Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year

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ABSTRACT

Background: Measurement of volumetric changes with MR might be a useful surrogate endpoint for clinical trials in frontotemporal lobar degeneration (FTLD). Because there is only limited longitudinal imaging data currently available, we measured the rate of change over 1 year of whole brain volume (WBV) and ventricular volume (VV) in patients with FTLD.

Methods: Subjects with an FTLD cognitive syndrome were recruited from five centers using standard clinical diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia (PNFA), semantic dementia (SMD), and progressive logopenic aphasia. Structural brain imaging, using three-dimensional T1-weighted sequences at 1.5 teslas, and cognitive, behavioral, and functional assessments were performed at baseline and approximately 1 year later. The boundary shift integral algorithm was used to determine change in WBV and VV.

Results: There were 76 patients (mean age 64 years; 41 men and 35 women) who had usable baseline and annual scans. The group-wise annualized change was −1.62% (SD 1.03, range +0.69 to −3.6) for WBV and 11.6% (SD 5.9, range −1.3 to 23.9) for VV. Rates of change were similar among bvFTD, PNFA, and SMD groups. Longitudinal changes in WBV and VV were correlated with decline on clinical global and cognitive measures.

Conclusions: Multicenter, serial measurements of whole brain volume (WBV) and ventricular volume (VV) from magnetic resonance scans were feasible in patients with frontotemporal lobar degeneration (FTLD). Using WBV or VV as outcome measures would require recruiting (at 80% power) 139 or 55 subjects per group to detect a small (25%) or medium-sized (40%) effect in a randomized, placebo-controlled trial of a putative agent for FTLD. *Neurology*® 2009;72:1843–1849

GLOSSARY

AD = Alzheimer disease; **BSI** = boundary shift integral; **bvFTD** = behavioral variant frontotemporal dementia; **CBD** = corticobasal degeneration; **CI** = confidence interval; **FTLD** = frontotemporal lobar degeneration; **FTLD-CDR** = frontotemporal lobar degeneration modified Clinical Dementia Rating Scale; **MMSE** = Mini-Mental State Examination; **MR** = magnetic resonance; **NS** = not significant; **PLA** = progressive logopenic aphasia; **PNFA** = progressive nonfluent aphasia; **PSP** = progressive supranuclear palsy; **SMD** = semantic dementia; **TIV** = total intracranial volume; **VV** = ventricular volume; **WBV** = whole brain volume.

Brain imaging might be a useful measure of disease progression in clinical trials in neurodegenerative diseases. For example, reductions in whole brain volume (WBV) have paralleled clinical progression in several Alzheimer disease (AD) clinical trials, including ones testing milameline,[1] AN-1792,[2] and donepezil.[3] Because of the greater syndromic heterogeneity of frontotemporal lobar degenerations (FTLDs), structural neuroimaging might be particularly useful across different clinical syndromes that share a common molecular basis. There is only limited information on the magnitude of change in longitudinal studies of FTLD, however.[4-7]

Supplemental data at www.neurology.org

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Table 1 Demographics and baseline imaging features of patients, by clinical syndrome and in group as a whole

	bvFTD	PNFA	SMD	PLA	All (no PLA)	All
n	34	17	16	9	67	76
Age, mean (SD), y	60.6 (8.6)	65.6 (7.0)	68.8 (8.0)	64.3 (8.1)	63.9 (8.7)	63.9 (8.6)
Sex (F:M)	11:23	9:8	7:9	8:1	27:40	35:41
Baseline MMSE, mean (SD)	26.1 (4.0)	22.6 (6.5)	23.8 (4.4)	21.9 (3.3)	24.7 (5.0)	24.3 (4.9)
Time between scans, mean (SD), y	1.11 (0.19)	1.12 (0.21)	1.10 (0.14)	0.99 (0.03)	1.11 (0.18)	1.10 (0.18)
Brain atrophy ratio (whole brain volume/ total intracranial volume)						
Mean (SD)	0.82 (0.04)	0.84 (0.02)	0.84 (0.04)	0.84 (0.03)	0.83 (0.04)	0.83 (0.04)
Minimum	0.71	0.81	0.76	0.77	0.71	0.71
Maximum	0.90	0.87	0.90	0.90	0.90	0.90
Baseline brain volume (uncorrected for total intracranial volume), mL						
Mean (SD)	1,303.98 (163.08)	1,272.60 (80.01)	1,331.15 (141.59)	1,226.43 (81.22)	1,302.51 (140.84)	1,293.50 (137.01)
Minimum	1,013.8	1,108.6	1,123.1	1,149.7	1,013.8	1,013.8
Maximum	1,647.9	1,410.6	1,518.6	1,359.6	1,647.9	1,647.9
Baseline ventricular volume (uncorrected for total intracranial volume), mL						
Mean (SD)	52.86 (22.03)	56.05 (39.09)	54.22 (16.54)	32.98 (6.75)	53.99 (26.02)	51.50 (25.44)
Minimum	14.9	19	19.2	22.4	14.9	14.9
Maximum	119.3	178.2	76.8	41	178.2	178.2

