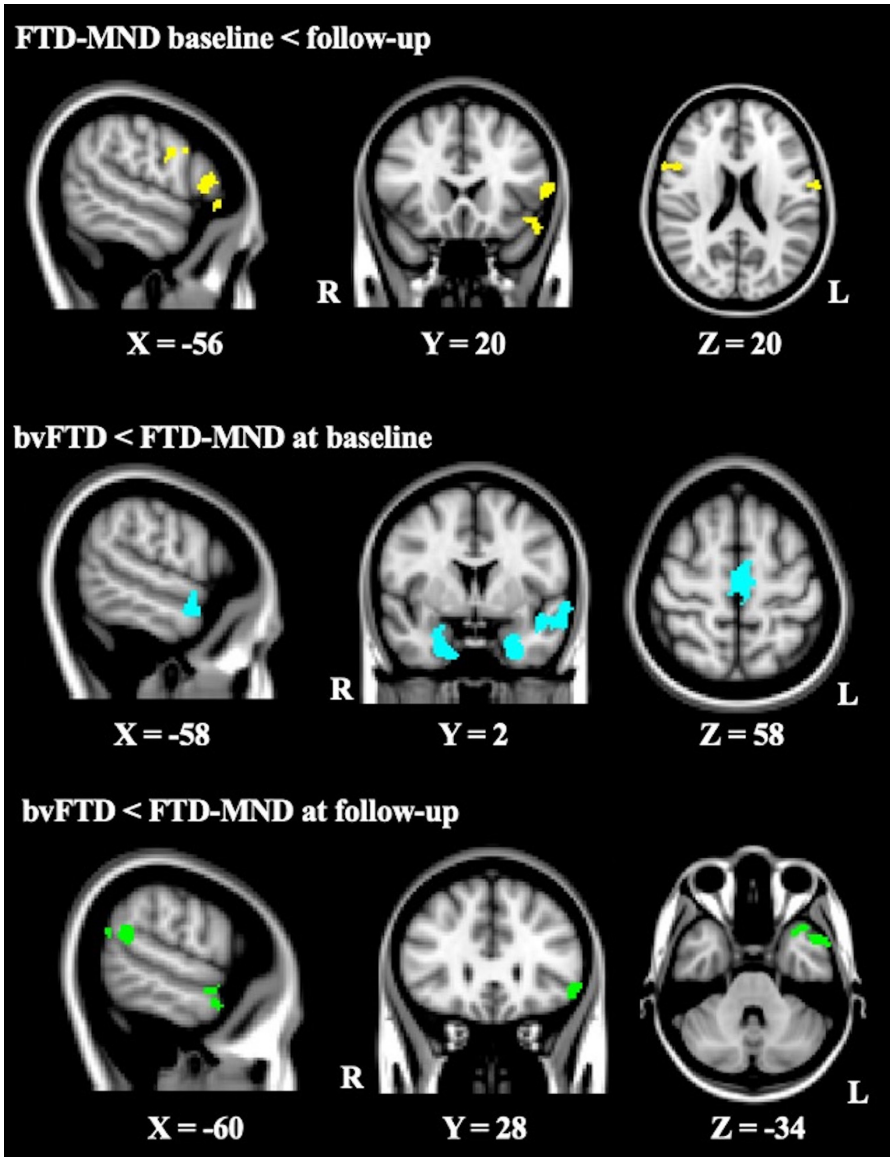

FIGURE 2 Progression pattern of atrophy in frontotemporal dementia–motor neuron disease (FTD-MND). Clusters are overlaid on the Montreal Neurological Institute standard brain. Age was included as a covariate in voxel-based morphometry (VBM) analysis for comparing FTD-MND baseline and follow-up. Age and onset duration were used as covariates in VBM for comparisons between FTD-MND and behavioural variant FTD (bvFTD) both at baseline and at follow-up. The upper panel illustrates differences in grey matter intensity in FTD-MND at follow-up relative to baseline. The middle panel illustrates differences in grey matter intensity between FTD-MND and bvFTD at baseline. The bottom panel illustrates differences in grey matter intensity in FTD-MND relative to bvFTD at follow-up. L, left; R, right. Coloured voxels show cortical regions that were significant in VBM at voxelwise $p < 0.01$ false discovery rate corrected [Colour figure can be viewed at wileyonlinelibrary.com]

these studies related the progression of behavioural disturbances to encroachment of atrophy into temporal and parietal regions, especially the anterior temporal region, and subcortical brain areas (e.g., amygdala, caudate) [42–46].

The pattern and pace of cognitive and behavioural deterioration in FTD-MND have not been studied previously to our knowledge. The current study suggested that factors predicting disease progression differ between FTD-MND and bvFTD. Specifically, progression in general cognition and disease severity may be partially predicted by semantic knowledge and syntactic comprehension dysfunction deterioration in FTD-MND, respectively, and executive deficits and semantic knowledge dysfunction appear to predict disease progression and cognitive deterioration in bvFTD, respectively. The amount of variance explained by these models is highly variable and seemed more useful in predicting ACE-III decline in FTD-MND. Models were less robust in predicting CDR-FTLD decline in bvFTD, a finding that is somewhat at odds with a recent study [25] indicating more rapid disease progression in bvFTD in the presence of known pathogenic mutations in *C9orf7*, *MAPT*, and *GRN*. Furthermore, the well-acknowledged progressive atrophy pattern in bvFTD was distinct with this study's findings in FTD-MND.

