



# Clinical and neuroimaging investigations of language disturbance in frontotemporal dementia–motor neuron disease patients

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## Abstract

This study systematically investigated the neuropsychological profile of language disturbance in frontotemporal dementia–motor neuron disease (FTD–MND) using a data-driven approach. Neuroanatomical correlates of language profiles were also examined. Patients with FTD–MND ( $N=26$ ), pure motor neuron disease ( $N=34$ ), progressive non-fluent aphasia ( $N=30$ ), semantic dementia ( $N=17$ ), and controls ( $N=31$ ) underwent comprehensive language assessments. Clinical assessments were complemented with the Sydney Language Battery (SYDBAT), to assess semantic abilities, and the Test for Reception of Grammar (TROG), to assess syntactic comprehension. Two-step cluster analysis examined patterns of language impairment in FTD–MND and voxel-based morphometry investigated neuroanatomical differences between clusters. Almost all (88.5%) FTD–MND patients had language impairment, with anomia in 73.1% and impaired sentence comprehension in 56%. Cluster analysis revealed two main profiles of language impairment in FTD–MND; a mild mixed semantic and syntactic impairment (mild mixed subgroup) seen in 12 cases and a subgroup with more marked impairment particularly of syntactic comprehension (PNFA-like subgroup) seen in 7 cases. VBM revealed disproportionate atrophy of the caudate head and putamen bilaterally in the PNFA-like subgroup. In conclusion, language disturbances in FTD–MND are heterogeneous and more mixed than seen in FTD language phenotypes. Atrophy of the caudate and putamen was correlated with disproportionate impairment of syntactic comprehension. A pure semantic dementia like syndrome appears to be rare in FTD–MND.

**Keywords** Frontotemporal dementia–motor neuron disease · Syntactic comprehension dysfunction · Semantic deficits · Basal ganglia

## Introduction

Over the last two decades, clinical, pathological, and genetic evidence has highlighted the relationship between frontotemporal dementia (FTD) and motor neuron disease (MND)

[1–3]. The diseases are often considered to be part of the same clinicopathological spectrum [4]. Indeed, recent pathological staging schemes for FTD [5] and MND [6] have emphasised patterns of convergence from initially disparate pathological processes.

Cognitive and behavioural deficits are well recognised in MND and a proportion of patients also meet diagnostic criteria for FTD (i.e., FTD–MND) [7, 8]. Most studies have emphasised an overlap with the behavioural variant of FTD

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with changes in behaviour and executive deficits [1, 2, 8, 9]. However, almost half of FTD patients present with progressive non-fluent aphasia (PNFA) or semantic dementia (SD), where any changes in behaviour or executive function are incidental to language disturbances, at least initially. Population-based studies of cognition in MND have revealed language deficits in almost a quarter (23.3%) of non-demented MND patients [9], however, testing has generally been confined to a single language modality such as naming [9] or sentence comprehension [10].

Recent studies [10, 11], including our own work [12, 13], have demonstrated semantic deficits and impaired syntactic comprehension in MND and FTD–MND. Primary language deficits in FTD–MND, resulting from pathological involvement of language centres, may not be surprising, given frontal and temporal lobe involvement [12, 13] and the observation of language disturbances in FTD more generally. It remains unclear, however, whether the aphasic syndrome seen in patients with FTD–MND mirror those seen in progressive aphasia (i.e., a SD-like or a PNFA-like language syndrome) or if there a unique language profile that occurs in FTD–MND.

The present study addressed several unresolved questions: (1) do patients with FTD–MND exhibit a specific profile of language impairment? (2) Is this profile distinct from those found in FTD language phenotypes? and (3) Does the pattern of cerebral atrophy in FTD–MND explain the profile of language impairment? We hypothesised that language disturbances in FTD–MND would be multimodal and heterogeneous, with varying degrees of semantic deficits and impaired syntactic comprehension. Furthermore, we predicted that atrophy of language centres in frontal and temporal lobes would correlate with language deficits.

## Methods

This study was approved by the South Eastern Sydney Local Health District and the ethics committees of the University of New South Wales and University of Sydney. Written informed consent was obtained from all participants, or their caregivers, in accordance with the Declaration of Helsinki.

## Participants

Patients diagnosed with FTD–MND, PNFA, SD, and MND were included in the study, along with control subjects. Patients with FTD–MND, PNFA, and SD were recruited from FRONTIER, the frontotemporal dementia research clinic, while MND patients were recruited from the multidisciplinary MND clinic at the Brain and Mind Centre, both in Sydney Australia. Healthy control participants were recruited from a database of volunteers. FTD was

diagnosed in accordance with the current consensus criteria and further classified into the acknowledged clinical phenotypes: behavioural variant FTD (bvFTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD) [14–16]. Briefly, bvFTD patients presented with behavioural disturbances and executive deficits and had frontotemporal atrophy on structural imaging. Patients with SD displayed impaired confrontational naming and single word comprehension. PNFA presented with speech dysfluency, along with either agrammatism or apraxia of speech. The diagnosis of MND was made according to the El Escorial and Awaji criteria for MND with progressive upper and lower motor neuron dysfunction affecting three or more non-contiguous regions of innervation [17, 18]. The diagnosis of FTD–MND was made when both FTD and MND diagnostic criteria [19] were fulfilled.

All patients in the FTD–MND group met diagnostic criteria for the syndrome at some time point, but not necessarily at initial presentation. For example, a language syndrome was the initial working diagnosis in more than one quarter (26.9%) of FTD–MND patients. Specifically, four cases were initially diagnosed with PNFA, one with mixed (semantic and syntactic) language disturbances, and two with language deficits combined with behavioural changes; all were eventually diagnosed with FTD–MND. Eight FTD–MND patients (30.7%) started with bvFTD or pure behavioural symptoms before the onset of motor symptoms and signs. A further four cases either had an initial diagnosis of FTD–MND or had motor deficits combined with behavioural/cognitive disturbances. The remainder of FTD–MND cases started either with a diagnosis of FTD-mixed (bvFTD combined PNFA and/or SD) or with mixed behavioural–cognitive symptoms that made an initial diagnosis difficult to reach. None of the FTD–MND patients started with pure MND/motor deficits, but this may have reflected enrolment bias. For those patients without FTD–MND at initial assessment, all had developed symptoms and signs sufficient to reach the diagnosis within 60 months of symptoms onset.

