MRI data-driven algorithm for the diagnosis of behavioral variant frontotemporal dementia

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† Data used in preparation of this article were obtained from the Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI) database (http://4rtni-ftldni.ini.usc.edu/). The investigators at NIFD/FTLDNI contributed to the design and implementation of FTLDNI and/or provided data but did not participate in analysis or writing of this report (unless otherwise listed). The FTLDNI investigators included the following individuals:
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Word Count: 3741

Abstract

Introduction: Structural brain imaging is paramount for the diagnosis of behavioral variant of frontotemporal dementia (bvFTD), but it has low sensitivity leading to erroneous or late diagnosis.

Methods: A total of 515 subjects from two different bvFTD cohorts (training and independent validation cohorts) were used to perform voxel-wise morphometric analysis to identify regions with significant differences between bvFTD and controls. A random forest classifier was used to individually predict bvFTD from deformation-based morphometry differences in isolation and together with semantic fluency. Ten-fold cross validation was used to assess the performance of the classifier within the training cohort. A second held-out cohort of genetically confirmed bvFTD cases was used for additional validation.

Results: Average ten-fold cross-validation accuracy was 89% (82% sensitivity, 93% specificity) using only MRI and 94% (89% sensitivity, 98% specificity) with the addition of semantic fluency. In the separate validation cohort of definite bvFTD, accuracy was 88% (81% sensitivity, 92% specificity) with MRI and 91% (79% sensitivity, 96% specificity) with added semantic fluency scores.

Conclusion: Our results show that structural MRI and semantic fluency can accurately predict bvFTD at the individual subject level within a completely independent validation cohort coming from a different and independent database.

Keywords

Frontotemporal dementia -Magnetic resonance -Deformation-based morphometry -

Classification- Machine learning

Abbreviations

FTD: frontotemporal dementia

GRN: progranulin

MAPT: microtubule-associated protein tau

C9orf72 : chromosome 9 open reading frame 72

bvFTD: behavioural variant of frontotemporal dementia

CNCs: cognitively normal controls

DBM: deformation-based morphometry

FTLDNI: frontotemporal lobar degeneration neuroimaging initiative

FTLD: frontotemporal lobar degeneration

T1w: T1 weighted

GENFI: Genetic frontotemporal dementia initiative

MMSE: Mini mental state examination

MoCA: Montreal cognitive assessment

FTLD-CDR: Frontotemporal lobar degeneration Clinical Dementia Rating score

CGI: Clinical global impression

FRS: Frontotemporal dementia rating scale

FDR: False Discovery Rate

PCA: Principal component analysis

PCs: Principal components

SF: Semantic fluency

ROC: Receiver operating characteristic curves

AUC: Area under the curve

LR+: positive likelihood ratio

LR-: negative likelihood ratio

INTRODUCTION

The heterogeneity of frontotemporal dementia (FTD) is a hallmark of the disease with significant variations in heritability, pathology and clinical presentations.[1] First, although most cases of FTD are sporadic, 10-30% are caused by an autosomal dominant mutation (most commonly progranulin -*GRN*-, microtubule-associated protein Tau -*MAPT*- and chromosome 9 open reading frame 72 -C9orf72-).[2 3] Second, in terms of the underlying pathology, there are three main groups according to the major protein involved, all of which are characterized by selective degeneration of the frontal and temporal lobes: Tau, transactive response DNA-binding protein of 43 kDa -TDP-43-, and the tumor associated protein fused in sarcoma -FUS-.[4 5] In the absence of molecular biomarkers, and when combined with the syndromic overlap with other neurodegenerative disorders and psychiatric disorders, a confirmed behavioral variant frontotemporal dementia (bvFTD) diagnosis is often difficult to achieve and heavily relies on brain imaging. [6]

While the presence of fronto-temporal atrophy on MRI increases the level of diagnostic confidence and has high specificity, it lacks sensitivity particularly in the initial stages of the disease, leading to erroneous or late diagnosis.[7 8] It is therefore necessary to extract MRI features that have better discriminatory power to aid in diagnosis. Recently, machine learning techniques have been applied to distinguish between bvFTD and Cognitively Normal Subjects (CNCs), Alzheimer Disease or other psychiatric and neurologic disorders on an individual level using MRI-based features.[9-17] These studies vary greatly on their population and methodology. In general, they achieved moderate to high accuracy distinguishing bvFTD. However, sample sizes were small, training and test cohorts did not come from the independent datasets and, therefore, the clinical applicability remains to be determined.[18] Further, it is uncertain if these classifiers would work in a clinical

population including genetic bvFTD cases in which the MRI patterns of atrophy share similarities with sporadic cases, but also have distinctive features for each mutation.[19-21]

In the present study, we developed a Random Forest classifier [22] using features derived from Deformation Based Morphometry (DBM) maps to identify bvFTD subjects from CNCs. To ensure the generalizability of the results, the machine learning model was trained on a mainly sporadic cohort and tested in a held-out population of genetic bvFTD, therefore relying on one of the gold standards for diagnosis (i.e., definite bvFTD). [7]

MATERIALS AND METHODS

Participants

A total of 515 subjects were examined in this study. The first cohort was used only for training (the '*training cohort'*). The training cohort included bvFTD patients and CNCs from the Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI) database who had T1-weighted (T1w) MRI scans matching with each clinical visit. The inclusion criteria for bvFTD patients was a diagnosis of possible or probable bvFTD according to the FTD consortium criteria [7], resulting in 70 patients with bvFTD and 123 CNCs in our study.

