

RESEARCH ARTICLE

# Predicting disease progression in behavioral variant frontotemporal dementia

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## Abstract

**Introduction:** The behavioral variant of frontotemporal dementia (bvFTD) is a rare neurodegenerative disease. Reliable predictors of disease progression have not been

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#### Funding information

German Federal Ministry of Education and Research, Grant/Award Number: FTLDc 01GI1007A; EU Joint Program—Neurodegenerative Disease Research (JPND) network, Genfi-Prox, Grant/Award Numbers: 01ED1512, 01ED2008B; Thierry Latran Foundation and German Research Foundation/DFG, Grant/Award Numbers: SFB1279, SCHR 774/5-1; Boehringer Ingelheim Ulm University BioCenter, Grant/Award Number: D.5009; Illidio Pinho professorship in iBiMED, Grant/Award Number: UIDB/04501/2020; University of Aveiro, Portugal

sufficiently identified. We investigated multivariate magnetic resonance imaging (MRI) biomarker profiles for their predictive value of individual decline.

**Methods:** One hundred five bvFTD patients were recruited from the German frontotemporal lobar degeneration (FTLD) consortium study. After defining two groups (“fast progressors” vs. “slow progressors”), we investigated the predictive value of MR brain volumes for disease progression rates performing exhaustive screenings with multivariate classification models.

**Results:** We identified areas that predict disease progression rate within 1 year. Prediction measures revealed an overall accuracy of 80% across our 50 top classification models. Especially the pallidum, middle temporal gyrus, inferior frontal gyrus, cingulate gyrus, middle orbitofrontal gyrus, and insula occurred in these models.

**Discussion:** Based on the revealed marker combinations an individual prognosis seems to be feasible. This might be used in clinical studies on an individualized progression model.

#### KEYWORDS

behavioral variant frontotemporal dementia, brain volume, classification models, disease progression, frontotemporal dementia, prognosis

## 1 | BACKGROUND

The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative disease that is characterized by progressive changes in personality, social behavior, and cognition. Unlike Alzheimer’s disease (AD), patients fall ill at a younger age and develop psychiatric symptoms first, which often has resulted in wrong or late correct diagnoses. Since Rascovsky et al. defined revised diagnostic criteria for bvFTD in 2011,<sup>1</sup> the likelihood of a timely discovery of the disease has been increased. This is crucial as an early detection of pathological alterations improves the likelihood of benefitting from potential disease-modifying therapies, such as tau aggregation inhibitors, active and passive anti-tau immunotherapies, or a treatment with antisense oligonucleotides. Nevertheless, predicting disease progression remains a challenge, and to date, all predictions about speed of symptom growth, time of need for care, and life expectancy are more or less speculative. Devenney et al. observed longitudinal outcomes and progression in bvFTD patients by identifying a number of clinical predictive features such as a family history of neurodegeneration, stereotypic and compulsive behaviors, and specific cognitive deficits.<sup>2</sup> Zhutovsky et al. used machine learning techniques to predict the conversion of unspecific behavioral changes into bvFTD within 2 years based on clinical and structural imaging data.<sup>3</sup> They found a classification algorithm that identified bvFTD patients across the combination of heterogeneous psychiatric and neurological disorders using a combination of clinical and voxel-wise magnetic resonance imaging (MRI) data. To identify potential endpoints for clinical trials in bvFTD and PPA, Staffaroni et al. examined longitudinal clinical changes as well as longitudinal changes in cortical volume, white matter integrity, and cerebral perfusion. The authors found that baseline imaging measures predicted the subse-

quent decline for many clinical variables although only looking at predefined large regions of interest.<sup>4</sup>

The present study aims to predict individual disease progression in bvFTD within 1 year after initial diagnosis using differentiated structural cerebral imaging data alone. According to the revised diagnostic criteria (Rascovsky et al.<sup>1</sup>), probable bvFTD is characterized by frontal and/or temporal atrophy on MRI—but there are pronounced individual differences in atrophy patterns within these brain areas: there is clinical and pathological diversity between bvFTD patients, especially at the beginning of the disease.<sup>5</sup> By detecting and quantifying cross-sectionally the volume loss of different specific frontal and temporal subregions in patients (given in milliliters), we intended to find atrophy patterns that allow us to predict individual disease progression rate between two investigations with a temporal distance of 1 year. This method could be suitable to address the complexity of this disorder and at the same time build a helpful tool in clinical trials to predict disease progression rate.

