Measuring disease progression in frontotemporal lobar degeneration

A clinical and MRI study

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ABSTRACT

Objectives: There is currently much interest in biomarkers of disease activity in frontotemporal lobar degeneration (FTLD). We assessed MRI and behavioral measures of progression in a longitudinal FTLD cohort.

Methods: Thirty-two patients with FTLD (11 behavioral variant frontotemporal dementia [bvFTD], 11 semantic dementia [SemD], 10 progressive nonfluent aphasia [PNFA]) and 24 age-matched healthy controls were assessed using volumetric brain MRI and standard behavioral measures (Mini-Mental State Examination, Frontal Assessment Battery, Clinical Dementia Rating Scale, Neuropsychiatric Inventory with Caregiver Distress scale) at baseline and 1 year later. A semi-automated image registration protocol was used to calculate annualized rates of brain atrophy (brain boundary shift integral [BBSI]) and ventricular expansion (ventricular boundary shift integral [VBSI]). Associations between these rates and changes in behavioral indices were investigated.

Results: Rates of whole brain atrophy were greater in the entire FTLD cohort and in each subgroup compared with controls (all $p \leq 0.004$). Rates of ventricular expansion were greater in the entire cohort ($p < 0.001$) and the SemD ($p = 0.002$) and PNFA ($p = 0.05$) subgroups compared with controls. Changes in Mini-Mental State Examination, Frontal Assessment Battery, and Clinical Dementia Rating Scale scores were associated with MRI measures of progression, though not uniformly across FTLD subgroups. Both BBSI and VBSI yielded feasible sample size estimates for detecting meaningful treatment effects in SemD and PNFA language subgroups. Sample sizes were substantially larger using MRI biomarkers for the bvFTD subgroup, and using behavioral biomarkers in general.

Conclusions: Semi-automated MRI atrophy measures are potentially useful objective biomarkers of progression in frontotemporal lobar degeneration (FTLD); however, careful stratification of FTLD subtypes will be important in future clinical trials of disease-modifying therapies.

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GLOSSARY

AD = Alzheimer disease; **BBSI** = brain boundary shift integral; **bvFTD** = behavioral variant frontotemporal dementia; **CDR-SB** = Clinical Dementia Rating Scale-Sums of Boxes; **FTLD** = frontotemporal lobar degeneration; **SemD** = semantic dementia; **PNFA** = progressive nonfluent aphasia; **VBSI** = ventricular boundary shift integral.

Frontotemporal lobar degeneration (FTLD) is a group of degenerative conditions characterized by progressive focal frontal and temporal lobe atrophy that constitutes a common cause of young-onset dementia.¹ Three major FTLD syndromes are recognized: behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SemD), and progressive nonfluent aphasia (PNFA).^{2–4} These clinical phenotypes are associated with different patterns of brain atrophy on MRI and are histopathologically heterogeneous.⁵

Recent advances in Alzheimer disease (AD) have shown that disease-modifying treatment in the degenerative dementias is a realistic prospect, and quantification of brain atrophy rates has emerged as a potentially valuable biomarker for clinical trials.^{6–8} In the case of FTLD, recent progress in pathology and molecular biology has transformed our understanding of disease

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mechanisms.^{9,10} In contrast to AD, a relatively high proportion of FTLN cases are familial,¹¹ significantly boosting the potential for early (presymptomatic) intervention. In this respect, FTLN is an attractive degenerative disease model for developing new approaches to disease modification. Early diagnosis of FTLN remains problematic and effective therapy is not yet available; however, emerging information suggests that longitudinal magnetic resonance measures of whole brain and ventricular volume provide feasible indices of disease progression that could support future trials of disease-modifying therapy in FTLN.^{12,13}

Here we assessed the value of serial brain MRI measures and standard cognitive and behavioral indices as biomarkers of disease progression in a well-characterized longitudinal FTLN cohort. Whole brain atrophy, ventricular expansion, and change in standard cognitive and behavioral indices were measured over a 1-year follow-up period in each of the major FTLN syndromic subgroups. Our objective was to generate sample size estimates based on these biomarkers for the design of future therapeutic trials in FTLN and each of its canonical subtypes.