The primary goals of the FTLDNI, funded through the National Institute of Aging, are to identify neuroimaging modalities and methods of analysis for tracking frontotemporal lobar degeneration (FTLD) and to assess the value of imaging versus other biomarkers in diagnostic roles. For up-to-date information on participation and protocol, please visit: http://4rtni-ftldni.ini.usc.edu/ .

The second cohort was completely independent from the first and used only for validation (the '*validation cohort'*) of the model created with the training cohort. The validation cohort included bvFTD patients and CNCs from the third data freeze (12/2017) of the Genetic Frontotemporal Dementia Initiative 2 (GENFI2- http://genfi.org.uk/),[23] which includes 23 centres in the UK, Europe and Canada. GENFI2 participants included known symptomatic carriers of a pathogenic mutation in *C9orf72*, *GRN* or *MAPT* and their first-degree relatives who are at risk of carrying a mutation, but who did not show any symptoms (i.e., presymptomatic). Non-carriers were first-degree relatives of symptomatic carriers who did not carry the mutation. The inclusion and exclusion criteria are described in detail elsewhere.[23] Since the aim of the present study was to differentiate bvFTD patients from CNCs, presymptomatic carriers and symptomatic carriers whose clinical diagnosis was other than bvFTD were excluded. The CNC group consists of subjects who are first degree relatives of patients with FTD genetic mutations, but who are asymptomatic and were tested negatively for the mutation that is present in their family. This validation cohort contained 75 patients with bvFTD and 247 CNCs and was never used for feature selection, parameter identification or model tuning during the training phase.

Clinical assessment

All subjects were regularly assessed clinically yearly/every six-months by site investigators. Neuropsychological assessment included Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), FTLD clinical dementia rating (FTLD-CDR), Clinical Global Impression (CGI), verbal fluency, Frontotemporal dementia rating scale (FRS) amongst other cognitive and functional scores[24-28].

Image acquisition and preprocessing

For the FTLDNI training cohort, 3.0T MRIs were acquired at three sites (T1w MPRAGE, TR=2 ms, TE=3 ms, IT=900 ms, flip angle 9°, matrix 256x240, slice thickness 1mm, voxel size $1mm^3$).

For the GENFI2 validation cohort, participants underwent volumetric T1w MPRAGE MRI at multiple centers, according to the GENFI imaging protocol using either Siemens Trio 3T, SiemensSkyra3T, Siemens1.5T, Phillips3T, General Electric (GE) 1.5T or GE 3T scanners. Scan protocols were designed at the outset of the study to ensure adequate matching between the scanners and image quality control.

The T1w scans of the subjects were pre-processed through our longitudinal pipeline[29] that included image denoising,[30] intensity non-uniformity correction[31], and image intensity normalization into range (0−100) using histogram matching. Each native T1w volume from each timepoint was linearly registered first to the subject-specific template which was then registered to the ICBM152 template.[32] All images were then non-linearly registered to the ICBM152 template using ANTs diffeomorphic registration pipeline.[33] The images were visually assessed by two experienced raters to exclude cases with significant imaging artifacts (e.g. motion, incomplete field of view) or inaccurate linear/nonlinear registrations. This visual assessment was performed blind to diagnosis. Out of 1724 scans, only 43 (2.5%, 36 scans in GENFI2, and 7 in FTLDNI) did not pass this visual quality control. For the purpose of this study, scans from subjects other than bvFTD or CNCs, or those that did not have a matching clinical visit were excluded from this analysis. This resulted in a total of 515 subjects that were included in this study.

Deformation based morphometry

DBM [34 35] analysis was performed using Montreal Neurological Institute (MNI) MINC tools. [29] The local deformation obtained from the non-linear transformations was used as a measure of tissue expansion or atrophy by computing the determinant of the Jacobian at each voxel. Local contractions can be interpreted as shrinkage (e.g., tissue atrophy) and local expansions are often related to ventricular or sulci enlargement. DBM was used to assess both voxel-wise and atlas-based cross-sectional group related volumetric differences.

Classification bvFTD versus CNCs

To obtain a region of interest map reflecting the patterns of difference between bvFTD and CNCs, a voxel-wise mixed effects model analysis was performed only within the training dataset. The mixed effects model included *age* as a continuous fixed variable and diagnosis and *sex* as fixed categorical variables. *Subject* was included as a categorical random variable. The variable of interest was *diagnosis,* reflecting the brain regions that were significantly different between bvFTD and CNCs, controlling for age and sex. The results were corrected for multiple comparisons using the False Discovery Rate (FDR) with a P value < 0.05 threshold. Figure 1 shows the resulting map reflecting areas of significant difference between bvFTD and CNCs.[36]