## 2 | METHODS

### 2.1 | Study sample

One hundred five bvFTD patients were selected from the German FTLDc study, an observational follow up-study<sup>6</sup> with the aim to develop and evaluate parameters that will help clinicians diagnose FTLD at an early stage and follow its progression. It was conducted in 11 university hospitals according to the principles expressed in the Declaration of Helsinki. Collection and analysis of samples were approved by the local ethics committees of the universities

participating in the German FTLD Consortium (Ethics Committee University of Ulm approval number 20/10). All patients or their legal representatives gave written informed consent. Patients were recruited between August 2011 and April 2017.

The patients were diagnosed according to published criteria for bvFTD<sup>1</sup> including extensive clinical and neuropsychological assessment, cerebrospinal fluid biomarkers, a high-resolution 3T-MRI scan, and a fluorodeoxyglucose positron emission tomography (FDG-PET) at baseline. Genetic testing was performed depending on the consent of the participants in 78 cases; 27 patients chose to withhold from genetic testing. Our group comprised 14 gene mutation carriers (10 C9orf72, 2 GRN, 1 TBK1, 1 SQSTM) and therefore classified as “behavioral variant FTD with definite FTLD pathology.” At timepoint of initial examination 64 of our subjects have been diagnosed as “probable bvFTD,” and 31 as “possible” as we tried to include patients especially at disease onset. All patients later showed disease progression to “probable bvFTD.” In each case all assessments have been carried out within 4 weeks and judgments were based on multiprofessional consensus. The age of the included patients ranged from 36 to 82 years with an average age of 62.3 years; 63% were male, 88% right-handed. The (estimated) average disease duration (onset of first symptoms) was 3.8 years. As behavioral disturbances are the main symptoms of the disease, 35 of our patients were under antipsychotic medication in case of agitation, aggressiveness, or delusional disorders; 52 participants of the study have taken antidepressant drugs. Thirty-seven patients received anti-dementia medication. Seventeen patients have not taken any medicines.

## 2.2 | Rating of disease severity

The FTLD-modified Clinical Dementia Rating (FTLD CDR) has been conducted as a functional assessment instrument and a global rating of disease severity.<sup>7</sup> It contains self-reported and caregiver information about memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. In its standard version, the CDR is widely used in AD. Knopman et al. included two additional domains—language and behavior—to capture FTLD patient characteristics. Every domain can be rated from 0 (no symptoms) to 3 (severe), so that the maximum total score (sum of boxes, SOB) is 24. It has already been shown that in bvFTD the average increase on the FTLD CDR SOB within 12 months was 3.47 points.<sup>7</sup> The FTLD CDR was obtained at baseline and at the annual follow-up visits. In our sample this value increased by 2.6 points within 12 months (standard deviation [SD] = 3.4).

We then defined two patient groups based on disease progression as defined by FTLD CDR scores. Because there is no published definition of fast progressors we defined them as patients whose FTLD CDR SOB increase was within the upper third of all our patients. This corresponded to an increase of four or more points within 1 year, reflecting a higher loss of everyday functioning and a higher need for care compared to patients with an average progression rate of disease. The group of fast progressors consisted of 39 patients; 66 patients

## RESEARCH IN CONTEXT

1. **Systematic Review:** The authors reviewed the existing literature concerning the individual prognosis of behavioral variant frontotemporal dementia (bvFTD). Until now reliable predictors of disease progression have not been sufficiently identified. In particular, differentiated magnetic resonance imaging biomarkers have not been taken into account.
2. **Interpretation:** Using advanced classification models an individual prognosis is feasible. Various combinations of frontal and temporal brain areas have been detected to have high predictive power.
3. **Future Directions:** This study provides a potential approach to predict individual disease progression rates in bvFTD by combining brain volumes through advanced statistical classification models. Future research is now necessary to validate our results and to proof generalization as we believe that this method could be a powerful tool in future clinical trials: it enables us to classify participating patients prior to treatment and could be used to capture disease progression rates under treatment.

were defined as “slow progressors” (see Figure 3A). The distribution of genetic and sporadic patients was the same for both groups.