METHODS Subjects. Sixty-two consecutive patients fulfilling current consensus criteria for FTLN² attending the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, London, UK, between 2005 and 2008 were assessed for eligibility. Patients with logopenic/phonologic progressive aphasia were not recruited because of emerging evidence that a high proportion have underlying AD pathology.¹⁴ Patients were excluded if they were unable to tolerate MRI, if they had brain imaging features of vascular dementia (assessed using National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l’Enseignement en Neurosciences criteria¹⁵), or if disease severity precluded reliable neuropsychological assessment. Nineteen patients (30% of all clinic attenders with FTLN over the interval—14 with bvFTD, 4 with SemD, 1 with PNFA) declined entry or failed to meet these criteria: these patients were comparable in age to the cohort entering the study. The FTLN cohort eligible to enter the study comprised 43 patients representing each of the 3 canonical clinical syndromes: bvFTD (n = 22), SemD (n = 11), and PNFA (n = 10). One patient in the bvFTD group was known to have a pathogenic mutation (Q130fs) in the progranulin gene. The SemD cohort described here partly overlaps with a cohort on whom data were published previously.¹⁶ Twenty-four healthy age-matched control subjects also participated.

MRI acquisition. At recruitment, all subjects had volumetric brain MRI on a 1.5 T Signa scanner. The acquisition protocol for all scans included a 3-dimensional, coronally acquired, T1-

weighted volumetric sequence (magnetization-prepared, rapid acquisition gradient echo, 240 mm field of view, 256 × 256 matrix, repetition time 15 msec, echo time 5.4 msec, flip angle 15°, inversion time 650 msec) comprising 124 contiguous 1.5-mm slices. All baseline scans were evaluated by an experienced cognitive neurologist blinded to diagnosis. To reduce the likelihood of including FTLN phenocopies,^{17,18} 4 patients with normal baseline MRI scans were excluded; a further 7 patients with bvFTD (18% of the entry cohort) declined or were deemed too severely affected to have a second study assessment. The remaining 32 patients and the healthy control group underwent a second MRI scan on the same scanner using an identical protocol; imaging and behavioral data from these subjects formed the substance of this study. Mean (SD) scan interval from baseline to follow-up was 13.1 (2.6) months; 27 patients (84%) had follow-up scans within 10–14 months from baseline visit, 4 were scanned between 14 and 18 months, and 1 was scanned 23 months after the initial assessment.

Measurement of brain atrophy and ventricular expansion rates. Regions representing whole brain were segmented on baseline and follow-up scans by experienced segmenters and volumes generated using MIDAS software.¹⁹ Scans underwent affine registration to spatially align baseline and follow-up regions. The brain boundary shift integral (BBSI) technique was subsequently applied, providing automatic quantification of whole brain volume loss.²⁰ Brain atrophy rates were modeled assuming a constant rate between time points and expressed as an annual percentage loss from baseline volume.

Scans were then registered into MNI-305 template space²¹ for ventricular segmentation. Ventricular volumes were outlined on the baseline and follow-up images using 60% of mean brain region intensity as an upper threshold. Ventricular regions included the lateral ventricles and temporal horn of the lateral ventricles but excluded the third and fourth ventricles. A local registration (using the ventricular regions as masks)²² aligned these structures to estimate a representative ventricular boundary shift integral (VBSI). Ventricular expansion was modeled directly as mL/y.

Cognitive and behavioral assessments. In this study, we sought to compare MRI biomarkers of disease progression with widely available, standard behavioral indices not requiring a trained neuropsychologist. Cognitive and behavioral assessments were carried out in a single semi-structured interview session by a qualified clinician on the same day as the initial MRI acquisition, and repeated at the time of the follow-up MRI scan. Instruments used^{23–26} are presented in table 1.