Clinical diagnoses were made by a multidisciplinary team comprising senior neurologists and neuropsychologists based on detailed neurological assessment, cognitive testing, and structural neuroimaging. Patients with logopenic progressive aphasia (LPA), considered an aphasic phenotype of Alzheimer's disease [16, 20], and the so-called right temporal variant of FTD, were excluded from the study, as were patients with other neurological diseases that could impact the clinical diagnosis (e.g., extensive cerebrovascular disease, movement disorders, significant head injury, prior history of mental illness, alcohol and other drug abuse). Patients with limited English proficiency were also excluded from the study, given our focus on language testing.

## Cognitive and disease severity screening

The Addenbrooke's Cognitive Examination, either the second (ACE-R) [21] or third (ACE-III) [22] iteration were used as a screen of cognitive function. To ensure validity of comparisons across patients, ACE-R scores were transformed to ACE-III score according to recently validated methods [23]. FTD disease stage was assessed using the Frontotemporal Dementia Rating Scale (FRS), a validated questionnaire designed to detect, grade, and stage functional deterioration [24].

## Neuropsychological assessments

Sustained attention and working memory were assessed using digit span forwards and backwards tasks [25–27]. Processing speed and divided attention were assessed using the Trail Making Test Parts A and B, respectively [28]. Finally, verbal fluency was assessed using letter fluency (F, A, S) [29].

## Language assessment

Language clinical features were assessed by experienced behavioural neurologists (JRB and JRH) using a comprehensive and consistent approach. Key language features were recorded as present or absent. Specifically, the presence or absence of dysarthria, including features of spastic (i.e., harsh, strained voice) and flaccid (i.e., moist, indistinct, nasal) dysarthria, slowed speech rate, motor speech apraxia, phonological errors, syntax errors, word finding difficulties, anomia, impaired repetition (single words and sentences), impaired comprehension (single words and sentences), surface dyslexia, and dysgraphia was recorded systematically. Features of aphasia, such as phonological errors (i.e., selection of incorrect phonemes on single word production) or motor speech apraxia (i.e., effortful, distorted, and incorrect production of phonemes on single word production) [30], were distinguished from those of dysarthria (i.e., correct phoneme selection, but impaired production due to motor weakness).

## Sydney Language Battery

The Sydney Language Battery (SYDBAT) subtasks were used to assess confrontational naming, word comprehension, semantic association, and single word repetition [31]. Each SYDBAT subtask contains 30 words worth 30 points. To avoid the potential confounding of test performance due to dysarthria, the single word repetition component of the SYDBAT was excluded from the final analysis, making a modified SYDBAT total of 90 points. The other components of the SYDBAT can be completed without the ability

to produce speech and performance on these subtasks is unlikely to be affected by dysarthria.

## Test for reception of grammar

Syntactic (i.e., sentence) comprehension was systematically assessed using the Test for Reception of Grammar (TROG). The TROG consists of 80 items grouped into 20 blocks with four items each. Later blocks are more syntactically complex than earlier blocks [32]. For each item, participants were presented with a sentence (e.g., “The boy chasing the horse is fat”) and were required to select the picture that best matched the scenario indicated by the sentence from four possibilities. To avoid patient fatigue interfering with performance, the TROG was shortened to two rather than four sentences across 20 blocks. The gradation of syntactic difficulty across the blocks was maintained. Our previous study identified no difference between completing sentences 1 and 3, sentences 2 and 4, or the complete TROG, in FTD–MND patients and controls [13]. The total correct score for the abbreviated-TROG ranged from 0 to 40. Like the included components of the SYDBAT, the TROG can be completed without the ability to produce speech and performance is unlikely to be affected by dysarthria.

A short break was allowed if patients exhibited or voiced signs of fatigue. In practice, most patients completed the tasks without voicing or exhibiting fatigue.

## Statistical analyses

Behavioural analyses were conducted using IBM SPSS Statistics version 24. Data are presented as mean  $\pm$  standard deviation for continuous variables and proportions for categorical variables. Normal distribution of continuous variables was assessed via Kolmogorov–Smirnov tests. Group differences were compared using one-way analysis of variance (ANOVA) with post hoc Sidak (parametric data) for pairwise comparisons. For non-normally distributed data, non-parametric Kruskal–Wallis tests were run to investigate group differences, followed by post hoc Mann–Whitney *U* tests. Group comparisons for categorical variables were examined via Chi-square tests. A *p* value  $< 0.05$  was considered statistically significant. Bonferroni correction was employed to account for post hoc tests (ten comparisons with a corrected threshold of  $p < 0.005$ ). Z-transformed scores for SYDBAT and TROG totals were used to examine whether the severity of semantic and syntactic impairments was comparable in FTD–MND, MND, PNFA and SD.

To identify the pattern of language impairment, and to avoid the definition of mixed impairments based on arbitrary SYDBAT and TROG cut-offs, a two-step cluster analysis was conducted using FTD–MND, PNFA and SD cases. Euclidean distance and Bayes Information Criterion

(BIC) were used as proximity measure and clustering criterion, respectively, and numbers of clusters were determined automatically by the algorithm. The validity of the clustering model was then assessed by splitting the dataset into two halves randomly to analyse each separately using the same settings, and conducting one-way analysis of variance (ANOVA) tests to estimate differences between resulting clusters for the relevant continuous variables [33].

To examine whether language impairments in FTD–MND could be attributable to reduced cognitive processing speed, and other cognitive deficits, multivariate analysis of covariance (MANCOVA) was employed to compare: (i) language test performance in FTD–MND and controls controlling for Trails A time; and (ii) language and neuropsychological task performance in FTD–MND subgroups controlling for ACE total.

### Imaging: data acquisition and analysis

Structural T1-weighted, 3-dimensional images were acquired for the majority of participants on a 3T Philips MRI scanner with an 8-channel head coil according to the following acquisition sequences: coronal orientation, matrix  $256 \times 256$ , 200 slices,  $1 \times 1$  mm in-plane resolution, 1 mm slice thickness, TE/TI = 2.6/5.8 ms, flip angle  $\alpha = 8^\circ$ . Structural scans were not available for MND participants.