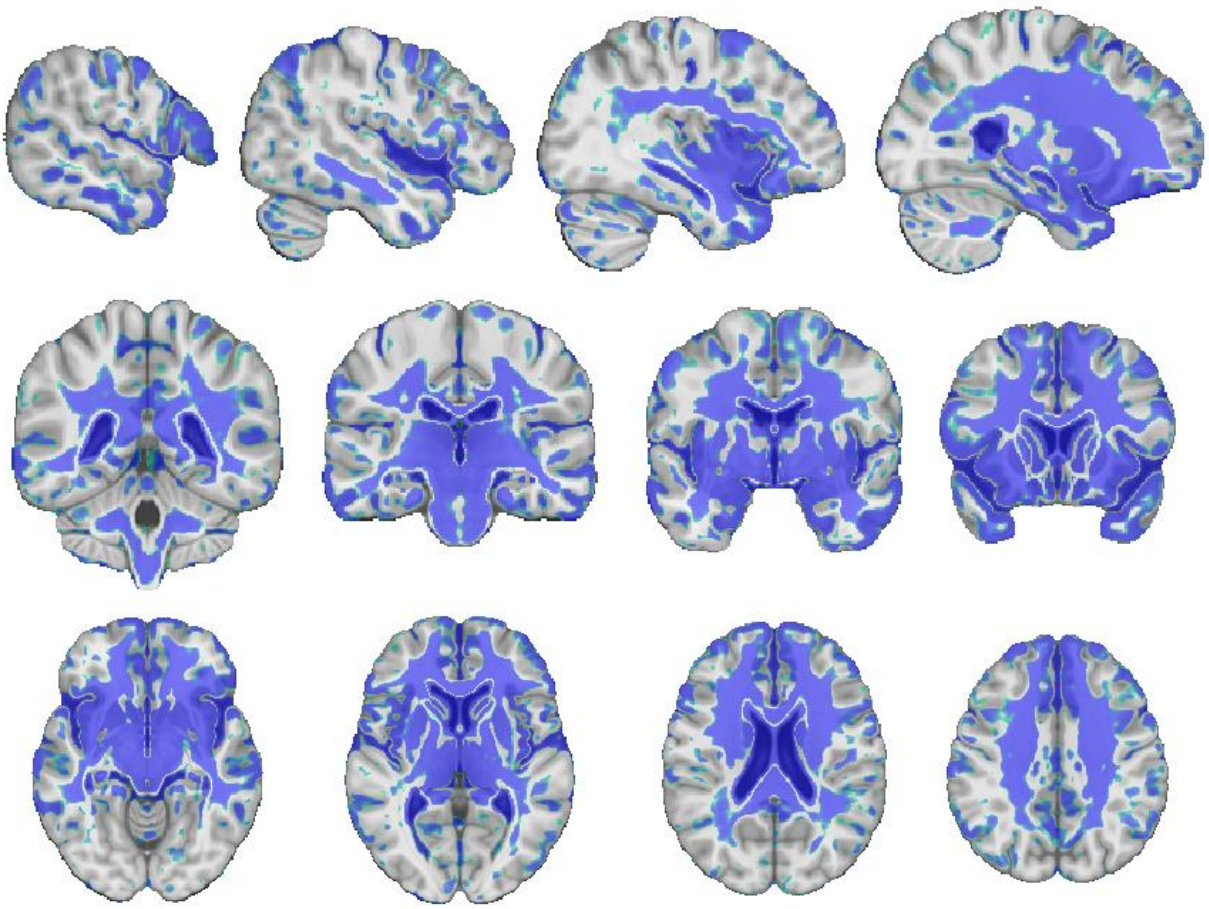

Figure 1. Region of interest map reflecting the significant patterns of difference between bvFTD and CNCs, obtained based on the training data.

A principal component analysis (PCA) was then performed on the DBM voxels within this region of interest. To avoid any leakage (i.e., double dipping), only the baseline information from the training data was used for this PCA. Two sets of features were then used to train a random forests classifier [22] with 500 trees: 1) the first five principal components (PCs, selected based on scree plots of the obtained eigenvalues) as well as age and sex, and 2) the first five PCs, age, sex, and a neuropsychological score. The Semantic Fluency score (SF) was used as the cognitive score feature since it is a reliable simple bedside test associated with executive and language deficits in

bvFTD[37] and was available for most of the subjects in both training and validation datasets. Executive deficits are considered a core characteristic of FTD, though in themselves, are insufficient to establish a diagnosis and thus not used here. [38] [39] Classifications were run using DBM in isolation and DBM + SF. Ten-fold cross validation was used to assess the performance of the classifier within the training data. To obtain a single ROI and consistent features across folds, the voxel-wise group comparison and PCA were performed outside of the cross-validation loop on the training dataset, since we use an independent dataset for validation. However, to demonstrate that this choice does not lead to leakage in the training set experiments, we also repeated the cross validation for the training set with the mixed effects model and PCA analyses performed inside the cross-validation loop and obtained similar results (see the supplementary materials for details).

To perform classification on the held-out GENFI2 validation dataset, the coefficients calculated based on the PCA on the training dataset were used to calculate the first five PCs features for the subjects from the validation dataset. Using the random forest classifier trained on FTLDNI, we then classified all the subjects from the validation dataset as either bvFTD or CNCs (based on their baseline information). A probability score was also obtained from the random forest classifier, indicating the likelihood of each observation belonging to the bvFTD class. The mixed effects modelling, PCA, and random forest classification were carried out using MATLAB (version R2017b).

Statistical analyses

All statistical analyses were conducted using MATLAB (version R2017b). Two-sample t-Tests were conducted to examine demographic and clinical variables at baseline. Categorical variables were analysed using chi-square analyses. Results are expressed as mean ± standard deviation and median [interquartile range] as appropriate. Receiver Operator Characteristics (ROC) analysis was used to define sensitivity and specificity at different cut-points within the validation cohort. The optimal cut-point was estimated by the use of Youden index (J= Sensitivity+Specificity-1). Positive and negative likelihood ratios were also estimated for different cut points.