bvFTD = behavioral variant frontotemporal dementia; PNFA = progressive nonfluent aphasia; SMD = semantic dementia; PLA = progressive logopenic aphasia; MMSE = Mini-Mental State Examination.

We performed serial volumetric magnetic resonance (MR) scans in a group of patients with FTLD who were part of a multicenter, 1-year, simulated clinical trial. We analyzed the scans using automated methodology to measure WBV and ventricular volume (VV). The design of the parent study and the longitudinal cognitive, functional, and behavioral data[8] have been reported.

METHODS

Subjects. Patients with an FTLD cognitive/behavioral syndrome were recruited from five academic medical centers over 2 years. Patients or their responsible family member provided written informed consent. The study was approved by the institutional review boards of all five clinical sites. The inclusion and exclusion criteria have been previously reported.[8] Standard clinical diagnostic criteria were used for the syndromes of behavioral variant frontotemporal dementia (bvFTD), progressive nonfluent aphasia (PNFA), progressive logopenic aphasia (PLA), and semantic dementia (SMD). Because of a concern that patients with PLA might have AD pathology rather than an FTLD pathology,[9-12] these subjects were excluded from group analyses. Subjects were required to have frontal, temporal, or insular atrophy or dysfunction by brain imaging. Structural brain imaging and cognitive, behavioral, and functional assessments were performed at baseline and approximately 1 year later.

Cognitive and behavioral assessments. A battery of cognitive, functional, and behavioral assessment were performed baseline and then at the annual follow-up visit. These have been previously described.[8] These included the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change,[13] an FTLD-specific Clinical Dementia Rating (FLTD-CDR)[8] that included two additional domains: language and behavior and the Mini-Mental State Examination (MMSE).[14]

We constructed two cognitive test composites to express the neuropsychological test results in a concise manner. The composition and development of the composites are described in detail elsewhere.[8] One composite, the executive composite, included six variables (Trails, backward digit span, Digit Symbol, Stroop, number cancellation, and total errors on Stroop interference test, Trails, and delayed recognition). The other, a language composite, included five variables (Boston Naming test, the two verbal fluency scores, Similarities, and immediate recall). We also constructed a global composite by combining the elements of both the executive and language composites.

Imaging. MR images were acquired using three-dimensional volumetric T1-weighted imaging sequences at 1.5 teslas. The scanning parameters were as follows: A coronal volume with 124 contiguous partitions, each 1.6 mm in thickness, was acquired. The field of view was 24 × 24 cm, with 256 × 192 matrix, bandwidth 16 kHz, 25° flip angle, repetition time = 23 msec, and echo time = minimum full echo time. The boundary shift integral (BSI) algorithm was used to determine change in WBV and VV.[15,16] Differences were calculated in pairwise fashion between the baseline and follow-up scans. After intensity normalization of both scans and spatial registration of the follow-up to the baseline scan, intensity differences between the two scans at the brain–CSF boundary were used to compute change in volume. The algorithm corrects drifts or discontinuities in gradient calibration between the baseline and follow up scans by using 9 degrees of freedom registration to a brain/skull composite target. The whole brain atrophy rate reflects shrinkage of the brain on

the follow-up scan relative to the baseline scan from out-to-in at the cortical surface and from in-to-out at the ventricular surface. The ventricular atrophy rate was derived by creating a binary mask for each subject that selectively extracted ventricular change. The binary mask was an approximate area overlaying the ventricles within which the BSI was measured. Quality control testing in our laboratory shows that the nonparametric intraclass correlation coefficient for test–retest reproducibility of rate measurements from serial MRI scans with the BSI method was 0.91 for ventricle and 0.89 for brain.[17]

Total intracranial volume (TIV) was determined by tracing the margin of the inner table of the skull on consecutive slices from a T1-weighted sagittal sequence with 5-mm contiguous sections.[18] We used the TIV value to calculate a baseline brain atrophy measure, by taking the ratio of WBV and TIV, for descriptive purposes.