Voxel-based morphometry (VBM) analysis was conducted using the FSL FMRIB software package (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). First, the FSL Brain Extraction Tool (BET) [34] was used for brain extraction with the resultant images subsequently segmented into grey matter (GM) white matter (WM) and cerebral spinal fluid (CSF). Spatial intensity variations (bias field or radio-frequency inhomogeneities) were corrected via FMRIB's Automated Segmentation Tool (FAST v4.0) [35]. The resulting GM volumes were concatenated and averaged to Montreal Neurological Institute standard space (MNI152) through non-linear registration by FNIRT [36]. A study-specific template was created, to which all grey matter images were registered nonlinearly using a b-spline representation of the registration warp field. To compensate for contraction/enlargement caused by registration transformation, each voxel was modulated using the Jacobian of the warp field. Finally, the normalised and modulated grey matter images were smoothed by an isotropic Gaussian kernel ( $\sigma = 3$  mm).

Patterns of grey matter intensity decrease in each group from cluster analysis were explored using a whole-brain general linear model (GLM) with age included as a nuisance variable. Non-parametric permutation-based testing was conducted with 5000 permutations per contrast [37].

Next, correlation analysis between grey matter intensity and language performance were investigated in FTD–MND group combined with controls, consistent with previous

methodology, to increase the statistical power [38]. Two separate covariate-only statistical models were run, employing positive *t*-contrasts, to explore the relationship between grey matter intensity and (i) semantic (SYDBAT total), and (ii) syntactic comprehension (TROG corrected total) abilities, with age and general cognition (ACE-III total) included as nuisance variables in each model.

Finally, profiles of atrophy specific to each FTD–MND language subgroup were explored using group-based comparisons also with age and general cognition (ACE-III total) included as nuisance variables.

Clusters were extracted using voxel-based method and corrected for False Discovery Rate (FDR) at  $p < 0.05$ , both for correlation and atrophy pattern analyses. A cluster threshold of 100 contiguous voxels was employed to further reduce the potential for false-positive results.

## Results

### Demographics

In total, 138 subjects, including 26 FTD–MND, 34 MND, 30 PNFA, 17 SD, and 31 controls, were included in the study. As presented in Table 1, participant groups were matched for years of formal education ( $p = 0.200$ ), but not for age ( $p = 0.002$ ). The FTD–MND group was younger than controls ( $p = 0.004$ ), while the MND group was younger than PNFA ( $p = 0.004$ ). Sex was not evenly distributed across groups ( $p < 0.01$ ) with more male patients in the MND group relative to PNFA ( $p = 0.001$ ). No significant difference was present between FTD–MND and MND in terms of the proportion of bulbar-onset cases ( $p = 0.429$ ). Consistent with previous studies, patients with SD had a longer disease duration relative to all other patient groups (FTD–MND  $p < 0.001$ , MND  $p = 0.003$ , PNFA  $p = 0.003$ ) [39, 40]. Importantly, age did not correlate with performance on SYDBAT (age  $p = 0.092$ , sex  $p = 0.452$ ) and TROG (age  $p = 0.124$ , sex  $p = 0.356$ ) in controls, and no difference was observed between male and female participants.

### Cognitive and neuropsychological profile

All patient groups performed significantly worse on the ACE-III total ( $p < 0.001$ ) than the control group. Post hoc tests revealed no difference between FTD–MND and PNFA or SD (Table 1). The FTD–MND group exhibited functional impairment, reflected in the FRS logit score, comparable to the SD and MND groups, but less than PNFA ( $p < 0.001$ ).

Table 1 displays neuropsychological performance for each group. Groupwise comparisons revealed significant (all  $p < 0.001$ ) differences in tests of all cognitive domains (i.e., digit span tasks, trail-making tests and letter fluency). Post