RESULTS

Demographics

Table 1 shows the demographic and cognitive testing performances in bvFTD and CNCs. There was no difference in age between bvFTD patients and CNCs (62±6 and 63±6 years respectively, $p = 0.36$), but there was a higher proportion of males in bvFTD patients than CNCs (67% vs 43%, $p = 0.001$). As expected, bvFTD subjects showed greater cognitive and functional impairment: significant differences were found between the two cohorts in MMSE, FTLD-CDR, MoCA, letter fluency Z-score and semantic fluency Z-score (all $p < 0.001$).

Demographic differences and cognitive testing performances between patients and controls for the GENFI cohort are also shown in Table 1. Considering the CNCs from this dataset comes from non-carrier members of families at risk of genetic mutation related to FTD, they were, as expected, significantly younger than bvFTD subjects. The mean age was 48±14 years for CNCs and 64±8 years for bvFTD ($p < .001$). The median disease duration (age at visit – age of symptom onset) for the bvFTD group was 5.1[3.5-8.2] and the estimated years to onset (age at baseline – average age

of disease onset in the family) 5.2±5.7 years. Compared to non-carriers, bvFTD subjects showed greater cognitive and functional impairment. Significant differences were found between the two cohorts in MMSE, FTLD-CDR, MoCA, FRS, letter fluency Z-score and semantic fluency Z-score ($p < .001$). Regarding the mutated gene, half of the bvFTD subjects carried a *C9orf72* mutation, while 22.7% and 25.3% belonged to the *MAPT* and *GRN* groups respectively.

Table 1. Demographic and clinical characteristics in bvFTD and healthy controls

		Training cohort (FTLDNI) N=193			Validation cohort (GENFI) N=322		
		CNCs N= 123	bvFTD N=70	P value	CNCs* N=247	bvFTD N=75	P value
Age, y		63±6	62±6	0.36	48±14	64±8	< 0.001
Male sex		53(43%)	47(67%)	0.001	106(43%)	41(55%)	0.07
Education, y		17.5±1.9	15.6±3.4	< 0.001	13.9±3.5	11.8±4.03	< 0.001
Estimated years of onset, y		-	N/A	-	-	5.2±5.7	-
Disease duration, y						5.1[3.5-8.2]	-
MMSE score		29.4±0.8	23.6±4.9	< 0.001	29.4±1.1	21.9±7.2	< 0.001
FTLD-CDR Score		0.04±0.2	6.3±3.3	< 0.001	0.21±0.7	9.7±1.4	< 0.001
MoCA Score		23.6±11	16.8±8.3	< 0.001	N/A	N/A	
FRS %		N/A	N/A		88.01±28.7	33.5±26.6	< 0.001
Letter Fluency Z-score		0.7±0.7	-0.9±0.6	< 0.001	-0.03±1	-1.3±1.4	< 0.001
Semantic Fluency Z-score		0.6±0.6	-1.06±0.7	< 0.001	0.1±1	-2.2±1.02	< 0.001
Genetic	C9orf72	-	-			39(52%)	
Group	MAPT	-	-			17(22.7%)	
	GRN	-	-			19(25.3%)	

*CNCs in GENFI2 cohort correspond to non-carrier first degree relative of a family member with a documented genetic mutation related to FTD

Values expressed as mean ± standard deviation, median [interquartile range]. Data available is specified for each clinical variable as N. N/A: data not available from the original databases.

FTLD: frontotemporal lobar degeneration neuroimaging initiative; GENFI: genetic frontotemporal dementia initiative; bvFTD: behavioural-variant frontotemporal dementia. CNCs: cognitively normal controls; MMSE: Mini Mental State Examination. FTLD-CDR: Frontotemporal lobar degeneration clinical dementia rating. MoCA: Montreal Cognitive Assessment. CGI: Clinical Global Impression. FRS: Frontotemporal dementia rating scale.

Voxel-wise DBM group differences.

Greater gray and white matter atrophy were found in the medial and inferior lateral portions of the frontal lobes as well as dorsolateral prefrontal cortex, insula, basal ganglia, medial and anterior

temporal regions bilaterally and regions of brainstem and cerebellum in bvFTD. Correspondingly, volume increase was shown in the ventricles and sulci, being more evident in frontal horns and lateral sulcus. [36] Supplementary material shows the high similarity (Dice similarity index (SI) of 0.93 ± 0.01) between DBM maps when mixed effects model and PCA steps are included inside each loop of the 10-fold validation compared to the DBM map in Figure S1.

Random forest classification

Cross-validation results within the training cohort (FTLDNI)

The accuracy achieved for discrimination between bvFTD and CNCs using solely morphometric MRI features (DBM) was 89%, with a sensitivity of 82% and specificity of 93%. When adding one cognitive score (i.e., DBM+SF) the classifier accuracy reached 94%, with 89% sensitivity and 98% specificity. When mixed effects model and PCA steps are included inside each loop of the 10-fold validation, the average accuracy is 89% using DBM features and 93% when adding semantic fluency (details in supplementary material).

