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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).

‡ List of other GENFI Consortium Members in Appendix

Abbreviations

FTD: frontotemporal dementia

GRN: progranulin

MAPT: microtubule-associated protein tau

C9orf72 : chromosome 9 open reading frame 72

bvFTD: behavioural variant of frontotemporal dementia

MRI: magnetic resonance imaging

CNCs: cognitively normal controls

DBM: deformation-based morphometry

FTLDNI: frontotemporal lobar degeneration neuroimaging initiative

T1-w: 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

Abstract

INTRODUCTION: Brain structural 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 databases (training and validation cohorts) were included to perform voxel-wise deformation-based morphometry analysis to identify regions with significant differences between bvFTD and controls. A random forest classifier was used to individually predict bvFTD from morphometric differences in isolation and together with bedside cognitive scores.

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 a separate validation cohort of genetically confirmed bvFTD, accuracy was 88% (81% sensitivity, 92% specificity) with MRI and 91% (79% sensitivity, 96% specificity) with added cognitive scores.

DISCUSSION: The random forest classifier developed can accurately predict bvFTD at the individual subject level.

Keywords

Frontotemporal dementia -Magnetic resonance -Deformation-based morphometry -

Classification- Machine learning

1. Introduction

The heterogeneity of frontotemporal dementia (FTD) is frequently considered a hallmark of the disease with significant variations in heritability, pathology and clinical presentations (1). First, although most cases of FTD are sporadic, there is a positive familiar history in 30-50% of the cases, and 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)

Finally, regarding its clinical presentation, FTD is divided into three major clinical syndromes: the behavioral variant (bvFTD) and two language variants (Semantic Dementia and Non-Fluent Primary Progressive Aphasia). As the initially focal brain involvement spreads to involve larger regions in the frontal and temporal lobes, the symptoms of the three variants described can converge (5). Yet, there is also a considerable overlap between FTD and other neurodegenerative diseases; i.e. some patients with FTD may develop motor neuron disease, or symptoms of a Parkinsonian disorder (6).

Due to the aforementioned heterogeneity in pathology and heritability, as well as the syndromic overlap with psychiatric disorders and other dementias, a confirmed bvFTD diagnosis is often difficult to achieve in the absence of a dominant genetic mutation. Indeed, although brain imaging with magnetic resonance imaging (MRI) is paramount to increase the level of diagnostic

confidence, it lacks sensitivity, particularly in the initial stages of the disease, leading to erroneous or late diagnosis (7, 8).

It has been recognized that the pattern of atrophy in sporadic bvFTD differed but also shared some similarities from that observed in mutation carriers. While frontal -particularly the anterior cingulate gyrus- and anterior temporal atrophy was associated to sporadic bvFTD, genetic variants showed distinct but overlapping patterns of atrophy (9-11). In *MAPT* mutation carriers, atrophy predominantly affects the anterior and medial temporal lobes, orbitofrontal lobe and insula; in *GRN* mutation carriers atrophy in the dorsolateral and ventromedial prefrontal, superolateral temporal and lateral parietal lobes as well as the anterior cingulate, insula, precuneus and striatum has been described; and *C9orf72* carriers showed relatively widespread cortical atrophy including posterior areas, and with particular involvement of the thalamus and superoposterior cerebellum (11).

Lately, 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 (12-20). Studies vary greatly on the subjects included and the methodology. In the present study, we developed a Random Forest classifier (21) 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 bvFTD diagnosis (i.e., definite bvFTD)(7).

2. Materials and Methods

2.1. Participants

A total of 515 subjects were examined in this study. The first cohort ('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. Data was accessed and downloaded through the LONI platform in August 2018. 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 FTLDNI was funded through the National Institute of Aging and started in 2010. The primary goals of FTLDNI 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. The project is the result of collaborative efforts at three sites in North America. For up-to-date information on participation and protocol, please visit: http://4rtni-ftldni.ini.usc.edu/

The second cohort ('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/) (22), which consists of 23 centres in the UK, Italy, The Netherlands, Sweden, Portugal 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 (22). 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. Non-carriers were considered as CNCs for the purpose of this study. This validation cohort contained 75 patients with bvFTD and 247 CNCs.