Statistical analyses and calculation of sample sizes. Differences in rates of whole brain, ventricular, and behavioral change between the FTLN group and controls were assessed using linear regression in STATA 8.0[®] (Stata Corp, College Station, TX). Whole brain rates were expressed on a log scale and behavioral change score data on a continuous scale for regression analyses. FTLN subgroups were compared with controls in separate analyses and pairwise comparisons between the FTLN subgroups were also carried out. Relationships between longitudinal MRI and cognitive measures were investigated for the entire FTLN cohort and for each patient subgroup. All analyses were adjusted for age, gender, and baseline volume, baseline cognitive score, floor, and ceiling effects where applicable. Robust standard errors were used to account for potential between-group differences in variances. Sample sizes needed to detect 25%

Table 1 Mean (SD) baseline demographic information and outcome measures for the entire FTLD cohort, the individual FTLD subgroups, and healthy controls^a

	FTLD cohort (n = 32)	bvFTD (n = 11)	SemD (n = 11)	PNFA (n = 10)	Controls (n = 24)
Age, y	65.6 (8.0)	65.8 (7.5)	63.3 (9.3)	68.0 (7.1)	68.2 (7.0)
M:F	(24:8) ^b	(11:0) ^{b,c}	(4:7) ^{b,d}	(9:1) ^b	(12:12)
Disease duration, y	5.9 (2.8)	6.7 (4.1)	4.6 (1.5) ^d	6.4 (2.0)	N/A
Brain volume, mL	1,081 (93)	1,097 (96)	1,082 (69)	1,062 (115)	1,087 (113)
Ventricular volume, mL	49.9 (26.3) ^b	52.8 (35.6) ^b	43.6 (18.0) ^b	53.7 (23.5) ^b	31.2 (23.7)
MMSE (/30)	25.1 (4.2) ^b	27.0 (3.4) ^{b,c}	23.4 (4.3) ^b	24.8 (4.3) ^b	29.8 (0.5)
Missing	1	0	0	1	0
FAB (/18)	13.6 (3.4) ^b	14.2 (4.5) ^b	14.2 (2.5) ^b	12.0 (2.3) ^{b,e}	17.7 (0.6)
Missing	3	0	1	2	0
CDR-SB (/18)	3.2 (2.2) ^b	5.7 (2.2) ^{b,c}	2.3 (1.0) ^b	1.9 (1.1) ^{b,e}	0
CDR-R					
0 No dementia	2	0	1	1	24
0.5 Very mild	16	1	8	7	0
1 Mild	8	6	1	1	0
2 Moderate	2	2	0	0	0
Missing	4	2	1	1	0
NPI-D, total (/144)	15.9 (15.1)	28.8 (16.1) ^c	9.1 (7.1)	7.8 (9.3) ^e	n/a
Missing	2	0	1	1	0

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CDR-R = Clinical Dementia Rating Scale–Global Rating; CDR-SB = Clinical Dementia Rating Scale–Sums of Boxes; FAB = Frontal Assessment Battery; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; NPI-D = Neuropsychiatric Inventory with Caregiver Distress scale; PNFA = progressive nonfluent aphasia; SemD = semantic dementia. ^aTotal possible scores for each behavioral measure are shown in parentheses. The NPI was not administered to controls. By definition, all controls had an unchanging CDR-R = 0. Statistical differences ($p < 0.05$) between groups are indicated as follows: ^bdisease group vs healthy controls; ^cbvFTD vs SemD; ^dSemD vs PNFA; ^ebvFTD vs PNFA.

(small) and 40% (moderate) reductions in MRI and behavioral rates of change with 80% power were estimated using standard formulae.^{27,28}

Standard protocol approvals and patient consents. The study received approval from the local institutional ethical standards committee on human experimentation. Written informed consent was received from all patients participating in the study.

RESULTS Baseline demographic, clinical, and neuropsychological characteristics. Mean baseline measures for patients with FTLD and controls are summarized in table 1.

Change in whole brain volumes and ventricular volumes. Mean annual rates of whole brain and ventricular change for the FTLD cohort and each subgroup are displayed in table 2. Compared with healthy controls, the FTLD cohort as a whole and each subgroup exhibited more rapid whole brain atrophy assessed using the BBSI. Ventricular expansion assessed using the VBSI was more rapid in the FTLD cohort as a whole, the SemD and PNFA subgroups, and there was also some evidence for a difference between the

bvFTD subgroup and controls (table 2). Rates of whole brain and ventricular change were not influenced by age ($p = 0.50$ [whole brain], $p = 0.80$ [ventricular]), gender ($p = 0.80$ [whole brain], $p = 0.20$ [ventricular]), or disease duration ($p = 0.81$ [whole brain], $p = 0.10$ [ventricular]) in the FTLD cohort.