Classification within the validation cohort (GENFI2) using solely DBM and DBM + SF

The model resulted in an accuracy of 88% when discriminating bvFTD patients from CNCs when applied to the independent validation cohort. Sensitivity and specificity were 81% and 92%, respectively using a probability score with an optimal cut point of 0.4 as threshold. This led to a positive likelihood ratio (LR+) of 10.13 and negative likelihood ratio (LR-) of 0.21.

The inclusion of semantic fluency in the classification model resulted in an accuracy of 91%, sensitivity of 79% and specificity of 96%; resulting in LR+ of 19.75 and LR- of 0.22. The ROC

for DBM and DBM + SF classifiers are shown in Figure 2. Figure 3 shows the true positive rates for bvFTD and CNCs according the probability score for DBM (panel A) and DBM+SF (panel B). Table 2 shows the corresponding accuracy, sensitivity, specificity and likelihood ratios for the two models (DBM and DBM+SF) using different thresholds on the probability scores (e.g., for probability scores > 0.4).

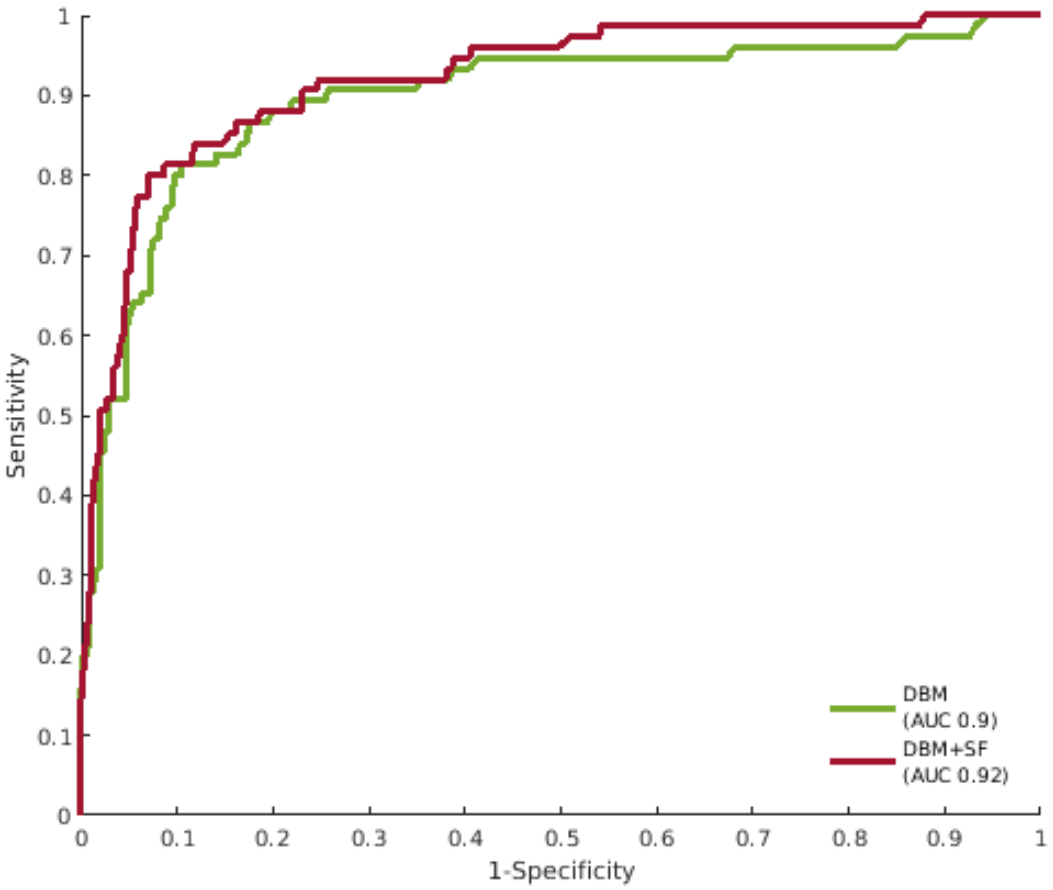

Figure 2. Receiver operating characteristic curves (ROC) for DBM and DBM+SF classifiers. Abbreviations: DBM: deformation-based morphometry; SF: semantic fluency; AUC: area under the curve.