2.2. Clinical assessment

All FTLDNI subjects were regularly assessed every six-months for clinical characteristics (motor, non-motor and neuropsychological performance) by site investigators. Neuropsychological assessment included Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), Frontotemporal lobar degeneration clinical dementia rating (FTLD-CDR), Clinical Global Impression (CGI), verbal fluency, Frontotemporal dementia rating scale (FRS) amongst other cognitive and functional scores.

2.3. Image acquisition and preprocessing

For the FTLDNI training cohort, 3.0T MRIs were acquired at three sites. In all sites, a volumetric MPRAGE sequence was used to acquire T1w images of the entire brain. The acquisition parameters of the T1w images, using volumetric MPRAGE sequence, were RT/ET/IT: 2.3/3/900 ms, flip angle 9°, matrix 256x240, slice thickness 1mm, voxel size 1x1mm.

For the GENFI2 validation cohort, participants underwent volumetric T1w MRI at multiple centers, according to the GENFI imaging protocol. Sites used different types of scanners: Siemens Trio 3T, SiemensSkyra3T, Siemens1.5T, Phillips3T, General Electric (GE) 1.5T and

GE 3T. 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 (23) that included image denoising (24), intensity non-uniformity correction (25), 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 (26, 27). All images were then non-linearly registered to the ICBM152 template using ANTs diffeomorphic registration pipeline (28). 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 without any knowledge of the 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.

2.4. Deformation based morphometry

DBM analysis was performed using Montreal Neurological Institute (MNI) MINC tools (23). The principle of DBM is to warp each individual scan to the template by introducing high-dimensional deformations (29, 30). Then, the morphological differences between the two are encoded in the deformations estimated for the warp. 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.

2.5. Classification bvFTD versus CNCs

To obtain a region of interest reflecting the difference between bvFTD and CNCs, a voxel-wise mixed effects model analysis was performed in the training dataset to assess the pattern of volumetric change according to diagnosis. 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 resulting maps were corrected for multiple comparisons using False Discovery Rate (FDR) with a *P value* < .05 threshold to identify regions associated with differences between bvFTD and CNCs; i.e. the diagnosis variable in the mixed effects model. A principal component analysis (PCA) was then performed on the DBM voxels within this region of interest. To avoid any leakage, only the training data was used for this PCA. Two sets of features were then used to train a random forests classifier (21) with 500 trees: 1) the first five principal components (PCs) 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 (31) 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 (32, 33). 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 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 that was trained on FTLDNI, we then classified all the subjects from the validation dataset as either bvFTD or CNCs. 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).

2.6. Statistical analyses

All statistical analyses were also 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.

3. Results

3.1. 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 value = 0.36), but there was a higher proportion of males in bvFTD patients than CNCs (67% vs 43%, *P value* = .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 value* < .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 value* < .001). The mean estimated disease duration for the bvFTD group was 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 value* < .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	.36	48±14	64±8	**< .001**
Male sex	53(43%)	47(67%)	**.001**	106(43%)	41(55%)	.07
Education, y	17.5±1.9	15.6±3.4	**< .001**	13.9±3.5	11.8±4.03	**< .001**
Years of onset, y	-	N/A	**-**	-	5.2±5.7	**-**
MMSE score	29.4±0.8	23.6±4.9	**< .001**	29.4±1.1	21.9±7.2	**< .001**
FTLD-CDR Score	0.04±0.2	6.3±3.3	**< .001**	0.21±0.7	9.7±1.4	**< .001**
MOCA Score	23.6±11	16.8±8.3	**< .001**	N/A	N/A	
FRS %	N/A	N/A		88.01±28.7	33.5±26.6	**< .001**
Letter Fluency Z-score	0.7±0.7	-0.9±0.6	**< .001**	-0.03±1	-1.3±1.4	**< .001**
Semantic Fluency Z-score	0.6±0.6	-1.06±0.7	**< .001**	0.1±1	-2.2±1.02	**< .001**
Genetic Group C9orf72	-	-		87(35.2%)	39(52%)	
MAPT	-	-		40(16.2%)	17(22.7%)	
GRN	-	-		120(48.6%)	19(25.3%)	

NOTE: 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.
Abbreviations: 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.