## 2.3 | MRI acquisition and processing

Baseline structural MRI data were acquired on 3T MR systems in every study center following a harmonized, standard MRI protocol to ensure maximum comparability of the data. This protocol included, among others, a 3D T1 magnetization prepared rapid gradient echo (MPRAGE) sequence for structural analysis with a spatial resolution  $1 \times 1 \times 1$  mm in analogy to Alzheimer's Disease Neuroimaging Initiative (ADNI) standard protocol<sup>8</sup> as well as a 3D fluid attenuation inversion recovery sequence (3D FLAIR) to outline vascular lesions/white matter lesions with a spatial resolution  $1 \times 1 \times 1$  mm.

The analysis of our neuroimaging data was done by using automated voxel-based volumetry (ABV) with the help of predefined masks derived from two different digital brain atlases with 56 brain structures in total. ABV has proven its worth in numerous cross-sectional and longitudinal studies regarding frontotemporal lobar degeneration (FTLD)<sup>9–11</sup> and has been described in detail elsewhere.<sup>12</sup> For general overview, first, T1-weighted MPRAGE images are converted from Digital Imaging and Communications in Medicine (DICOM) data format into Neuroimaging Informatics Technology Initiative (NIfTI) data format, followed by segmentation of the 3D T1 image into gray matter, white matter, and cerebrospinal fluid components on a voxel level. ABV then warps the resulting tissue probability maps into a

template space using elastic image registration. Finally, it uses an atlas of predefined regions of interest in the same space to extract regional brain volumes.<sup>13</sup> Volumes of brain lobes, cerebellum, and brain stem were calculated using the University of Southern California Laboratory of Neuroimaging (LONI) Probabilistic Brain Atlas, LPBA40;<sup>14</sup> for the subcortical structures caudate, accumbens, pallidum, and thalamus the probabilistic maps of the Harvard-Oxford atlas were used.<sup>15</sup>

This automated method allows determining volumes of various brain structures in an observer-independent, time-efficient fashion at individual subject level.<sup>13</sup>

## 2.4 | Statistical analysis

Statistical analyses of demographic and clinical data, as well as data regarding cognitive state, were performed in IBM SPSS Statistics 25. Differences between patient groups were assessed using nonparametric tests; specifically, Chi-square tests and two-sided Wilcoxon rank-sum tests were performed. The statistical analysis of the brain volumes was conducted in R 4.0.0. The individual brain volumes were screened for statistically significant median differences between the group of fast progressors ( $\Delta$ -FTLD-CDR  $\geq 4$ ) and slow progressors ( $\Delta$ -FTLD-CDR  $< 4$ ) by applying two-sided Wilcoxon rank-sum. Bonferroni correction was applied to adjust for multiple testing ( $n = 27$ ). We additionally tested for differences between the two hemispheres. Again, the two-sided Wilcoxon rank-sum was applied (Bonferroni correction,  $n = 11$ ). The pairwise Spearman correlation between brain values, the  $\Delta$ -FTLD-CDR, and the diagnostic groups was evaluated (Bonferroni correction,  $n = 812$ ).

## 2.5 | Nearest neighbor classifiers (1-NN)

Multivariate analysis was based on the evaluation of classification models, which were trained to predict the disease progression of a patient (fast vs. slow progressor) by analyzing a profile (subset) of brain volumes. The mean accuracy, sensitivity, and specificity achieved by a classification model can be seen as an indirect performance measure of the underlying profile. They allow us to compare different profiles for the same type of classification model.

A classification model is first trained on a subset of samples and then tested on the remaining ones (independent test set). To omit sampling effects this process was repeated in a leave-one-out cross-validation (LOOCV) strategy<sup>16</sup> (Section 2.5.1).

We provide a large and exhaustive screening of more than  $1.6 \times 10^7$  profiles (Section 2.5.2). Therefore the nearest neighbor classifier (1-NN) was chosen as an extremely efficient base classification model.<sup>17</sup> The 1-NN classifies a patient by identifying the training sample with the smallest Euclidean distance (nearest neighbor). The class of the nearest neighbor is being predicted.