Change in behavioral measures. Longitudinal behavioral data over the follow-up interval of approximately 1 year are presented in the figure and table 2. Numbers of subjects with longitudinal data available for each measure are shown; missing data were ignored in the analysis. The figure presents a categorical summary of change scores for the FTLD cohort.

The decline in Mini-Mental State Examination performance from baseline to follow-up for the FTLD cohort as a whole and for the language subgroups was greater than for healthy controls. There was also strong evidence for a greater deterioration on Clinical Dementia Rating Scale–Sums of Boxes (CDR-SB) scores for the FTLD cohort compared with controls, apparently driven by the PNFA subgroup.

Relationship between annualized atrophy rate and change in cognitive and behavioral measures. Relations between MRI and behavioral change measures are summarized in table 3. Decline in Mini-Mental State Examination score at 1 year was associated with increased whole brain atrophy rates for the FTLD cohort as a whole and the bvFTD subgroup, and associated with increased ventricular expansion rates in the language variant subgroups (SemD and PNFA). Deterioration in CDR-SB score was associated with higher rates of whole brain atrophy and ventricular enlargement for the FTLD cohort as a whole and for the bvFTD subgroup. Other relations between MRI and behavioral change measures were less consistent.

Sample size estimates. Estimated sample sizes for detection of a small (25%) and a moderate (40%) reduction in rates of change with 80% power (adjusting for control rates and assuming an annual trial attrition percentage of 10%) are summarized in table 4. Using BBSI measurements, 128 undifferentiated patients with FTLD, 115 patients with SemD, and 26 patients with PNFA would be required to detect a small treatment effect and correspondingly fewer patients in each group for detection of a moderate effect. Using VBSI measurements, larger patient cohorts would be required to detect an equivalent effect. For both BBSI and VBSI measures, detection of equivalent effects in the bvFTD subgroup would require a substantially larger sample.

Table 2 Mean (SD) annual rates of change of MRI and behavioral measures, and relationship of these outcome measures in FTLD patient groups to measures in healthy controls

	FTLD cohort (n = 32)	bvFTD (n = 11)	SemD (n = 11)	PNFA (n = 10)	Control (n = 24)
Whole brain atrophy					
% Baseline volume loss/y	2.3 (1.5)	1.4 (1.5)	2.6 (1.6)	2.9 (0.9)	0.1 (0.5)
Additional annual % loss compared with controls (95% CI)	2.30 (1.7 to 2.9)	1.40 (0.5 to 2.4)	2.50 (1.6 to 3.5)	2.80 (2.1 to 3.5)	—
<i>p</i>	<0.001 ^b	0.004 ^b	<0.001 ^b	<0.001 ^b	—
Ventricular expansion					
Expansion in mL per year	6.1 (5.2)	5.5 (6.7)	7.1 (4.9)	5.6 (3.8)	0.5 (1.1)
Additional annual gain compared with controls, mL/y (95% CI)	3.6 (1.6 to 5.5)	2.5 (−0.3 to 5.3)	4.8 (1.9 to 7.9)	2.8 (−0.1 to 5.7)	—
<i>p</i>	0.001 ^b	0.08	0.002 ^b	0.05	—
MMSE change					
Change from baseline score ^a	−2.2 (3.9)	−0.8 (4.7)	−2.9 (2.9)	−3.3 (3.7)	0.1 (0.8)
Additional change in score compared with controls (95% CI)	−2.5 (−4.7 to −0.2)	−1.4 (−4.4 to 1.6)	−2.8 (−5.6 to 0.1)	−4 (−7.5 to −0.5)	—
<i>p</i>	0.03 ^b	0.36	0.05	0.03 ^b	—
FAB change					
Change from baseline score ^a	−0.6 (2.7)	0.4 (1.8)	−0.9 (1.8)	−1.4 (4.0)	0.1 (0.7)
Additional change in score compared with controls (95% CI)	−0.8 (−2.1 to 0.5)	−0.1 (−1.7 to 1.5)	−1 (−2.5 to 0.6)	−2.2 (−5.0 to 0.5)	—
<i>p</i>	0.20	0.90	0.20	0.10	—
CDR-SB change					
Change from baseline score ^a	−1.8 (1.9)	−1.6 (2.3)	−1.5 (2.4)	−2.2 (1.2)	0
Additional change in score compared with controls (95% CI)	−1.8 (−2.9 to −0.7)	−0.5 (−3.9 to 2.9)	−1.1 (−2.6 to 0.3)	−1.9 (−3.1 to −0.6)	—
<i>p</i>	0.002 ^b	0.76	0.13	0.003 ^b	—
NPI-D change					
Change from baseline score ^a	0.8 (11.1)	4.6 (14.8)	−3.6 (10.7)	1.5 (5.8)	N/A