**Table 1** Demographic, cognitive and disease severity profile of study samples

	FTD–MND ( <i>n</i> = 26)	MND ( <i>n</i> = 34)	PNFA ( <i>n</i> = 30)	SD ( <i>n</i> = 17)	Controls ( <i>n</i> = 31)	Overall <i>p</i> value	Gradation from post hoc test
Age	60.6 ± 7 <sup>a</sup>	59.3 ± 11.7 <sup>d</sup>	67.4 ± 9.2 <sup>c</sup>	62.9 ± 7.5	66 ± 6.9 <sup>b</sup>	**	FTD–MND < controls; MND < PNFA
Education (years)	12.4 ± 3	13.2 ± 3.1	12.9 ± 2.7	13.6 ± 2.9	14.2 ± 2.5	NS	
Disease duration	2.4 ± 1.1 <sup>e</sup>	3.6 ± 3.9 <sup>e</sup>	3.6 ± 2.3 <sup>e</sup>	5.3 ± 2.2 <sup>b,c,d</sup>	–	**	FTD–MND, PNFA, MND < SD
Sex (male %)	18(69.2%)	26(76.5%) <sup>d</sup>	11(36.7%) <sup>c</sup>	10(58.8%)	14(45.2%)	*	PNFA < MND
Bulbar-onset (%)	1(50%)	4(21.1%)	–	–	–	NS	
ACE-III							
Attention (18)	14.8 ± 3.8 <sup>a,c</sup>	17.6 ± 0.9 <sup>b,d,e</sup>	15.9 ± 2.4 <sup>c</sup>	15.3 ± 2.1 <sup>a,c</sup>	17.1 ± 1.3 <sup>b,e</sup>	**	FTD–MND, SD, PNFA < MND, controls
Memory (26)	15.5 ± 5.9 <sup>a,c</sup>	22.8 ± 3.5 <sup>b,d</sup>	19 ± 6 <sup>e</sup>	13 ± 4.9 <sup>a,c,d</sup>	22.9 ± 3.5 <sup>b,e</sup>	**	SD, FTD– MND < PNFA, MND, controls <sup>A</sup>
Verbal fluency (14)	4 ± 3.8 <sup>a,c</sup>	10.4 ± 3.1 <sup>a,b,d,e</sup>	5.5 ± 3.2 <sup>a,c</sup>	5.5 ± 3 <sup>a,c</sup>	12.7 ± 1.1 <sup>b,c,d,e</sup>	**	FTD–MND, SD, PNFA < MND, controls
Language (26)	17.8 ± 4.8 <sup>a,c,e</sup>	23.1 ± 3 <sup>a,b,d,e</sup>	19.7 ± 4.2 <sup>a,c,e</sup>	13.2 ± 4.9 <sup>a,b,c,d</sup>	25.5 ± 1 <sup>b,c,d,e</sup>	**	SD < FTD–MND, PNFA < MND < con- trols
Visuospatial (16)	12.7 ± 2.7 <sup>a,c,d,e</sup>	14.7 ± 2.3 <sup>b</sup>	14.7 ± 1.6 <sup>b</sup>	15.1 ± 1.5 <sup>b</sup>	15.6 ± 0.6 <sup>b</sup>	**	FTD–MND < PNFA, MND, SD, controls
Total (100)	66.1 ± 19.4 <sup>a,c</sup>	88.6 ± 9.7 <sup>a,b,d,e</sup>	76.4 ± 14.2 <sup>a,c,e</sup>	62.6 ± 14.8 <sup>a,c,d</sup>	95.7 ± 2.7 <sup>b,c,d,e</sup>	**	SD, FTD–MND, PNFA < MND < con- trols <sup>B</sup>
FRS logit score (5.39)	0.6+/1.8 <sup>d</sup>	1.4 ± 1.3	2.7 ± 1.5 <sup>b,e</sup>	1.1 ± 1.5 <sup>d</sup>	–	**	FTD–MND, SD < PNFA
FRS stage							
Very mild	2	0	6	0	0		
Mild	3	6	13	3	0		
Moderate	13	8	8	9	0		
Severe	7	2	0	3	0		
Trails A time (s)	66.3 ± 40.2 <sup>a,c</sup>	49.2 ± 44	61 ± 36.9 <sup>a,e</sup>	39 ± 18.3 <sup>b,d</sup>	31.2 ± 7.9 <sup>b,d</sup>	**	FTD–MND, PNFA < SD, controls
Trails B time (s)	124.9 ± 40.2 <sup>a</sup>	127.9 ± 125.8 <sup>a</sup>	150.9 ± 79.7 <sup>a</sup>	137.8 ± 119.8	71.8 ± 23.3 <sup>b,c,d</sup>	**	PNFA, MND, FTD– MND < controls
Trails B–A time (s)	82.8 ± 35 <sup>a</sup>	89.4 ± 119.5	100 ± 66.6 <sup>a</sup>	98.8 ± 104.5	40.5 ± 19.6 <sup>b,d</sup>	**	PNFA, FTD– MND < controls
Letter fluency	3.4 ± 3.0 <sup>a,c,e</sup>	12.1 ± 5.8 <sup>a,b,d</sup>	6.2 ± 4.3 <sup>a,c</sup>	10.0 ± 4.1 <sup>a,b</sup>	17.4 ± 14.7 <sup>b,c,d,e</sup>	**	FTD–MND, PNFA < SD, MND < controls <sup>C</sup>
Digit span forwards	5.5 ± 0.9 <sup>a,c</sup>	6.7 ± 1.2 <sup>b,d</sup>	5 ± 1.2 <sup>a,c,e</sup>	6.5 ± 1.3 <sup>a,b,d</sup>	7.4 ± 1 <sup>b,d</sup>	**	PNFA, FTD– MND < MND, SD, controls <sup>D</sup>
Digit span backwards	2.7 ± 1.2 <sup>a,c,e</sup>	4.5 ± 1.5 <sup>b</sup>	3.4 ± 1.1 <sup>a</sup>	4.2 ± 1.5 <sup>a,b</sup>	5.6 ± 1.2 <sup>b,d,e</sup>	**	FTD– MND < SD < controls

Patients with FTD–MND had no difference with PNFA or SD on general cognition, and milder than PNFA on FRS logit score. FTD–MND patients presented comparable performance on all neuropsychological assessments to that in PNFA, but more impaired than that in SD on Trails A time, letter fluency and digit span tasks

FRS stage available for 25 FTD–MND, 16 MND, 27 PNFA and 15 SD cases. Trails A time available for 24 FTD–MND, 15 MND, 29 PNFA cases. Trails B/B–A time available for 12 FTD–MND, 14 MND, 24 PNFA cases. Letter fluency available for 15 FTD–MND, 16 MND, 25 PNFA, 14 SD cases and 30 controls. Digit span backward/forward available for 18 MND, 29 PNFA and 30 controls

FTD–MND frontotemporal dementia–motor neuron disease, MND motor neuron disease, PNFA progressive non-fluent aphasia, SD semantic



**Table 1** (continued)

dementia, *ACE-III* Addenbrooke's Cognitive Examination-version III, *FRS* Frontotemporal Dementia Rating Scale

Data presented as mean  $\pm$  standard deviation. \* $p < 0.05$ ; \*\* $p < 0.01$ ; -: not applicable; NS: nonsignificant

<sup>a</sup>vs. Controls ( $p < 0.005$ ), <sup>b</sup>vs. FTD–MND ( $p < 0.005$ ), <sup>c</sup>vs. MND ( $p < 0.005$ ), <sup>d</sup>vs. PNFA ( $p < 0.005$ ), <sup>e</sup>vs. SD ( $p < 0.005$ )

<sup>A</sup>No difference between FTD–MND and PNFA

<sup>B</sup>SD group was more impaired than PNFA on ACE-III total

<sup>C</sup>No difference between PNFA and SD

<sup>D</sup>No difference between FTD–MND and SD

hoc tests revealed that the FTD–MND and PNFA groups were impaired compared to controls, but did not differ from each other on any individual test. Meanwhile, the SD group displayed working memory and executive function impairments (both  $p$  values  $< 0.001$ ) relative to controls. Patients with MND displayed impaired executive function ( $p = 0.004$ ) but relatively intact performance on other tested neuropsychological domains. Results of neuropsychological post hoc tests are provided in Table 1.

## Language performance

Table 2 displays the frequency of language impairments in FTD–MND. The majority (88.5%) of FTD–MND patients

had language disturbances detected on clinical assessment. Clinically detected language disturbances included PNFA features, such as impaired sentence comprehension (56.0%), motor speech apraxia (39.1%) and syntactic deficits in spontaneous speech (28.0%), as well as SD features including anomia (73.1%), impaired single word comprehension (34.6%) and surface dyslexia (45.8%).