In terms of limitations, detailed motor system assessments, the results of genetic testing, and detailed pathological characterization were not available for the present study cohort, making it difficult to explore links between motor involvement/genetic abnormalities/pathological subtyping and disease progression in FTD-MND. The number of FTD-MND cases with complete follow-up data and imaging was relatively small, potentially because the disease is rare and rapid deterioration is common. As such, a possible selection bias, with the inadvertent exclusion of very rapidly progressive cases, cannot be excluded. In addition, FRONTIER specifically focuses on patients who present with cognitive and/or behavioural disturbances, meaning that a cohort of cognitively and behaviourally normal MND patients was not available for inclusion in the present study. Nonetheless, this study is the first to systematically

TABLE 6 Grey matter intensity changes in FTD-MND and bvFTD at follow-up relative to baseline

Contrast name	Regions	Side	Voxels, *n*	Peak MNI coordinates x	y	z	*t*
FTD-MND baseline < follow-up	Superior lateral occipital cortex	Left	385	−22	−82	38	3.85
	Precentral/postcentral gyrus	Left	185	−68	−4	18	3.47
	Inferior frontal gyrus	Left	125	−56	22	8	3.61
	Temporal pole, frontal orbital cortex	Left	107	−52	24	−22	3.47
	Inferior frontal gyrus, precentral gyrus	Right	100	64	14	22	3.47
bvFTD baseline < follow-up	No significant clusters						
bvFTD < FTD-MND at follow-up	Temporal pole	Left	296	−40	20	−40	4.20
	Angular gyrus, posterior supramarginal gyrus	Left	157	−58	−52	18	4.20
	Inferior frontal gyrus, frontal orbital cortex	Left	136	−52	24	−22	3.91
	Anterior superior/middle temporal gyrus	Left	113	−62	4	−22	3.45
FTD-MND < bvFTD at follow-up	No significant clusters						

Note: Age was used as a covariate in voxel-based morphometry analysis for comparisons between baseline and follow-up in each disease group. Age and onset duration were used as covariates for comparisons between FTD-MND and bvFTD. Significant clusters were reported voxelwise at $p < 0.01$ corrected for false discovery rate, with a cluster extent threshold of 100 contiguous voxels. Peak MNI coordinates indicate the coordinates of the voxel that had the most grey matter atrophy in each significant cluster.

Abbreviations: bvFTD, behavioural variant FTD; FTD-MND, frontotemporal dementia–motor neuron disease; MNI, Montreal Neurological Institute standard space.

investigate the progression of cognitive and behavioural deficits, and the factors predicting such deterioration, in FTD-MND relative to bvFTD.

In conclusion, as FTD-MND progresses, deterioration in general cognition and language is prominent. Such deterioration likely reflects the spread of pathology into brain structures critical for language production and semantic processing. Our results suggest that language impairments should be closely monitored in FTD-MND. In contrast, bvFTD is characterized by progressive, but slower, deterioration in general cognition and behaviour. The differences in patterns of progression between FTD-MND and bvFTD reinforce the concept that these two entities represent related but distinct clinical syndromes.

AUTHOR CONTRIBUTIONS

Zhe Long: Conceptualization (equal); formal analysis (lead); investigation (lead); methodology (lead); project administration (supporting); writing – original draft (lead); writing – review and editing (equal). **Muireann Irish:** Data curation (equal); funding acquisition (equal); project administration (equal); supervision (supporting); writing – review and editing (equal). **John R. Hodges:** Data curation (equal); funding acquisition (equal); project administration (equal); supervision (supporting); writing – review and editing (equal). **Olivier Piguet:** Data curation (equal); funding acquisition (equal); project administration (equal); supervision (supporting); writing – review and editing (equal). **James R. Burrell:** Conceptualization (equal); data curation (equal); funding acquisition (equal); investigation (supporting); methodology (supporting); project administration (equal); supervision (lead); validation (equal); writing – review and editing (equal).

ACKNOWLEDGMENTS

We are grateful to the research participants and their families. Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

This work was supported by funding to Forefront, a collaborative research group dedicated to the study of frontotemporal dementia and amyotrophic lateral sclerosis, from the National Health and Medical Research Council of Australia (NHMRC) program grant (#1037746) and the Australian Research Council Centre of Excellence in Cognition and its Disorders Memory Node (#CE110001021). In addition, J.R.B. was supported by an NHMRC Early Career Fellowship (#1072451). M.I. is supported by an ARC Future Fellowship (FT160100096). O.P. is supported by an NHMRC Senior Research Fellowship (APP1103258).

CONFLICT OF INTEREST

The authors have no conflicts to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Long Z, Irish M, Hodges JR, Piguet O, Burrell JR. Distinct disease trajectories in frontotemporal dementia–motor neuron disease and behavioural variant frontotemporal dementia: A longitudinal study. *Eur J Neurol*. 2022;29:3158-3169. doi: 10.1111/ene.15518