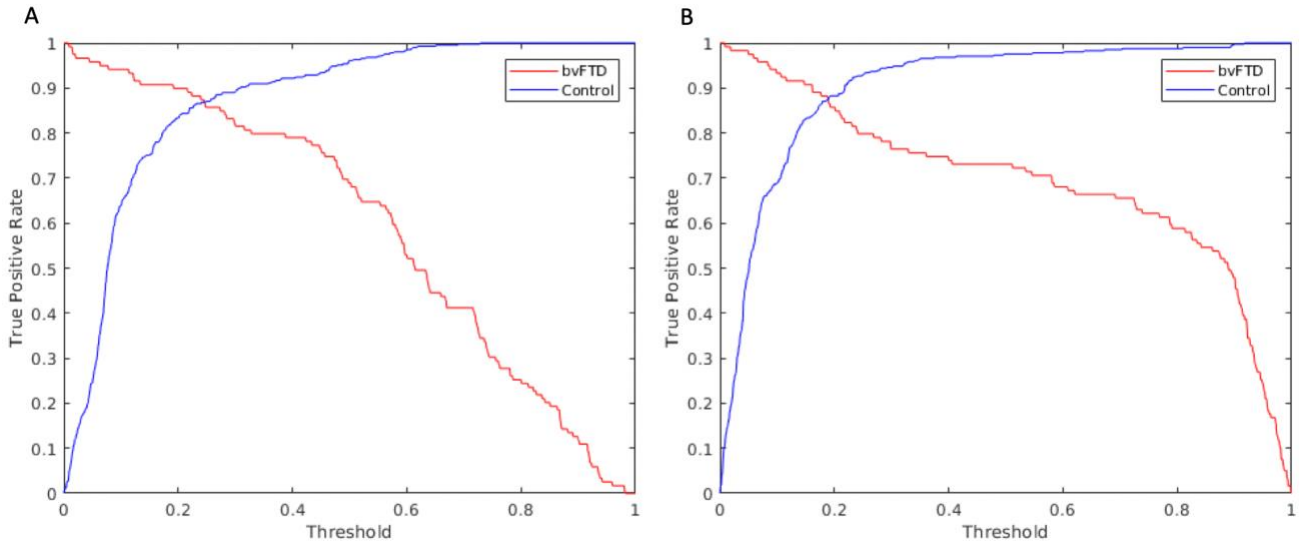

Figure 3. True positive rates for bvFTD and controls according to the probability score threshold for classification using DBM (panel A) or DBM + SF (panel B).

Abbreviations: bvFTD: behavioural-variant frontotemporal dementia. CNCs: cognitively normal controls.

Table 2. Classification performance using DBM and DBM + SF

	Accuracy	Sensitivity	Specificity	LR+	LR-
		DBM			
Probability score threshold*					
0.60	0.90	0.53	0.98	26.50	0.48
0.55	0.91	0.64	0.97	21.33	0.37
0.50	0.90	0.71	0.96	17.75	0.30
0.45	0.89	0.77	0.93	11.00	0.25
0.40	0.88	0.81	0.92	10.13	0.21
0.35	0.86	0.81	0.91	9.00	0.21
0.30	0.84	0.83	0.88	6.92	0.19
0.25	0.81	0.87	0.87	6.69	0.15
0.20	0.78	0.89	0.83	5.24	0.13
0.15	0.70	0.91	0.74	3.50	0.12
0.10	0.60	0.95	0.64	2.64	0.08
		DBM + SF			
Probability score threshold*					
0.60	0.92	0.71	0.98	35.50	0.30
0.55	0.92	0.73	0.98	36.50	0.28
0.50	0.92	0.77	0.98	38.50	0.23
0.45	0.91	0.77	0.96	19.25	0.24
0.40	0.91	0.79	0.96	19.75	0.22
0.35	0.91	0.80	0.96	20.00	0.21
0.30	0.90	0.80	0.95	16.00	0.21
0.25	0.88	0.81	0.93	11.57	0.20
0.20	0.83	0.87	0.87	6.69	0.15
0.15	0.78	0.91	0.92	11.38	0.10
0.10	0.65	0.93	0.68	2.91	0.10

*Performances for each probability score threshold above which a subject is identified as bvFTD. Shaded rows correspond to the optimal cut-point estimated by Youden index.

Abbreviations: DBM: deformation-based morphometry; SF: semantic fluency score; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

False negative cases within the validation cohort (GENFI2)

The classification using DBM resulted in 19% of false negatives. These subjects were significantly younger than the bvFTD subjects correctly classified (57±10 vs. 66±7 years respectively, $p < 0.001$) and the estimated time from onset was also shorter (2±7 years vs 6±5 years; $p = 0.01$). However, the disease duration was not significantly shorter than true positives (3.9[2.2-7.1] vs 5.3[3.6 8.2] years, respectively; $p=0.16$). No significant differences were found in FTLD-CDR score between true positives and false negatives ($p = 0.07$). The distribution of the genetic mutations did not show significant differences either between the false negatives and true positives. *GRN* corresponded to 22.7 % of all false negatives and 25.4% of all true positives ($p = 0.7$); for *C9orf72* the distribution was 45.5% and 54.7% respectively ($p = 0.5$) while for *MAPT* it was 31.8% of the false negatives and 18.9% of the correctly classified bvFTD ($p = 0.3$)

False positive cases within the validation cohort

Only 10 out of 247 CNCs (4%) were erroneously classified as bvFTD. These subjects were significantly older than the subjects accurately classified as healthy subjects (70±12 years vs. 47±13 years, respectively; P value < 0.001). No significant differences were found in the mean FTLD-CDR score (P value $= 0.9$). Of note, subjects with false positives had slightly lower mean MMSE scores (28.27±2.2) compared to true negatives (29.4±1; P value < 0.001).

Defining strategic cut-points

Three cut-offs for both DBM and DBM+SF were defined by giving consideration to the sensitivity, specificity, positive and negative likelihood ratios of different points of the ROC: 1) the optimal cut-point according to Youden index; 2) a sensitive (i.e., “rule-out”) cut-point; and 3) a specific

(i.e., “rule-in”) cut-point (Figure 4). The sensitivity, specificity, LR- and LR+ expressed in the Figure 4 were estimated for each of these defined cut-points (e.g., for probability score = 0.4) .