### 2.5.1 | Leave-one-out cross-validation

The evaluation of each profile (subset of brain volumes) was based on a LOOCV strategy.<sup>16</sup> That is, each patient was independently used as test sample while the remaining patients were used for training the classification model. The procedure is repeated for each sample. The mean accuracy, sensitivity, and specificity are reported. The R package Tune-Pareto was used for standardized analysis.<sup>18</sup>

### 2.5.2 | Exhaustive screening

We performed an exhaustive screening for profiles (subsets) of brain volumes that allow an accurate prediction of the disease progression of a patient (fast vs. slow progressor). All profiles that include 1 up to 10 brain volumes ( $> 1.6 \times 10^7$  combinations) were evaluated and compared in LOOCV<sup>16</sup> based on 1-NN.<sup>17</sup> The procedure was implemented in R and C.

## 3 | RESULTS

To investigate the possible predictive power of imaging data in patients with bvFTD, we first divided the study cohort into fast and slow progressors by using  $\Delta$ -FTLD-CDR SOB scores for disease severity. Comparing these groups revealed significantly more male patients in the slow progressor group than in the fast progressor group. No significant differences were found between the two groups in age, years of education, age of initial symptoms, or duration of illness (Table 1).

Moreover, we found no differences in disease severity between fast and slow progressors at baseline. Both groups started with mild to moderate deficits regarding memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care, behavior, and language as judged by FTLD-CDR. After 1 year, slow progressors remained almost stable whereas in fast progressors the FTLD-CDR SOB score increased by an average of 7 points ranging from 8 to 15 points (Table 2). In detail, the largest worsenings were seen in FTLD-CDR subdomains "home and hobbies" with 84% of all fast progressors showing an increase in scoring of 1 or more points. That means that after 1 year these patients are at least mild but definitely impaired in functioning at home. More difficult tasks are abandoned, more complicated hobbies and interests as well. Also, the competencies in "judgment and problem solving" and "community affairs" fell significantly in  $>70\%$  of fast progressors. The fewest changes in this group were seen in "language" and "orientation."

The pattern that was seen for the FTLD-CDR became also apparent in the cognitive screening tool Mini-Mental State Examination (see Table 2): Slow progressors showed almost equal test performances after 1 year, whereas the fast progression group progressed rapidly from mild to moderate dementia within the same time frame.

We first screened for single brain regions with a high (absolute) Spearman correlation to disease progression and the  $\Delta$ -FTLD-CDR

**TABLE 1** Descriptive data of study groups

	Fast progressors (n = 39)	Slow progressors (n = 66)	P
Men, n (%)	56%	67%	.01*
Handedness, n (right/left/both)	36/2/0	56/4/5	.21
Age [years], mean (SD)	60.0 (9.6)	63.6 (9.7)	.5
Education [years], median (range)	13 (0–20)	12 (8–20)	.85
Age of initial symptoms [years], mean (SD)	56.4 (10.2)	58.8 (11.9)	.98
Duration of illness [years], mean (SD)	2.9 (2.6)	4.4 (5.2)	.27

Note: BvFTD patients were divided into fast and slow progressors. Fast progressors were defined as patients with an increase of four or more points on the FTLD-CDR within 1 year.

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; SD, standard deviation.

**TABLE 2** Disease severity and cognitive state of study groups

	Fast progressors (n = 39)	Slow progressors (n = 66)	P
FTLD-CDR SOB, Visit 1, mean (SD)	8.2 (4.2)	7.2 (5.4)	.29
FTLD-CDR SOB, visit 2, mean (SD)	15.0 (4.8)	8.3 (5.4)	.00*
CDR SOB, Visit 1, mean (SD)	6.1 (3.6)	5.2 (4.1)	.23
CDR SOB, visit 2, mean (SD)	11.5 (3.9)	6.2 (4.2)	.00*
MMSE, Visit 1, mean (SD)	22.5 (6.2)	25 (4.3)	.03*
MMSE, Visit 2, mean (SD)	16.7 (8.7)	24.1 (5.3)	.00*

Note: BvFTD patients were divided into fast and slow progressors. Fast progressors were defined as patients with an increase of four or more points on the FTLD-CDR within 1 year. Disease severity was objectified using the FTLD-CDR SOB score, the MMSE indicated cognitive state of patients.