3.2. 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 (34).

3.3. Random forest classification

### 3.3.1. Cross-validation results within the training cohort

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.

3.3.2. Classification within the validation cohort using solely DBM and DBM + SF

The application of the random forest classification model based on the training cohort to the validation cohort resulted in an accuracy of 88% when discriminating bvFTD patients from CNCs. 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 1. Figure 2 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 1. Receiver operating characteristic curves (ROC) for DBM and DBM+SF classifiers
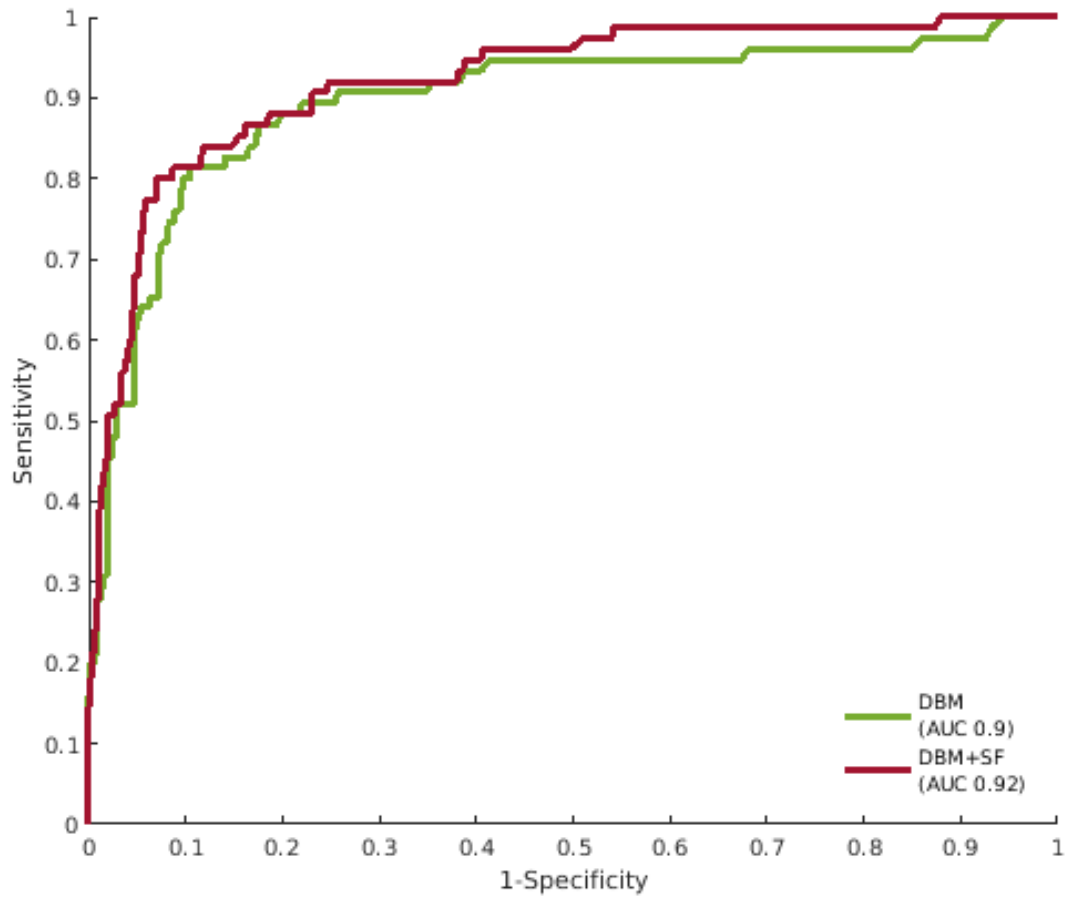
Abbreviations: DBM: deformation-based morphometry; SF: semantic fluency; AUC: area under the curve