Analyses. The differences between baseline and follow-up scans were analyzed in each syndromic subgroup and in the group as a whole, after excluding subjects with PLA. The difference in WBV and VV between the first and second scans was expressed as a percent change from the first scan, and was then annualized by dividing by the interval between scans/365 days. Descriptive statistics for the baseline and change values for WBV and VV are given in tables 1 and 2. Spearman correlation coefficients were derived to describe the relationship between change in imaging features and change in cognitive and behavioral assessments. Linear regression analyses were also performed, with annual percent change in WBV and VV as the dependent variables, and FTLD-CDR and cognitive composites as independent variables, controlling for age, sex and diagnostic group (modeling with indicator variables), time between scans (years), and baseline MR value. To assess the adequacy of using annualized percent change as an outcome variable, Bland–Altman plots were constructed between the annualized percent change and the geometric mean of the MR data. Finally, we performed power calculations by assuming the use of a two-tailed t test for a two-group study, an α of 0.05, and a β of 0.80. We derived numbers of subjects per group after taking attrition into account.

RESULTS

Demographics/descriptives. Of 107 patients who were enrolled at baseline, 103 (96%) successfully completed an MR scan at baseline. The other 4 had technically unacceptable scans (excessive motion artifact). At the follow-up visit, 79 (of the 90 patients who returned for the follow-up visit, 88%) had MR scans of sufficient quality to be analyzed. The current analysis set included 76 patients (mean age 64 years; 41 men and 35 women) who had usable MR scan pairs and had full clinical data. Of the 76 subjects, 34 had bvFTD, 17 had PNFA, 16 had SMD, and 9 had PLA. Table 1 shows demographic and clinical features of patients. Sixty-nine patients had follow-up scans performed within 11 to 16 months of the baseline scan; the remaining 7 had scans that were performed between 17 and 22 months after the baseline visit. Table 1 also shows the baseline imaging values.

Annual change values. In the group as a whole (excluding PLA subjects), the annualized percent change was −1.6% for WBV and 11.6% for VV

Table 2 Annual percent change and absolute change in imaging and key clinical measures

	bvFTD	PNFA	SMD	PLA	All (no PLA)	All
Brain volume						
Annual % change, mean (SD)	−1.60 (1.11)	−1.61 (0.89)	−1.66 (1.04)	−2.08 (1.00)	−1.62 (1.03)	−1.67 (1.03)
Annual % change, maximum	−3.51	−3.53	−3.6	−3.86	−3.6	−3.86
Annual % change, minimum	−0.08	0.06	0.69	−0.59	0.69	0.69
Annual change, mean (SD), mL	−20.83 (14.53)	−20.46 (11.48)	−21.79 (14.43)	−25.09 (11.81)	−20.97 (13.61)	−21.46 (13.40)
Percent of patients within 2 SDs (>−1.06%) of normal range	38	22	19	0	30	26
Ventricular volume						
Annual % change, mean (SD)	11.19 (6.80)	11.04 (4.40)	13.23 (5.40)	14.78 (5.56)	11.64 (5.94)	12.01 (5.95)
Annual % change, maximum	23.89	17.5	23.85	24.1	23.89	24.1
Annual % change, minimum	−1.33	1.32	4.99	7.89	−1.33	−1.33
Percent of patients within 2 SDs (<5.06%) of normal range	24	18	7	0	18	16
Annual change, mean (SD), mL	5.94 (4.40)	6.33 (4.47)	7.42 (3.95)	4.79 (1.89)	6.39 (4.29)	6.21 (4.11)
Clinical measures, mean (SD)						
FTLD-CDR	2.76 (2.95)	2.94 (3.77)	3.47 (2.44)	4.56 (5.13)	2.98 (3.04)	3.16 (3.34)
MMSE	−2.79 (4.41)	−4.20 (4.81)	−8.43 (4.91)	−5.89 (4.86)	−4.40 (5.08)	−4.59 (5.04)
Executive composite	−7.92 (8.26)	−4.43 (6.08)	−6.59 (9.85)	−9.60 (6.41)	−6.73 (8.29)	−7.13 (8.08)
Language composite	−7.45 (6.55)	−4.94 (4.88)	−6.49 (4.38)	−8.20 (5.60)	−6.67 (5.74)	−6.87 (5.71)
Global composite	−7.58 (6.70)	−4.31 (3.91)	−6.15 (4.87)	−8.90 (5.02)	−6.45 (5.76)	−6.80 (5.69)

bvFTD = behavioral variant frontotemporal dementia; PNFA = progressive nonfluent aphasia; SMD = semantic dementia; PLA = progressive logopenic aphasia; FTLD-CDR = frontotemporal lobar degeneration modified Clinical Dementia Rating Scale; MMSE = Mini-Mental State Examination.