Relative to controls, FTD–MND patients presented deficits on all formal language tasks (i.e., SYDBAT subdomains/total and TROG corrected total, all  $p \leq 0.005$ ), which persisted after controlling for cognitive processing speed (see *Methods*). FTD–MND patients demonstrated intermediate impairment on a measure of overall semantic ability (Fig. 1). Specifically, group-wise analysis revealed

**Table 2** Language impairments profile in FTD–MND

	Impaired proportion, $N$ (%) ( $n = 26$ )	FTD–MND mild mixed subgroup <sup>a</sup> , $N$ (%) ( $n = 12$ )	FTD–MND syntactic subgroup <sup>b</sup> , $N$ (%) ( $n = 7$ )	Mild mixed vs. syntactic subgroups, $p$ value
Language impairment	23 (88.5%)	10 (83.3%)	7 (100.0%)	0.509
Dysarthria	19 (73.1%)	9 (75.0%)	7 (100.0%)	0.263
Slowed speech rate	20 (76.9%)	9 (75.0%)	7 (100.0%)	0.263
Motor speech apraxia	9 (39.1%)	4 (33.3%)	4 (80.0%)	0.079
Phonological errors	8 (30.8%)	4 (33.3%)	2 (28.6%)	0.829
Syntax errors	7 (28.0%)	4 (33.3%)	1 (16.7%)	0.457
Word finding difficulties	16 (64.0%)	5 (41.7%)	6 (100.0%)	0.038*
Anomia	19 (73.1%)	8 (66.7%)	5 (71.4%)	0.829
Impaired repetition of words	21 (52.0%)	5 (45.5%)	6 (85.7%)	0.088
Impaired repetition of sentences	9 (36%)	3 (25.0%)	5 (71.4%)	0.074
Impaired word comprehension	9 (34.6%)	1 (8.3%)	4 (57.1%)	0.038*
Impaired sentence comprehension	14 (56.0%)	3 (25.0%)	6 (100.0%)	0.009*
Surface dyslexia	11 (45.8%)	4 (33.3%)	4 (66.7%)	0.180
Dysgraphia	8 (40.0%)	2 (22.2%)	6 (85.7%)	0.012*

Between the two main FTD–MND subgroups, higher frequency of impairments was identified on word finding difficulties, impaired word comprehension, impaired sentence comprehension and dysarthria in syntactic subgroup

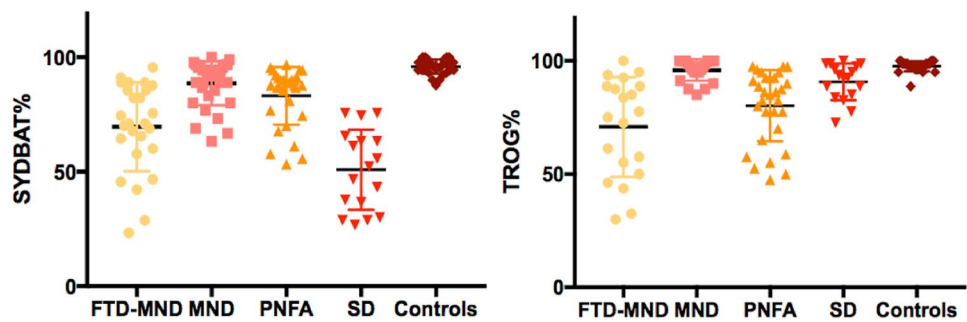
Not examined: three on motor speech apraxia; one on syntax errors, word finding difficulties, impaired words/sentences repetition and impaired sentence comprehension; two on surface dyslexia

*FTD–MND* frontotemporal dementia–motor neuron disease, *MND* motor neuron disease, *PNFA* progressive non-fluent aphasia, *SD* semantic dementia

<sup>a</sup>FTD–MND mild mixed subgroup: impaired words repetition available for 11 cases, dysgraphia available for 9 cases

<sup>b</sup>FTD–MND syntactic subgroup: word finding difficulties available for five cases, syntax errors, word finding difficulties, impaired sentence comprehension and surface dyslexia available for six cases; \* $p < 0.05$

**Fig. 1** Language performance across groups. Performance of FTD–MND patients on the TROG and SYDBAT was highly heterogeneous. Compared to MND, FTD–MND generally performed worse on language tasks



a significant difference on SYDBAT total. Post hoc tests revealed the following pattern: SD < FTD–MND < PNFA, MND < controls. The FTD–MND group demonstrated comparable impairments on the single word comprehension and semantic association components of the SYDBAT relative to SD, but not on confrontation naming and total (both  $p \leq 0.003$ ) (Table 3). Meanwhile, FTD–MND

patients had similar degree of syntactic comprehension impairment as seen in PNFA. Specifically, syntactic comprehension, as reflected by the TROG corrected total, differed across the groups, with post-hoc tests revealing the following pattern of impairment: FTD–MND, PNFA < SD < MND, controls (SD did not differ from PNFA or MND) (Table 3).

**Table 3** Language impairments severity across groups

	FTD–MND (n=26)	MND (n=34)	PNFA (n=30)	SD (n=17)	Controls (n=31)	Overall p value	Gradation from post hoc test
<b>SYDBAT</b>							
Naming (30)	17.7 ± 7.1 <sup>a,c,e</sup>	24.9 ± 4.6 <sup>b,d,e</sup>	21 ± 6.5 <sup>a,c,e</sup>	7.3 ± 4.9 <sup>a,b,c,d</sup>	27.7 ± 1.8 <sup>b,d,e</sup>	**	SD < FTD–MND, PNFA < MND, controls
Repetition (30)	24.3 ± 7.3 <sup>a</sup>	26.7 ± 8.4 <sup>d</sup>	21.3 ± 8.9 <sup>a,c,e</sup>	28.8 ± 1.4 <sup>a,d</sup>	29.9 ± 0.4 <sup>b,d,e</sup>	**	PNFA, FTD–MND < MND, controls; PNFA < SD <sup>A</sup>
Comprehension (30)	23.6 ± 5 <sup>a,c,d</sup>	27.6 ± 2.5 <sup>a,b,e</sup>	27.9 ± 2.7 <sup>a,b,e</sup>	19.4 ± 7.2 <sup>a,c,d</sup>	29.5 ± 0.8 <sup>b,c,d,e</sup>	**	SD, FTD–MND < MND, PNFA < controls
Semantic association (30)	21.4 ± 6.9 <sup>a,c,d</sup>	27.3 ± 2.6 <sup>a,b,e</sup>	26 ± 3.7 <sup>a,b,e</sup>	19.1 ± 4.8 <sup>a,c,d</sup>	29.2 ± 0.9 <sup>b,c,d,e</sup>	**	SD, FTD–MND < PNFA, MND < controls
Total (90, no repetition)	62.7 ± 17.5 <sup>a,c,d,e</sup>	79.8 ± 8.7 <sup>a,b,e</sup>	74.9 ± 11.3 <sup>a,b,e</sup>	45.8 ± 15.7 <sup>a,b,c,d</sup>	86.4 ± 2.8 <sup>b,c,d,e</sup>	**	SD < FTD–MND < PNFA, MND < controls
<b>TROG</b>							
Total corrected (40)	28.3 ± 8.8 <sup>a,c,e</sup>	38.4 ± 1.9 <sup>b,d</sup>	32.1 ± 6.3 <sup>a,c</sup>	36.3 ± 3.2 <sup>a,b</sup>	39 ± 0.9 <sup>b,d,e</sup>	**	FTD–MND, PNFA < MND, controls; FTD–MND < SD < controls