Figure 2. True positive rates for bvFTD and controls according to the probability score threshold for classification using DBM (panel A) or DBM + SF (panel B)
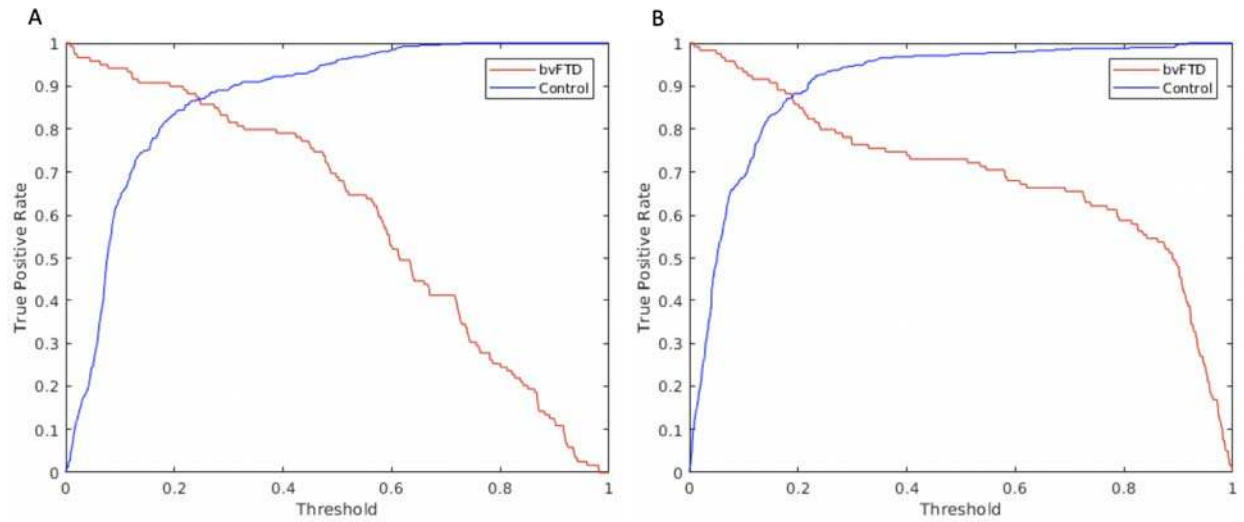
Abbreviations: bvFTD: behavioural-variant frontotemporal dementia. CNCs: cognitively normal controls

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

NOTE: *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.

3.3.3. False negative cases within the validation cohort

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 value* < .001) and the estimated time from onset was also smaller (2±7 years vs 6±5 years; *P value* = .01). However, no significant differences were found in FTLD-CDR score between true positives and false negatives (*P value* = .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 value* = .7); for *C9orf72* the distribution was 45.5% and 54.7% respectively (*P value* = .5) while for *MAPT* it was 31.8% of the false negatives and 18.9% of the correctly classified bvFTD (*P value* = .3)

3.3.4. 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* < .001). No significant differences were found in the mean FTLD-CDR score (*P value* = .9). There was a small difference between the MMSE score for the false positives (28.27±2.2) and for true negatives (29.4±1; *P value* < .001).

3.3.5. 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 3). The sensitivity, specificity, LR- and LR+ expressed in the figure 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 3 (lower panels). A LR- <0.1 allows to reliably exclude (i.e., rule-out) bvFTD when the probability score is below 0.2 and 0.1 for DBM and DBM+SF,

respectively. Probability scores over 0.4 for DBM and 0.25 for DBM+SF allow to confidently

diagnose (i.e., rule-in) the disease with a LR+ >10. Corresponding likelihood ratios for different

thresholds are shown in table 2.