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; SD, standard deviation; SOB, Sum of Boxes.

score. Only correlations of small effect size were found, the highest for the caudate nucleus ( $r = -0.32$ ) and right lateral orbitofrontal gyrus ( $r = -0.34$ ). The lowest (absolute) value was found for pallidum ( $r = -0.06$ ). For further details including correlations between the different brain regions see Figure 1.

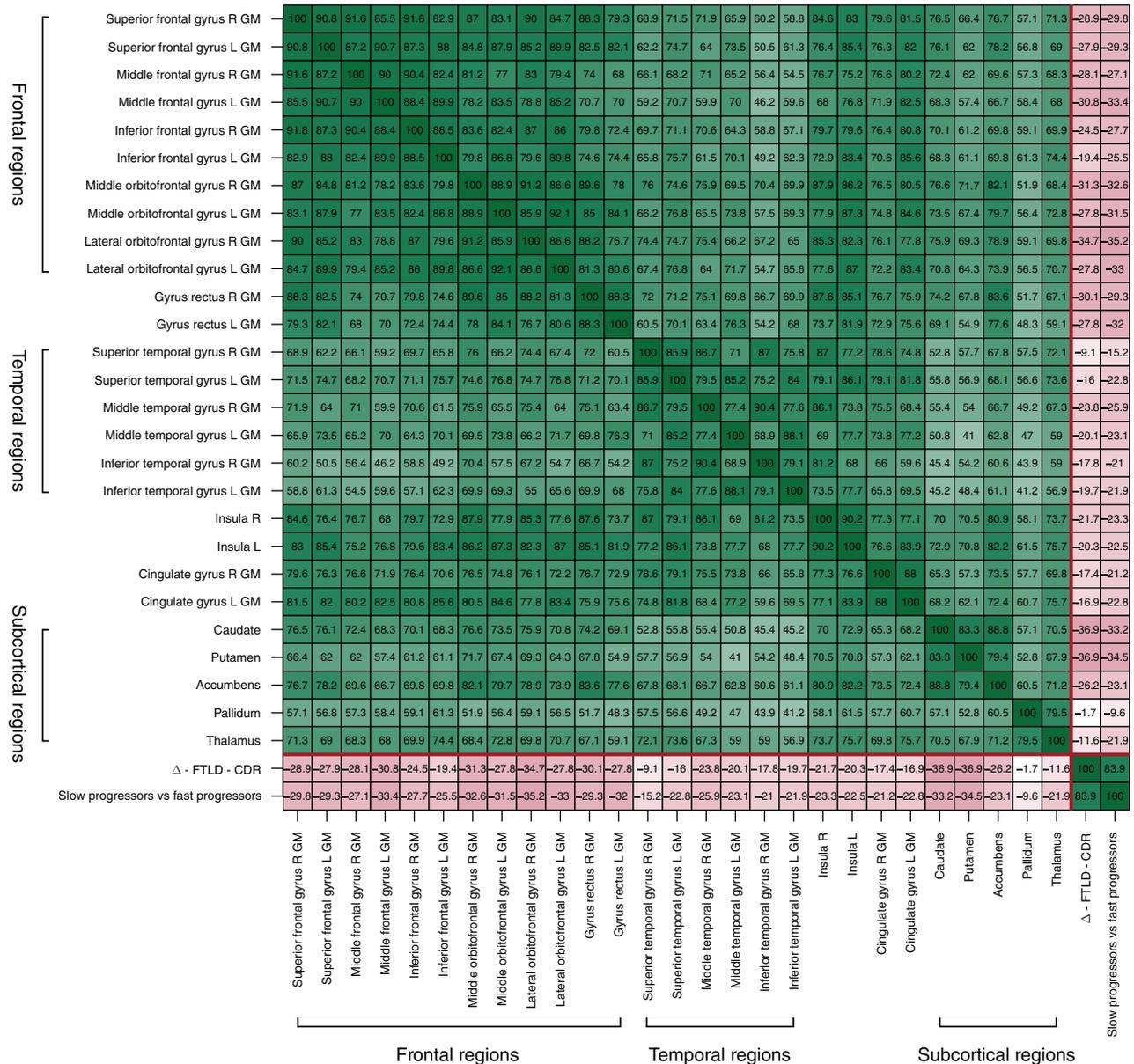
Pairwise Spearman correlations of brain volumes revealed high interrelations between the two hemispheres of different brain regions. A two-sided Wilcoxon rank-sum was applied to test if there are statistically significant differences between brain hemispheres and patient groups for different brain regions. *P*-values varied from 0.23 to 0.58 (regions considered: superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, middle orbitofrontal gyrus, lateral orbitofrontal gyrus, gyrus, rectus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, insula, cingulate gyrus).