SYDBAT available for 33 MND cases. TROG available for 20 FTD–MND, 22 MND cases

Data presented as mean ± standard deviation. The presented results were from Kruskal–Wallis test with post hoc Mann–Whitney U tests. MANCOVA analysis was used for controlling Trails A time between FTD–MND and controls, and also used for controlling disease duration and Trails A time between FTD–MND and SD on all language tasks. Importantly, the statistical significances did not change from Mann–Whitney U tests

FTD–MND frontotemporal dementia–motor neuron disease, MND motor neuron disease, PNFA progressive non-fluent aphasia, SD semantic dementia, SYDBAT Sydney Language Battery, TROG the test of reception of grammar

\* $p < 0.05$ ; \*\* $p < 0.01$ ; –: not applicable; NS: nonsignificant

<sup>a</sup>vs. Controls ( $p < 0.005$ ), <sup>b</sup>vs. FTD–MND ( $p < 0.005$ ), <sup>c</sup>vs. MND ( $p < 0.005$ ), <sup>d</sup>vs. PNFA ( $p < 0.005$ ), <sup>e</sup>vs. SD ( $p < 0.005$ )

<sup>A</sup>No difference between FTD–MND and MND

To examine whether the severity of semantic and syntactic impairments was comparable in FTD–MND, MND, PNFA and SD, Z-transformed scores for SYDBAT and TROG totals were used in a Wilcoxon signed rank test. No statistically significant difference was observed in FTD–MND ( $p=0.179$ ), suggesting comparable level of impairment across these two tasks. In contrast, TROG impairment predominated in PNFA ( $p=0.005$ ) and SYDBAT impairment predominated in SD ( $p<0.001$ ) and MND ( $p=0.017$ ).

### Cluster analysis

Cluster analysis performed on the SD, PNFA, and FTD–MND groups combined revealed three language subgroups. While all three language subgroups were more impaired relative to controls both on syntactic comprehension and semantic abilities, the relative proportion of impairment across tasks differed between the subgroups. Specifically, the first subgroup had mild mixed syntactic comprehension and semantic deficits (referred to as the ‘mild mixed’ subgroup), the second subgroup had disproportionate syntactic comprehension dysfunction (referred to as the ‘syntactic’ subgroup), and the third subgroup had disproportionate semantic deficits (referred to as the ‘semantic’ subgroup). The mild mixed subgroup comprised mainly PNFA with a smaller number of FTD–MND patients (FTD–MND  $n=12$ , PNFA  $n=22$ , SD  $n=7$ ). The syntactic subgroup was evenly split between FTD–MND and PNFA, (FTD–MND  $n=7$ , PNFA  $n=7$ ). The semantic subgroup comprised mainly SD patients (FTD–MND  $n=1$ , PNFA  $n=1$ , SD  $n=10$ ). The quality of the 3-cluster solution was ‘good’, as determined by a silhouette measure of cohesion and separation score of  $>0.5$  from the algorithm [41]. The cluster model revealed a high degree of stability. Details of cognitive, language, and neuropsychological assessments are reported in Supplementary Table 1. Most FTD–MND patients fell into the mild mixed and syntactic subgroups (60% in the mild mixed subgroup, 35% in the syntactic subgroup, and only 5% in the semantic subgroup).

### Demographic and cognitive profile in FTD–MND subgroups

Due to the limited number of FTD–MND cases in the semantic subgroup, demographic and cognitive were compared between FTD–MND patients in the mild mixed and syntactic subgroups only. The FTD–MND patients who fell into the syntactic subgroup performed worse than those in the mild mixed subgroup on ACE-III total and subdomains of attention, fluency, and visuospatial function.

After controlling for general cognition (i.e., MANCOVA using the ACE-III total as covariate, see “[Methods](#)”), the syntactic subgroup of FTD–MND was more impaired than

the mild mixed subgroup on syntactic comprehension ability (i.e., TROG correct total), processing speed (i.e., Trails A time), and working memory (i.e., digit span backward). No differences in disease duration, semantic abilities (i.e., SYDBAT total and subdomains), or other neuropsychological tasks were detected between the FTD–MND subgroups (Supplementary Table 2).

### Neuroimaging

#### All patients

Compared to controls, all language subgroups derived from cluster analysis displayed widespread atrophy affecting bilateral frontal, temporal, and peri-insular regions, as well as the basal ganglia, lateral occipital cortex, and left cerebellum. The syntactic subgroup demonstrated more atrophy of the middle and inferior frontal gyri bilaterally than the mild mixed language cluster, while the semantic language group had disproportionate atrophy of the temporal lobes bilaterally (Supplementary Table 3).