Table 3 Linear regression estimates describing the association between annualized percent changes in whole brain volume and ventricular volume for all patients with bvFTD, PNFA, and SMD and either FTLD-CDR or cognitive composites

	Estimate	95% CI	*p* Value
Whole brain volume: annual % change			
Change FTLD-CDR	−0.1809	(−0.2552, −0.1067)	<0.0001
Change executive composite	0.0396	(0.0057, 0.0734)	0.0263
Change language composite	0.0834	(0.0381, 0.1288)	0.0007
Change global composite	0.0797	(0.0325, 0.1270)	0.0018
Ventricular volume: annual % change			
Change FTLD-CDR	0.5650	(0.0684, 1.0616)	0.0296
Change executive composite	−0.2861	(−0.4863, −0.1039)	0.0034
Change language composite	−0.5340	(−0.7816, −0.2864)	<0.0001
Change global composite	−0.5720	(−0.8231, −0.3208)	<0.0001

Regression models adjusted for diagnosis (using indicator terms), age, sex, time between scans, and baseline frontotemporal lobar degeneration modified Clinical Dementia Rating Scale (FTLD-CDR) or composite scores.
CI = confidence interval; bvFTD = behavioral variant frontotemporal dementia; PNFA = progressive nonfluent aphasia; SMD = semantic dementia.

(table 2). These changes correspond to a mean annual decline in WBV of 21 mL and an increase in VV of 6.4 mL. The three syndromes—bvFTD, PNFA, and SMD—showed similar means, standard deviations, and ranges (all within-syndromic differences were $p > 0.10$). The PLA group exhibited slightly more atrophy than the other groups. Women had virtually identical annualized changes compared with men for both WBV (−1.73% vs −1.53%, not significant [NS]) and VV (13.1% vs 10.7%, NS). There was no correlation of age with either WBV or VV. Figures e-1 and e-2 on the *Neurology*® Web site at www.neurology.org show the percent annualized changes for WBV and VV in relation to baseline values. There was also no relationship using Spearman correlation coefficients between annualized change values for the syndromes of bvFTD, PNFA, and SMD combined and either baseline volumes (WBV, $r = 0.06$, NS; VV, $r = 0.12$, NS) or baseline brain atrophy (WBV, $r = -0.21$, $p = 0.07$; VV, $r = 0.15$, NS).

We identified 15 normal volunteers (mean age 70 years [range 51–75 years]; 7 men) from Mayo Clinic Rochester Alzheimer's Disease Research Center with serial scans and found that their annual percent change in WBV was −0.39 ± 0.36% (range −1.01 to 0.24) and in VV was 2.34 ± 1.36% (range 5.66 to −0.35) ($p < 0.001$ compared with the patients with FTLD, for both WBV and VV). Table 2 shows the number of cases in our study group with annual percent change values on imaging that fell within 2 SDs of the normal range. Some patients, mainly among the bvFTD group, did not exceed the normal rate of brain volume loss or ventricular expansion.

Correlations with baseline levels and change in cognitive measures. For the syndromes of bvFTD, PNFA, and SMD separately and as a group, baseline FTLD-CDR and WBV ($r \approx 0.3$) or VV ($r \approx 0.3$) were correlated ($p < 0.01$; for all except language and WBV, $p = 0.03$).

The results from the Bland–Altman analysis indicated that the annualized percent change was an adequate summary, in that there was no association between this transformation and the geometric mean of the MR data. Summaries from a series of linear regression analyses comparing change scores on the FTLD-CDR and the cognitive composites and changes in WBV and VV are shown in table 3. All but two reached a threshold of $p = 0.006$ when using the Bonferroni adjustment.