For several brain regions the fast progressors showed smaller brain volumes than the slow progressors (Figure 2). That means a higher degree of atrophy at baseline visit in certain regions of the brain accompanied a faster progression of the disease clinically. Two-sided Wilcoxon rank-sum tests revealed significant differences between patient groups in the left middle frontal gyrus ( $P = .02$ ), right middle orbitofrontal gyrus ( $P = .02$ ), left middle orbitofrontal gyrus ( $P = .04$ ), right lateral orbitofrontal gyrus ( $P = .01$ ), left lateral orbitofrontal gyrus ( $P = .02$ ), gyrus rectus ( $P = .03$ ), caudate ( $P = 0.02$ ), and putamen ( $P = .01$ ). A tabularized summary of all statistical analyses can be found in Tables S1–S3 in supporting information.

In a next step we performed a screening for profiles (subsets) of brain volumes that allow in synopsis an accurate prediction of the progression of a patient within 1 year (Figure 3). In contrast to single markers, these profiles can benefit from the synergistic effects and often outperform their individual components.<sup>19</sup> Overall, more than  $1.6 \times 10^7$  marker signatures were evaluated. A tabularized summary of the top-50 classification models can be found in Table S4 in supporting information. The top-50 achieved overall accuracies of approximately 0.8, sensitivities (fast progressors) between 0.61 and 0.74 and specificities (slow progressors) between 0.8 and 0.89 (Figure 3C). As expected, due to the heterogeneity of atrophy patterns in this disease entity, these models, which considered frontal, temporal, and subcortical subregions, were observed to be more effective than an analysis of entire frontal, temporal, and subcortical regions. Here, the accuracy that was achieved only was between 0.5 and 0.6 (see also Table S5 in supporting information).

The following brain areas occurred most frequently in the top-50 models: pallidum ( $n = 49$ ), right middle temporal gyrus ( $n = 40$ ), right inferior frontal gyrus ( $n = 39$ ), right cingulate gyrus ( $n = 36$ ), right middle orbitofrontal gyrus ( $n = 35$ ), left insula ( $n = 29$ ), and right insula ( $n = 28$ , Figure 3D). The best predictive model with a highest value of accuracy included pallidum, nucleus accumbens, cingulate gyrus, right inferior temporal gyrus, right middle temporal gyrus, left superior temporal gyrus, gyrus rectus, right middle orbitofrontal gyrus.