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CDR-SB = Clinical Dementia Rating Scale–Sums of Boxes, score/18; FAB = Frontal Assessment Battery, score/18; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination, score/30; NPI-D = Neuropsychiatric Inventory with Caregiver Distress scale, score/144; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

^aNegative change score represents a deteriorated performance at follow-up assessment.

^bSignificant.

Behavioral measures yielded generally larger estimated sample sizes than imaging measures, reflecting the considerably higher variance estimates of these behavioral measures.

DISCUSSION This study has several key findings. First, the data provide further evidence that rates of whole brain atrophy and ventricular enlargement obtained from semi-automated serial MRI measures are greater in patients with FTLD compared with controls and are comparable to previously published rates.^{13,16,29,30} The current rates of change were generally slightly higher in the language variants of FTLD (SemD and PNFA) than

the bvFTD group; however, this only reached significance when comparing PNFA with bvFTD for whole brain atrophy rates. The clinical utility of MRI biomarkers, based on estimated sample sizes needed to demonstrate a relevant therapeutic effect in future treatment trials, depends on the syndromic subtype of FTLD. Sample sizes may be more practical in the case of the language variants of FTLD as the behavioral variant is characterized by greater variability in atrophy rates (relative to the mean rate), which drives up projected sample sizes. Finally, while standard behavioral measures (Mini-Mental State Examination, Frontal Assess-

Figure Categorical summary of change scores for behavioral measures in the frontotemporal lobar degeneration (FTLD) cohort

Distributions of patients with FTLD demonstrating improved, stable, or deteriorated performance at follow-up assessment are shown (change scores coded as follows: improved ≥ 1 ; stable = 0; deteriorated ≤ -1). FAB = Frontal Assessment Battery **score/18; MMSE = Mini-Mental State Examination *score/30; CDR-R = Clinical Dementia Rating Scale-Global Rating; CDR-SB = Clinical Dementia Rating Scale-Sums of Boxes *score/18; NPI-D = Neuropsychiatric Inventory with Caregiver Distress scale *score/144.

ment Battery, and CDR-SB) provide some indication of disease progression in FTLD (as indexed by MRI outcomes), this depends on the FTLD subtype and the use of such behavioral biomarkers generates large sample size estimates.

An important issue concerns the comparability of our findings with previous work in this field, and in particular, the recent large US multicenter study.¹³ There are a number of factors that might account for discrepancies between studies: these factors include the composition of the FTLD study group (e.g., an uncertain proportion of genetic cases in the US study), methodology (e.g., use of an FTLD-optimized rather than standard CDR-SB measure in the US study), and analysis methods (e.g., correction for normal aging effects, reporting of ventricular volume change as an absolute rate rather than a proportion of baseline volume in our study). In addition, our FTLD cohort was substantially smaller than the US multicenter cohort. Finally, it is possible that there are true differences in the underlying FTLD populations in the two geographic regions (e.g., via differential operation of genetic or epigenetic effects).

Taking these various sources of difference into account, there is reassuringly a broad convergence of findings between the present study and previous data from the same single UK center,^{16,29} and more crucially, with US multicenter data.^{12,13} Comparable sample size estimates were generated for detection of an equivalent treatment effect. Furthermore, both the present study and the US multicenter study sug-