Figure 3. Strategic ROC cut-points
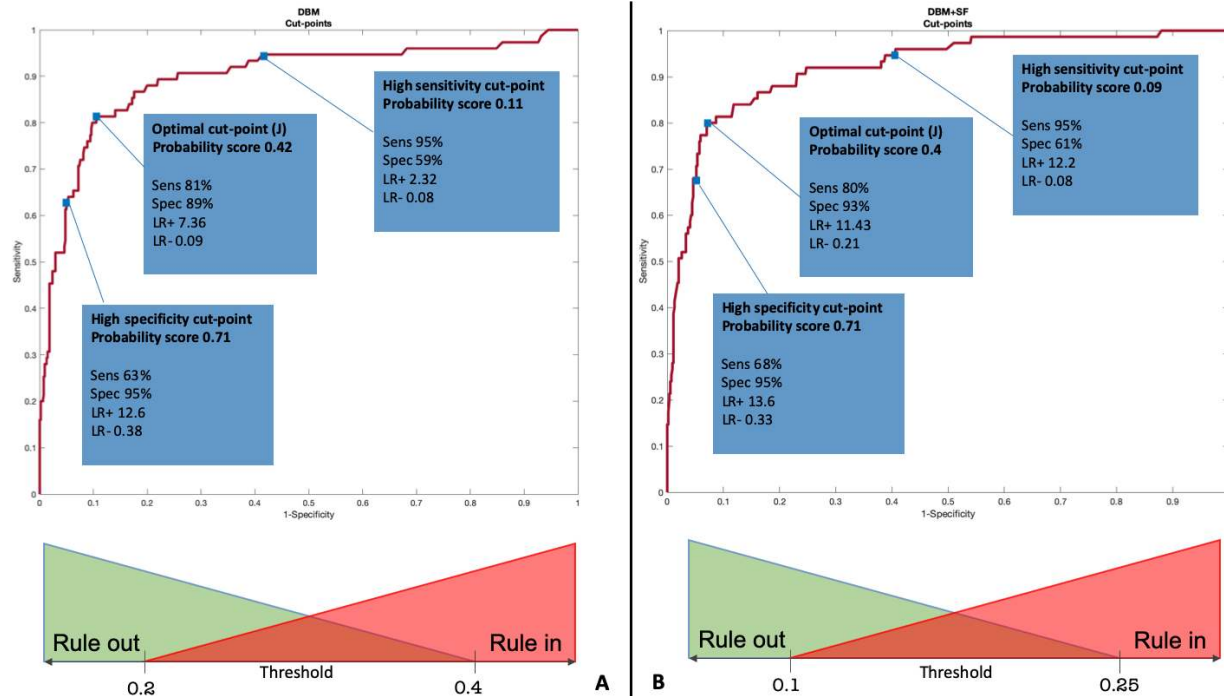
NOTE: **A, upper panel:** Cut-points for DBM classifier. **A, lower panel:** Thresholds for diagnosis using DBM classifier in relation to LR+ and LR-. **B, upper panel**: Cut-points for DBM+SF classifier. **B, lower panel:** Thresholds for diagnosis using DBM+SF classifier in relation to LR+ and LR-.
Abbreviations: DBM: deformation-based morphometry; SF: semantic fluency; J: Youden index; Sens: sensitivity; Spec: specificity; LR+: positive likelihood ratio; LR-: negative likelihood ratio

4. Discussion

In the present study we built a random forest classifier using morphometric 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(35, 36). For DBM only classifier in the independent 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 (37). 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 random forest classifier we developed in our training cohort can accurately predict bvFTD in individual subjects in a completely independent validation cohort coming from a different and independent 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(11). 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 (38). 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 (12-16). The best AUC was reported by Raamana et al (AUC 0.938, 100% sensitivity and 88% specificity). However, the main limitation of that study is that the bvFTD diagnosis from the validation cohort was based on clinical criteria (39). Contrarily, the bvFTD subjects from our validation cohort are known carriers of a pathogenic mutation and have therefore, 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 main strengths of this study along with the fact that our performance was estimated using one of the gold standards for FTD diagnosis (i.e., definite FTD supported by the presence of a pathogenic mutation). Of significant value, our algorithm is based on standard structural T1w MRI and a simple cognitive test that are already routinely acquired clinically, 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) (40). 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: 39, maximum age:79) was larger than the training set (FTLDNI, minimum age 46, maximum age 75). 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 NIFD 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. 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

Declaration of interests

Dr. Manera reports no disclosures
Dr. Dadar reports no disclosures
Dr. Collins is co-founder of True Positive Medical Devices.
Dr. Ducharme receives salary funding from the Fonds de Recherche du Québec - Santé. Dr. Ducharme is the co-founder of Arctic Fox AI.
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