#### FTD–MND patients only

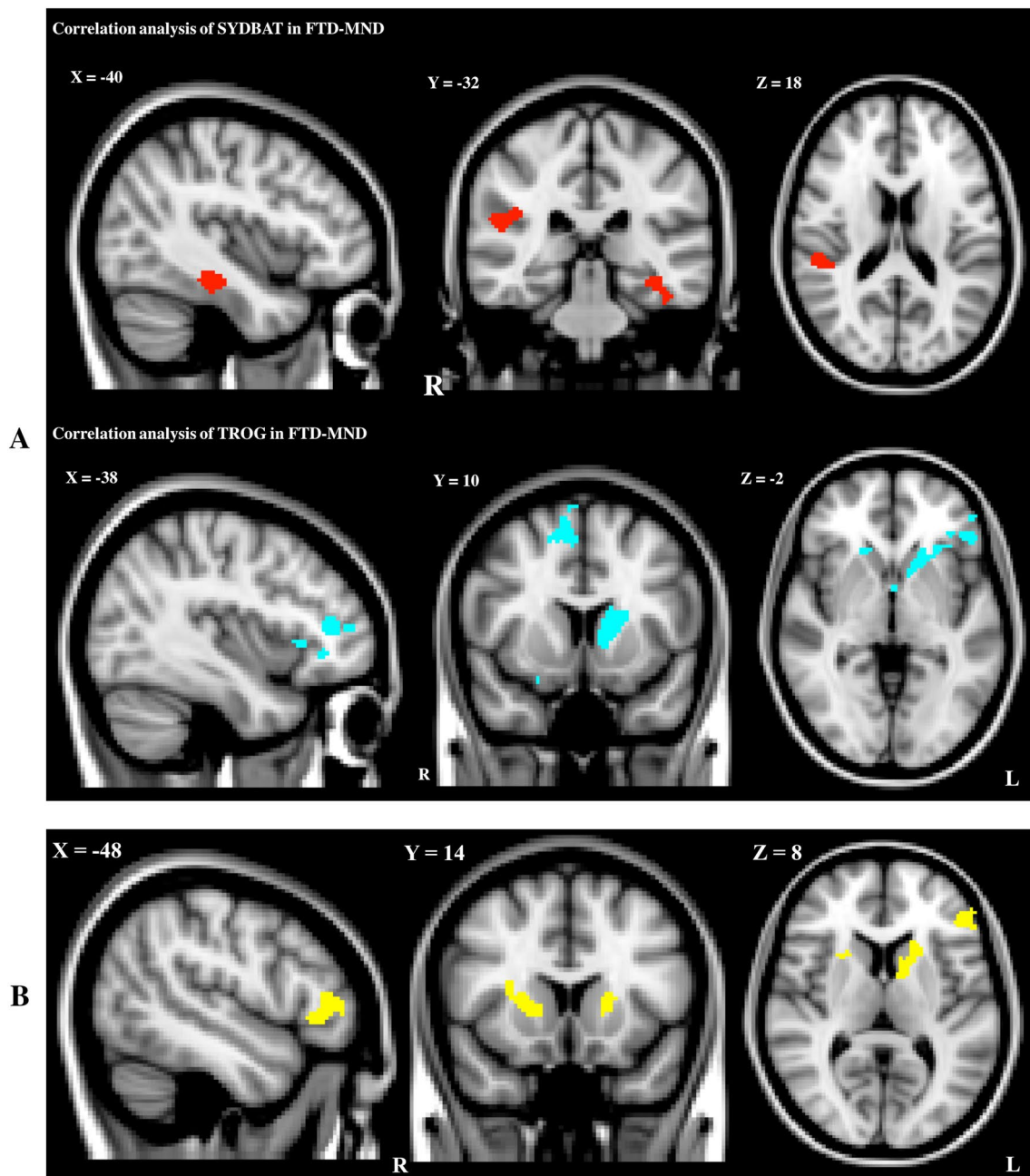
When analyses were confined to FTD–MND patients only, semantic deficits correlated with atrophy of the left inferior temporal gyrus and right peri-insular cortex. Meanwhile, impaired syntactic comprehension correlated with atrophy of the bilateral inferior and middle frontal gyri, frontal orbital cortex, caudate, left insular cortex, and putamen (Fig. 2a, Supplementary Table 4).

When FTD–MND subgroups were compared, both the mild mixed and syntactic subgroups had atrophy of the anterior temporal lobe, inferior frontal gyrus, peri-insular regions, basal ganglia, and cerebellum bilaterally relative to controls. The syntactic subgroup had greater atrophy of the inferior frontal gyrus, caudate, and putamen bilaterally, relative to the mild mixed subgroup (Fig. 2b, Supplementary Table 4).

### Discussion

This comprehensive study of language abilities FTD–MND, incorporating the same assessment methods as used in patients with progressive aphasia syndromes, revealed that language impairment in FTD–MND is extremely common and comparable in severity to that seen in FTD language phenotypes. Moreover, a data-driven cluster analysis identified two main patterns of language impairment in FTD–MND: a mild mixed language syndrome and predominantly syntactic comprehension disturbances (syntactic subgroup). No differences in demographic characteristics,





**Fig. 2** Neuroimaging results in FTD-MND. **a** Neuroanatomical correlates of SYDBAT and TROG performance in FTD-MND patients. Voxel-based morphometry correlation analyses showing brain regions which correlate significantly with SYDBAT and TROG performance. **b** Voxel-based morphometry results showing regions of atrophy between FTD-MND two main subgroups; the FTD-MND syntactic subgroup had more atrophy of the inferior frontal gyrus, caudate,

and putamen bilaterally than the mild mixed group. Coloured voxels show regions that were significant in the analyses at  $p < 0.05$  FDR corrected. Coloured voxels show regions that were significant in the analyses at  $p < 0.05$  FDR corrected. Clusters are overlaid on the Montreal Neurological Institute standard brain. ACE-III total score and age are included as covariates in the analyses. *R* right

disease duration, or functional impairment were detected between the two FTD-MND subgroups, but voxel-based morphometry suggested that bilateral caudate and left putamen involvement may drive disturbed syntactic comprehension in FTD-MND.

### Language impairment in FTD-MND is highly prevalent, multimodal, and heterogeneous

Almost all FTD-MND patients in the present study exhibited language impairment and one-third of cases were diagnosed

with an aphasic syndrome before the final diagnosis became apparent. Although the mode of presentation in FTD–MND patients included in the present study was markedly heterogeneous, all patients eventually met the diagnostic criteria. A range of language disturbances was identified, including anomia, impaired single word comprehension, impaired sentence comprehension, and syntactic deficits in spontaneous speech. Few studies [10, 12, 13] have systematically examined language in FTD–MND, but the reported findings are broadly similar to those of the present study. For example, one study found impaired confrontation naming in 66%, impaired word comprehension in 23%, and impaired sentence comprehension in 48% of patients diagnosed with FTD–MND [10]. Similarly, our previous studies, which included around 65% of the FTD–MND patients included in the present study, reported impaired confrontation naming in 78.9%, impaired semantic knowledge in 73.3% [12], and impaired syntactic comprehension in 92.9% of patients [10, 13] defined in reference to control performance.