gest that substantially smaller sample sizes are required for the language variants of FTLD than for bvFTD. These findings are in keeping with our emerging understanding of the heterogeneous disease biology of FTLD, and highlight the need for accurate syndromic stratification. Whole brain atrophy and ventricular expansion rates were high across the SemD subgroup. SemD is a well-defined clinical syndrome with a characteristic neuroanatomic profile and a relatively specific histopathologic substrate,^{31,32} and therefore an attractive target for disease modification in clinical trials. Whole brain rates for the SemD group here correspond well with previous data for this syndrome.^{16,29} Although the PNFA subtype of FTLD is more anatomically and pathologically heterogeneous than the SemD subtype,³³ the present PNFA patient sample exhibited comparably high rates of whole brain atrophy, and correspondingly reduced estimated sample sizes. This finding requires corroboration in larger PNFA cohorts. In contrast to the language subgroups, bvFTD is clinically, anatomically, and pathologically heterogeneous: rates of clinical evolution are very variable, and a subgroup of patients exhibits a slow or nonprogressive disease course.^{17,18} This heterogeneity was reflected in the bvFTD subgroup here, even though entry was restricted to individuals with abnormal baseline brain MRI to avoid inclusion of phenocopy cases. Patients with bvFTD exhibited the widest range of atrophy rates, overlapping substantially with the control range and making the detection of treatment effects inherently more difficult. This issue has been

Table 3 Relationship between rates of whole brain and ventricular MRI measures of change and change in behavioral measures MMSE, FAB, CDR-SB, and NPI-D

	Increase in annual whole brain atrophy (%) (95% CI) ^a	p Value	Increase in ventricular volume (mL) (95% CI) ^a	p Value
MMSE change				
FTLD cohort	0.3 (0.2 to 0.4)	<0.001 ^b	0.3 (−0.3 to 0.8)	0.4
bvFTD	0.2 (0.0 to 0.4)	0.05	0.4 (−0.3 to 1.4)	0.1
SemD	0.1 (−2.0 to 2.1)	0.8	0.8 (0.4 to 1.3)	0.01 ^b
PNFA	0.0 (−1.0 to 1.0)	0.9	1.2 (−0.4 to 2.8)	0.08
FAB change				
FTLD cohort	0.3 (0.1 to 0.5)	0.005 ^b	0.6 (0.1 to 1.1)	0.02 ^b
bvFTD	0.2 (−7.0 to 7.0)	0.7	0.9 (−2.9 to 4.6)	0.4
SemD	1.0 (−10.6 to 11.4)	0.5	2.3 (−2.9 to 7.4)	0.2
PNFA	0.1 (−0.3 to 0.5)	0.3	0.7 (−0.4 to 1.7)	0.1
CDR-SB change				
FTLD cohort	0.5 (0.2 to 0.7)	0.001 ^b	1.2 (0.6 to 1.9)	0.001 ^b
bvFTD	0.3 (−2.4 to 3.0)	0.04 ^b	1.7 (0.7 to 2.8)	0.03 ^b
SemD	0.2 (−2.9 to 3.1)	0.6	0.3 (−0.6 to 1.3)	0.1
PNFA	0.3 (0.0 to 0.7)	0.09	1.3 (−3.0 to 5.6)	0.4
NPI-D change				
FTLD cohort	0.0 (0.0 to 0.1)	0.5	0.2 (−0.1 to 4.3)	0.05
bvFTD	0.0 (−0.1 to 0.2)	0.5	0.2 (−0.1 to 0.4)	0.2
SemD	0.2 (−0.1 to 0.5)	0.1	0.3 (0.0 to 0.6)	0.04 ^b
PNFA	0.0 (−0.4 to 0.5)	0.7	0.5 (0.0 to 1.0)	0.05

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CDR-SB = Clinical Dementia Rating Scale–Sums of Boxes; FAB = Frontal Assessment Battery; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; NPI-D = Neuropsychiatric Inventory with Caregiver Distress scale; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

^aPer unit decline in cognitive score.

^bSignificant.

raised in previous imaging studies including bvFTD cases.^{13,29,34} Improved stratification of these cases is needed to distinguish reliably patients with more or less rapidly progressive disease, and thereby to reduce sample sizes needed for detection of a meaningful treatment effect.