Proposed thresholds for clinical decision-making for each classifier according to their likelihood ratios are proposed in Figure 4 (lower panels). A LR- <0.1 allows to reliably exclude (i.e., rule-out) bvFTD when the probability score is below 0.2 and below 0.1 for DBM and DBM+SF, respectively. Probability scores over 0.4 for DBM and over 0.25 for DBM+SF enable confident diagnosis (i.e., rule-in) of bvFTD with a LR+ >10. Corresponding likelihood ratios for different thresholds are shown in Table 2.

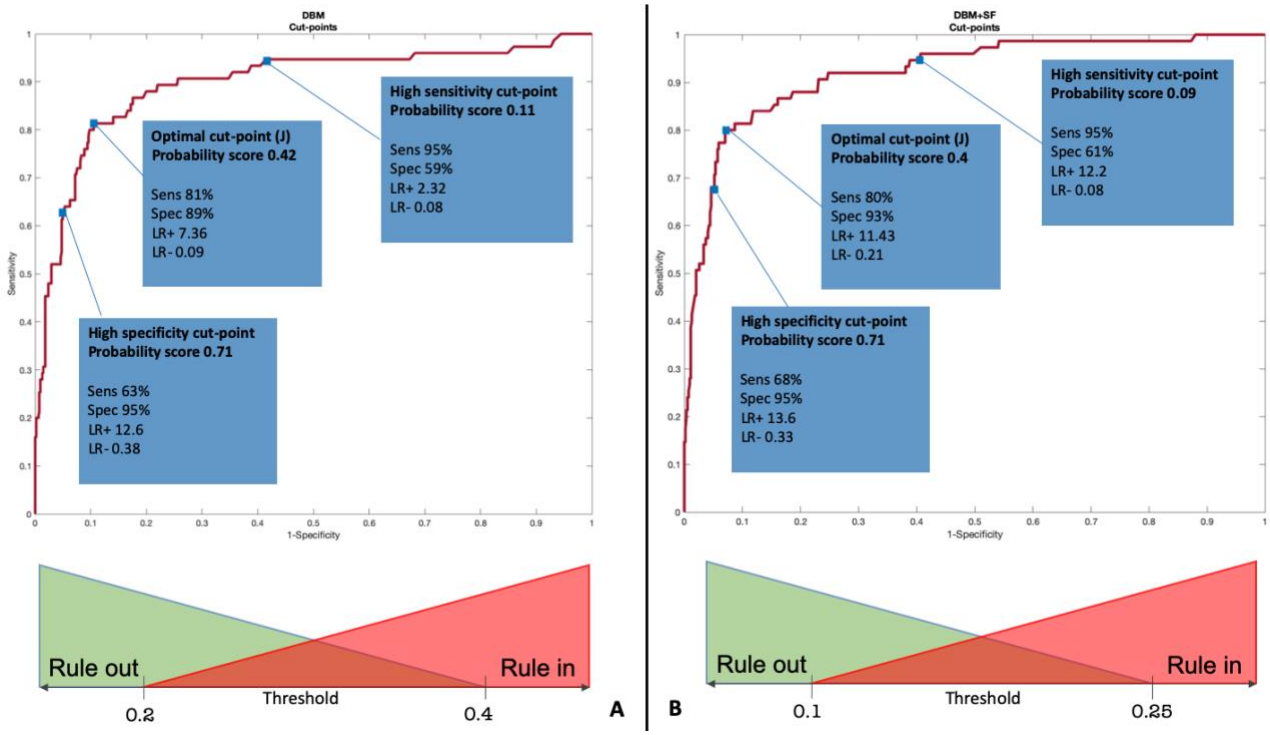

Figure 4. Strategic ROC cut points. **4A, upper panel**: Cut points for DBM classifier. **4A, lower panel**: Thresholds for diagnosis using DBM classifier in relation to LR+ and LR-. **4B, upper panel**: Cut points for DBM+SF classifier. **4B, lower panel**: Thresholds for diagnosis using DBM+SF classifier in relation to LR+ and LR-.

Abbreviations: DBM: deformation-based morphometry; SF: semantic fluency; J: Youden index; Sens: sensitivity; Spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

DISCUSSION

In the present study we built a random forest classifier using morphometric T1w MRI features for the individual prediction of bvFTD. The main findings are: 1) our random forest algorithm yielded areas under the curve of 0.90 and 0.92 using DBM and DBM+SF, respectively, in the independent validation cohort of genetically confirmed bvFTD cases; 2) the inclusion of a simple cognitive score (SF) improved the accuracies and specificity regardless of the probability threshold chosen,

while reducing the false negative rate for probability scores > 0.5; 3) we provide three cut-off values (a "statistically optimal" cut-point, a sensitive ("rule-out") cut-point and a specific ("rule-in") cut-point) for both DBM and DBM+SF classifiers; and 4) our results show good positive and negative likelihood ratios proving its reliability in ruling in and out the disease.

The likelihood ratio is the percentage of patients with a given test result divided by the percentage of controls with the same results. Meaning that ill people should be more likely to have an abnormal result of a given test than healthy individuals. [40 41] For the DBM-only classifier in the independent GENFI2 validation cohort, the optimal threshold yielded an area under the curve (AUC) of 0.9 with 81% sensitivity and 92% specificity leading to a positive LR+ of 10.13 and negative LR- of 0.21. Whereas, the AUC, sensitivity and specificity using the DBM+SF model were 0.92, 79% and 96%, respectively. These values result in LR+ of 19.75 and LR- of 0.22. To keep in mind, a test is moderately good at ruling in disease when LR+ is greater than 2 and very good at doing it when LR+ is greater than 10.[42] Furthermore, a test is moderately good at ruling out the disease with LR- below 0.5 and very good below 0.1. Hence, using the optimal thresholds, both models are very good at excluding non bvFTD subjects and moderately good at confirming the disease.