Sample size considerations. We performed sample size calculations (table 4) using the annual percent changes in WBV and VV and either small (25%) and

Table 4 Sample size (per group) estimates for enrollment in clinical trials in which brain volume or ventricular volume are outcome measures, for small (25%) or conservative medium (40%) effect sizes in a *t* test*

	bvFTD	PNFA	SMD	PLA	All (no PLA)	All
Brain volume: annual % change, mean (SD)	−1.60 (1.11)	−1.61 (0.89)	−1.66 (1.04)	−2.08 (1.00)	−1.62 (1.03)	−1.67 (1.03)
Small effect size	165	105	135	81	139	131
Medium effect size	66	42	54	32	55	53
Ventricular volume: annual % change, mean (SD)	11.19 (6.80)	11.04 (4.40)	13.23 (5.40)	14.78 (5.56)	11.64 (5.94)	12.01 (5.95)
Small effect size	127	55	58	50	90	85
Medium effect size	51	23	24	20	36	35

All estimates were multiplied by 1.35 to account for the observed attrition.
*$\beta = 80\%$, $\alpha = 0.05$, two sample.
bvFTD = behavioral variant frontotemporal dementia; PNFA = progressive nonfluent aphasia; SMD = semantic dementia; PLA = progressive logopenic aphasia.

medium (40%) effect sizes. We also took attrition of 26% into account to formulate the number of patients to be enrolled. VV exhibited somewhat more favorable estimates than WBV.

DISCUSSION We have shown that it was feasible to perform quantitative brain imaging in patients with FTLD over a 1-year interval. If a patient could be successfully scanned at the baseline visit, there was a nearly 90% probability that a follow-up scan could be completed. Serial measurements of WBV and VV in FTLD syndromes showed that there was a readily detectable change over that interval. The different clinical syndromes in the FTLD spectrum showed roughly similar quantitative changes. There was a moderate amount of individual variability in both baseline measurements and the amount of annual change. The declines in brain volume and concomitant increases in ventricular size were correlated with the declines in MMSE, FTLD-CDR, and the cognitive composites. If one measurement were to be designated as primary, VV seemed to be the more efficient measure based on the observed mean differences and their variances.

Prior studies of FTLD included fewer subjects, but the range of annual change in WBV and VV were similar to the values reported here. A study from London, UK,[6] found that the annual rate of WBV loss in a group of 30 patients with FTLD of various clinical subtypes was 3.15 ± 2.08%, slightly larger in magnitude and variation than our finding of 1.67 ± 1.04%. Another recent study from London in 21 patients with SMD found the rate of change in WBV to be 39.6 ± 31.9 mL and in VV to be 8.9 ± 4.4 mL.[7] Our values were somewhat smaller for WBV, 21.8 ± 14.4 mL, but similar for VV, 7.4 ± 4.0 mL. Some of the difference in the rate of brain volume loss could have arisen because of differences in inclusion criteria or clinical severity. However, simple correlational analyses in our cohort provided little support for an impact of baseline disease severity, as measured by baseline brain atrophy or brain volume, on rates of change in WBV and VV in our group of patients. A prior study of a small group of patients with pathologically proved FTLD with ubiquitin inclusions from our laboratory has shown that the rate of WBV seemed to accelerate over time.[4] If patients with an earlier stage of disease indeed have lower rates of brain loss, trialists need to take that into account in designing future trials in FTLD. Patients who are at the earliest stages of the disease may be preferred for conceptual reasons, but larger numbers would need to be recruited to accommodate a smaller decline in brain volume over time. Our inclusion criteria required that patients have focal atrophy or focal hypometabolism on imaging at baseline to avoid patients with nonprogressive conditions. Had we included patients with normal imaging, we almost certainly would have found smaller rates of brain volume loss and ventricular expansion.[19] Nonetheless, there were patients, particularly among the bvFTD group, who experienced brain volume loss and ventricular expansion that was within 2 SDs of normal controls from our laboratory.

Sample size calculations using our estimates of change and their variability show that imaging features seem to be more efficient than clinical features,[8] comparing equivalent effect sizes. The sample size needed to detect a conservative moderate effect was 99 subjects per group for the FTLD-CDR and 69 for the global cognitive composite,[8] whereas the equivalent sample sizes for WBV and VV were 41 and 27 subjects. Because there is no experience with a successful therapy in FTLD, it is impossible to know what kind of therapeutic effect sizes are feasible. Moreover, it is also not known whether a successful therapy would have the same magnitude of effect on clinical and imaging measures. It seems plausible that a therapy that produced a small change in brain volume, for example, could produce a moderate or large effect on a clinical marker. In contrast, it seems unlikely that the opposite would occur.