The cognitive and behavioral indices evaluated here demonstrated at best limited potential as biomarkers of FTLD progression in this sample. At baseline assessment the Mini-Mental State Examination, CDR-SB, and Frontal Assessment Battery scores differed between patients and controls, and total NPI-D score captured the increased behavioral symptoms in the bvFTD subgroup compared with the language subgroups. However, as longitudinal measures, only the Mini-Mental State Examination and CDR-SB demonstrated higher rates of decline compared with controls and associations between these rates of decline and whole brain atrophy rates. In addition, these associations were largely driven by

particular FTLD subgroups. While there is a need for caution in assuming that MRI measures give a true indication of disease progression against which behavioral markers can be evaluated, it is reasonable to assume that behavioral measures are intrinsically more subjective and so have a greater noise-to-signal ratio than automated MRI techniques measuring brain volume changes. Taking this caveat into account, our findings overall do not support the use of standard, widely available behavioral indices alone as longitudinal biomarkers in FTLD, because of the impractically large sample sizes required to detect meaningful treatment effects (table 4). This lack of utility may reflect at least in part the high proportion of patients who demonstrated longitudinally improved scores (figure). In line with previous findings,¹² this was particularly evident on behavioral and frontal executive measures (NPI-D and Frontal Assessment Battery). While neuronal loss and functional decline cannot be assumed to have a simple monotonic relationship, the current evidence does suggest that commonly used cognitive and behavioral indices lack sensitivity in detecting decline in FTLD. Although more tailored and detailed neuropsychological tests have shown increased sensitivity,¹³ our intention here was to evaluate global measures used widely in clinical and research settings. These observations support the need for more representative and customized behavioral indices that could be widely applied in the FTLD population, either alone or in conjunction with MRI biomarkers, and work on some promising candidates is already under way.^{12,13}

There are several limitations to the present study. Subjects agreeing to participate in a study of this kind might not accurately represent those subjects who would be recruited to a therapeutic trial. While the true magnitude of this potential limitation is difficult to assess, we attempted to guard against it by ascertaining consecutive patients meeting standard current diagnostic criteria with abnormal neuroimaging findings (i.e., likely entry criteria for future trials). Individuals declining entry or failing to complete the study had demographic characteristics broadly similar to those who were involved to completion. It is likely, however, there was a selection bias, in that most FTLD cases not recruited (or unable to complete the study) belonged to the bvFTD group and were more severely affected: this would tend to overestimate sample sizes needed to detect a treatment effect in the bvFTD group. On the other hand, this bias realistically reflects the anticipated recruitment pattern to future therapeutic trials, in which severely affected or poorly compliant patients would be unlikely to be targeted. Subject numbers were small, and pathologic data were not available.

Table 4 Sample size estimates for future clinical trials based on a small (25%) or moderate (40%) change in imaging and behavioral outcomes for FTL D cohort and subgroups

	FTLD cohort (n = 32)		bvFTD (n = 11)		SemD (n = 11)		PNFA (n = 10)	
	Small effect	Moderate effect	Small effect	Moderate effect	Small effect	Moderate effect	Small effect	Moderate effect
Whole brain atrophy								
% Loss from baseline brain	128	50	360	141	115	45	26	10
Ventricular expansion, mL/y	239	93	495	193	157	61	152	59
MMSE change	661	258	3,546	1,385	312	122	372	145
FAB change	4,895	1,912	8,013	3,130	1,074	420	2,206	862
CDR-SB change	298	116	582	227	691	270	85	33
NPI-D change	49,434	19,310	2,834	1,107	2,428	948	4,102	1,602

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CDR-SB = Clinical Dementia Rating Scale-Sums of Boxes; FAB = Frontal Assessment Battery; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; NPI-D = Neuropsychiatric Inventory with Caregiver Distress scale; PNFA = progressive nonfluent aphasia; SemD = semantic dementia.

Large longitudinal multicenter studies with pathologic confirmation will be essential to evaluate the predictive value of candidate biomarkers for specific histopathologic substrates that will be the ultimate target of treatment in FTL D. In addition, validation of effective neuroimaging measures of regional atrophy may offer improved disease differentiation and sensitivity for detection of change.^{16,34} However, as with AD research, the current data show that rates of whole brain and ventricular volume change (measured using automated BSI techniques) are promising as practical outcome measures for assessing treatment effects in future clinical trials in FTL D. The clinical syndromic subtype of FTL D importantly affects the utility of these imaging biomarkers, and it will be important that FTL D syndromes are carefully differentiated in future clinical trials of targeted disease-modifying therapies.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Elizabeth Gordon with guidance from Dr. Lois Kim.

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DISCLOSURE

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