Our results show that the proposed random forest classifier can accurately predict bvFTD in individual subjects in a completely independent validation cohort coming from a separate database. Furthermore, the GENFI2 validation cohort includes bvFTD patients with a definite diagnosis (positive genetic mutation). Of note, our algorithm was able to accurately classify patients with genetic bvFTD even though they tend to have more atypical atrophy patterns.[21] The performance

of our classifier is superior than the performance reported in several articles that have analyzed the standard diagnostic methods currently used in the clinical practice. Within a pathology-confirmed cohort, the sensitivity reported for the revised diagnostic criteria for bvFTD was 86% for possible diagnosis and 75% for probable bvFTD (with neuroimaging support).[7] However, these criteria reported a sensitivity of 85% and specificity of 27% for possible bvFTD diagnosis in a clinically relevant cohort of patients with mixed behavioral changes, reaching 82% specificity when adding a compatible MRI scan.[43] Within a cohort with late onset behavioral disorders, 70% sensitivity and 93% specificity have been reported for structural MRI alone for bvFTD assessed by an experienced neuroradiologist.[8] The latter results have comparable positive and negative likelihood ratios to ours, even though our method does not rely on the expertise of the radiological observer.

Previous studies classified bvFTD from a control group.[9-13] The best AUC was reported by Raamana et al [13](AUC 0.938, 100% sensitivity and 88% specificity). However, an important limitation is that they trained and tested on the same cohort which often results in an overestimate of the real rates when generalized to other populations. We addressed this particular issue using by using an independent dataset for validation. In addition, bvFTD diagnosis from the testing cohort was based on clinical criteria. Contrarily, the bvFTD subjects from our validation cohort have definite bvFTD diagnosis.

The performance of the classifier was tested on a held-out database which included multi-center and multi-scanner data from different scanner models of both 1.5T and 3T field strengths. This further reinforces the generalizability (i.e., external validity) of our results and ensures their applicability in a clinical scenario with different scanners, even with different magnetic field

strengths. This certainly constitutes one of the two main strengths of this study. The second strength is that our performance was estimated using one of the gold standards for FTD diagnosis supported by the presence of a pathogenic mutation. Remarkably, our algorithm is based on standard structural T1w MRI and a simple cognitive test routinely acquired in the clinic, making for strong translational potential. On the other hand, the main limitation is that these results are yet to be validated prospectively in a clinically representative cohort including patients with diverse primary psychiatric disorders (a common differential diagnosis from bvFTD).[44] The classification accuracy also remains to be demonstrated in cohorts with other types of dementias and cardiovascular comorbidities, as these were uncommon in our dataset and could have influenced our very high specificity. Finally, in our results the false negatives/positives were significantly younger/older than the subjects that were correctly classified. This is likely due to the fact that the age range for the validation dataset (GENFI: minimum age: 39y, maximum age:79y) was larger than the training set (FTLDNI, minimum age 46y, maximum age 75y). Subjects that were outside the operating range of the classifier were therefore more likely to be misclassified. Adding subjects with similar ages to the training dataset will likely improve the results. In addition, specifically for the false negative cases, although the difference did not reach statistical significance ($p=0.07$), the false negatives had lower FTLD-CDR scores than the true positive cases, implying an earlier stage of the disease. It is plausible that such subjects with milder symptoms were not as well represented in FTLDNI given the difficulty of diagnosing bvFTD in the very mild stages when there is no known genetic mutation.

To conclude, we propose an automatic method using structural MRI alone (already available and routinely used in the clinic) and including a simple cognitive test that could be administered by

any physician in few minutes for reliable individual prediction of bvFTD at the individual subject level. The main contributions of the method are its high accuracy along with its generalizability due to the use of a validation cohort coming from a different and independent database with multi-center and multi-scanner data. In addition, using a cohort with diagnosis of definite bvFTD adds reliability to the results. If validated in a prospective study, this algorithm has the potential to improve diagnostic accuracy, particularly in setting without access to specialized FTD care.

Acknowledgements

Data collection and sharing for this project was funded by the Frontotemporal Lobar Degeneration Neuroimaging Initiative (National Institutes of Health Grant R01 AG032306). The study is coordinated through the University of California, San Francisco, Memory and Aging Center. FTLDNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Brain scan acquisition at the McConnell Brain Imaging was supported by the Brain Canada Foundation with support from Health Canada and the Canada Foundation for Innovation (CFI Project 34874).

This work was supported by Italian Ministry of Health (CoEN015 and Ricerca Corrente).

Funding

Dr. Collins receives funding from the Canadian Institutes of Health Research (MOP- 111169), les Fonds de Research Santé Quebec Pfizer Innovation fund, and an NSERC CREATE grant (4140438 - 2012). We would like to acknowledge funding from the Famille Louise & André Charron.

Dr. Ducharme receives salary funding from the Fonds de Recherche du Québec - Santé.

Competing interests

Dr. Manera reports no disclosures
Dr. Dadar reports no disclosures
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