Prior longitudinal imaging studies of patients with dementia and autopsy-proved corticobasal degeneration (CBD),[5] a tauopathy related to FTLD, showed that the rate of WBV loss and ventricular expansion exceeded the rates we show here for the FTLD cognitive syndromes. In five CBD patients, the rate of WBV loss was 2.3% per year, and the VV expansion was 16.2% per year. In contrast, rates for patients with dementia and progressive supranuclear palsy (PSP) were 1% for WBV and 10.9% for VV.[5] Another study of PSP noted a rate for WBV loss of 1.2%.[20] Uncertainty about the range of severity of cases in other studies makes it difficult to draw conclusions about differential atrophy rates across different syndromes in the FTLD-tauopathy spectrum, but if CBD patients were to be included in an FTLD clinical trial, our sample size estimates would be appropriate but conservative. For PSP, larger sample sizes would be needed.

The correlations between changes in imaging features and changes in clinical measures provide support for the use of brain imaging as a surrogate outcome measure in clinical trials of FTLD. However, the key qualification of imaging as a surrogate marker—demonstration that a treatment-induced change in imaging correlates with treatment-induced changes in cognition and behavior—cannot be addressed with this study. Because only approximately

25% of the variance in WBV changes is shared with the FTLD-CDR change score, it is not a certainty that changes in brain imaging will correlate with treatment effects in therapeutic trials.

In comparison with AD,[21] the amount of annual change in brain volume and VV seems to be greater in our sample of subjects with FTLD. Among patients with "fast-progressing" AD,[21] the annualized percent change in WBV was 1.4%, whereas the mean change in our patients with FTLD was 1.6%. Similarly, the annualized percent change in VV in the patients with fast-progressing AD[21] was 6.4%, compared with 11.6% in our patients with FTLD. This observation must be tempered by the possibility that recruitment criteria for different studies may lead to enrollment of subjects at different stages of their disease. Our patients with FTLD may be at a point in their disease where loss of brain volume is high, whereas the patients with AD, drawn from the Mayo Alzheimer's Disease Research Center, may have been at some milder level. Taking the differences between patients with FTLD and patients with AD at face value, however, suggests that the higher rate of brain atrophy in FTLD makes this disorder a more favorable one in which to use brain imaging as a clinical trial outcome measure.

The amount of change among patients with FTLD is far greater than that seen in normal elderly subjects in our own group or in published series (0.5% for WBV[20,21] and 1.7% for VV[21]). Despite our attempts to identify patients with progressive disease, some of our patients with FTLD had small changes in WBV and VV that were in the range seen in the normal controls. We cannot say at this point whether subjects with FTLD and slower rates of brain volume loss have different pathologic processes than the other patients.

A weakness of using WBV and VV, as opposed to regional volumetric measures, is that the whole brain measures may be more insensitive to disease-related brain deterioration. SMD may be the most dramatic example of an FTLD characterized by regionally specific anterior temporal lobe atrophy.[10,22,23] The recent study that used manual segmentation of the temporal lobe for a longitudinal study of patients with SMD found that the value of the mean change/SD (Cohen *d*) was 1.24 for WBV but 2.33 for left temporal lobe volume.[7] These values indicate that the use of temporal lobe volumetric measurements would have far more power to detect change than WBV, at least in patients with SMD. A similar regional predilection for bvFTD or PNFA might also favor regional measurements over global ones. Measurement approaches are more complicated in bvFTD, however, because the regional involvement might involve any or all of cortices in orbital frontal, anterior cingulate, anterior insula, or anterior temporal locations bilaterally.[24,25] The situation in PNFA is equally challenging for regional volumetry because the inferior frontal and insular regions particularly involved in PNFA[10,26] would be difficult to delineate reliably by manual tracing. However, syndrome-specific regions, once known, could be embedded in a template that could then be used for automated regional morphometric measurements. Finally, there remains the problem of combining, in a clinical trial, patients with identical molecular pathologies who happen to have different clinical and anatomic signatures. With a variety of brain areas potentially affected, regional measurement perhaps could be individualized at entry into the trial. However, that might increase rather than decrease between subject variability. Further analyses are needed to determine which approach, whole brain or regional measurements, has the greatest reliability, precision, and effect size magnitude.

AUTHOR CONTRIBUTIONS

Statistical analyses were performed by N. Mercaldo under the supervision of D. Knopman.

DISCLOSURE

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