Deficits at word, sentence, or discourse processing levels have been reported in MND patients. For example, reduced verbal output [42], impaired object naming and semantic knowledge [9, 12], sentence processing difficulties [11, 13, 43, 44], and poor narrative cohesion [45, 46] have all been described with variable frequency. Overall, reported frequencies of naming disturbances range from 9.1 to 35.7% [9, 11, 12], while reported frequencies of syntactic comprehension dysfunction range from 25% [13, 47] to 83.3% [42, 44, 48].

The reasons for variability of impaired frequency between the present study and previous studies are not entirely clear. Different populations, sample sizes, and disease severity may be potential explanations. Separately, some studies have failed to distinguish between FTD–MND and MND [44, 46], or completely excluded FTD–MND cases from their analyses, making a direct comparison with the present study problematic.

### **The severity of language deficits in FTD–MND is similar to FTD language syndromes**

Very few studies, apart from our previous work, have specifically examined the profile of language impairment in FTD–MND compared to PNFA or SD. Rather, previous studies compared language impairment frequency in FTD–MND to bvFTD without considering the relative severity of deficits [10]. FTD–MND patients demonstrated language impairment independent of reduced cognitive processing speed, and broadly speaking, the severity of language deficits in FTD–MND were similar to those evident in FTD language phenotypes. For example, syntactic comprehension deficits were as severe in FTD–MND as in PNFA. FTD–MND and PNFA had comparable cognitive

dysfunction on all tested neuropsychological domains, suggesting that poor performance on the TROG in FTD–MND is not simply due to general cognitive decline, but reflects a specific impairment in syntactic comprehension. Similarly, while FTD–MND and MND had comparable disease duration and cognitive processing speed, all tested language domains were disproportionately impaired in FTD–MND relative to MND pure. As might have been expected, patients with SD had longer disease duration and faster cognitive processing speed than patients with FTD–MND. Importantly, controlling for these factors did not change the overall profile of results, suggesting that the severity of semantic deficits in FTD–MND was similar with that in SD which was not merely a secondary results of disease duration and reduced cognitive processing speed. Interestingly, syntactic comprehension difficulties and semantic deficits were of comparable severity in FTD–MND, unlike PNFA, SD and MND, where the clinical picture was dominated by one distinct feature (e.g., PNFA presented dominantly syntactic comprehension dysfunction, meanwhile SD displayed predominantly semantic deficits).

In the present study, language deficits were worse in FTD–MND than MND, across all language domains. Consistent with previous reports, mild impairments with confrontation naming [11, 49] and semantic association [43] were detectable in MND, but were less severe than in SD. Similarly, mild syntactic comprehension deficits were detected in MND, but were less severe than in PNFA. Very few studies have examined syntactic comprehension in MND, but at least one study suggested using syntactic comprehension deficits as a marker for cognitive impairment in MND [43]. In the present study, disease duration was similar in FTD–MND and MND, suggesting that language deficits in FTD–MND may be distinct from those seen in MND, rather than simply reflecting worse cognition at a later disease stage [6].

### **Neuroanatomical correlates of language profiles in FTD–MND**

More than half of the FTD–MND had mild mixed language impairments. The remaining FTD–MND patients exhibited disproportionate syntactic comprehension deficits (syntactic subgroup). Interestingly, patients with PNFA, another clinically heterogeneous syndrome [50], were also mainly grouped in the mild mixed and syntactic subgroups, while SD, which is usually distinct from other FTD syndromes, made up the majority of the semantic subgroup. No differences in patient demographics, disease duration, or functional impairment were detected between the two main FTD–MND subgroups, but future studies should determine whether the pattern of deficits seen in

the syntactic subgroup predicts more rapid disease progression and/or worse outcome.

FTD–MND patients in the syntactic subgroup had greater atrophy of subcortical structures. Specifically, the syntactic subgroup showed caudate and putamen atrophy compared with the other groups. The caudate has been linked to planning and goal-directed action, while the putamen appears to be involved in habit learning and stimulus–response associations [51]. Regarding language function, recent evidence from functional MRI (fMRI) and diffusion-MRI tractography (DTI) studies in healthy individuals implicates the caudate and/or putamen in the production of language. Specifically, bilateral caudate and right putamen activity on fMRI has been demonstrated during word retrieval tasks [52], while DTI revealed direct connections between Broca’s area and the anterior putamen [53]. Further supporting a role for the caudate in language production and processing, a Broca–striatum tract linking BA45 with the left caudate head has been correlated with syntactic processing [54]. In addition, studies have shown co-activation of the left anterior putamen with the regions directly associated with lexical processing, language production/comprehension, and language control [55].

Atrophy of the caudate has been previously reported in FTD language syndromes. Specifically, atrophy of both caudate nuclei, extending to the left putamen [50], has been reported in PNFA, while bilateral atrophy of the caudate has also been reported in SD [50]. Furthermore, progression of caudate atrophy has been associated with disease progression in PNFA and SD [56]. Although accumulating studies report a correlation between the caudate/putamen and language, many questions remain. For instance, do the left and right caudate/putamen support similar roles in syntactic comprehension? Is there a language processing circuit connecting the inferior frontal gyrus and the insula—regions considered important for production and processing of syntax—to the caudate or putamen?

In terms of potential limitations, the current study is a cross-sectional and clinic-based cohort instead of a longitudinal and population-based study. The sample size was relatively small once subgroup analyses were performed, even though the total number of participants was large compared to previous studies. Specifically, within the FTD–MND group, the sample size made the detailed and comprehensive picture of FTD–MND subgroups difficult to acquire and a larger cohort may be needed to validate the results of the cluster analysis. In addition, verbal fluency index was not available to control for severe dysarthria in FTD–MND, but to counter this potential confound only analysis of tests not directly affected by dysarthria were used in the main analyses.

## Conclusions

This study demonstrates that language dysfunction in FTD–MND is highly prevalent, multimodal, and heterogeneous. Syntactic comprehension dysfunction and semantic deficits in FTD–MND are as severe as those seen in PNFA and SD in general. Two main FTD–MND language subgroups were detected by a data driven approach; one subgroup had mild mixed language impairment and the other had predominantly syntactic comprehension difficulties. In addition, atrophy of bilateral caudate and left putamen was correlated with syntactic comprehension deficits in FTD–MND.

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## Compliance with ethical standards

**Conflicts of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical approval** This study was approved by the South Eastern Sydney Local Health District and the ethics committees of the University of New South Wales and University of Sydney.

**Informed consent** Written informed consent was obtained from all participants, or their caregivers, in accordance with the Declaration of Helsinki.

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