## Spearman correlation



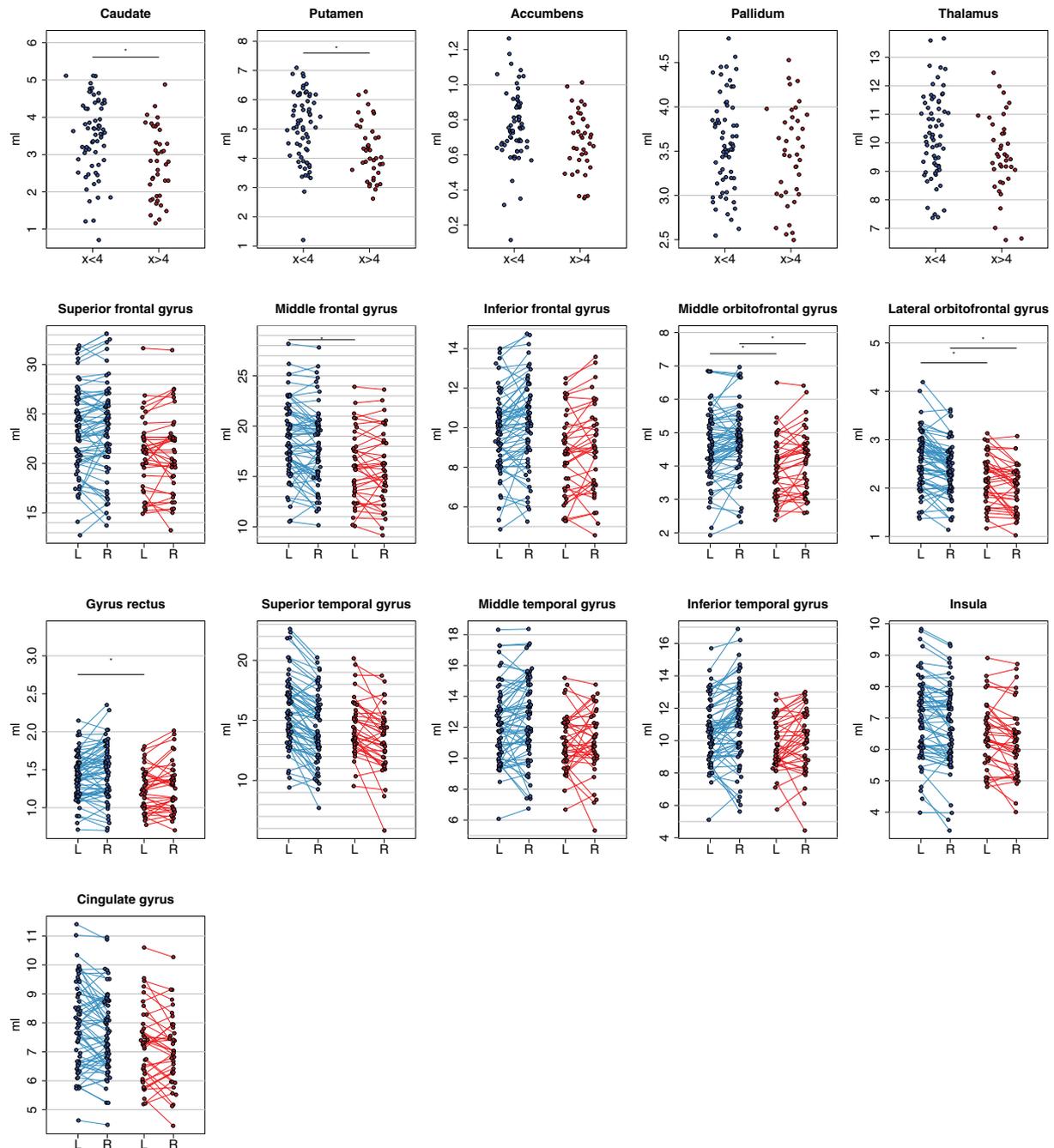
**FIGURE 1** Spearman correlation of brain volumes. The figure provides a heatmap of the pairwise Spearman correlations of the brain volumes (range: [0.41, 0.92]). Additionally, the correlations of the brain values to the  $\Delta$ -FTLD-CDR (range: [-0.35, -0.01]) and the diagnostic groups (range: [-0.37, -0.02]) are shown. The correlations are given numerically ( $\times 10^2$ ) and indicated by the color scheme (green: positive correlation, red: negative correlation). CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration

## 4 | DISCUSSION

Assessing the individual prognosis of a patient with bvFTD is one of the most difficult tasks in this disease entity. We used the FTLD-CDR, which has been developed as a functional assessment instrument and a global rating of disease severity,<sup>7</sup> to objectify disease progression rates within 1 year. We defined two patient groups according to their disease progression rate and examined whether it is possible to predict the amount of a person's clinical decline within 1 year by combining dif-

ferentiated brain volumes at baseline through statistical classification models. As there are pronounced individual differences in atrophy patterns within frontal, temporal, and subcortical brain areas in bvFTD, we asked if there are combinations of clearly defined subregions that may predict whether and how fast dementia severity will increase within 1 year.

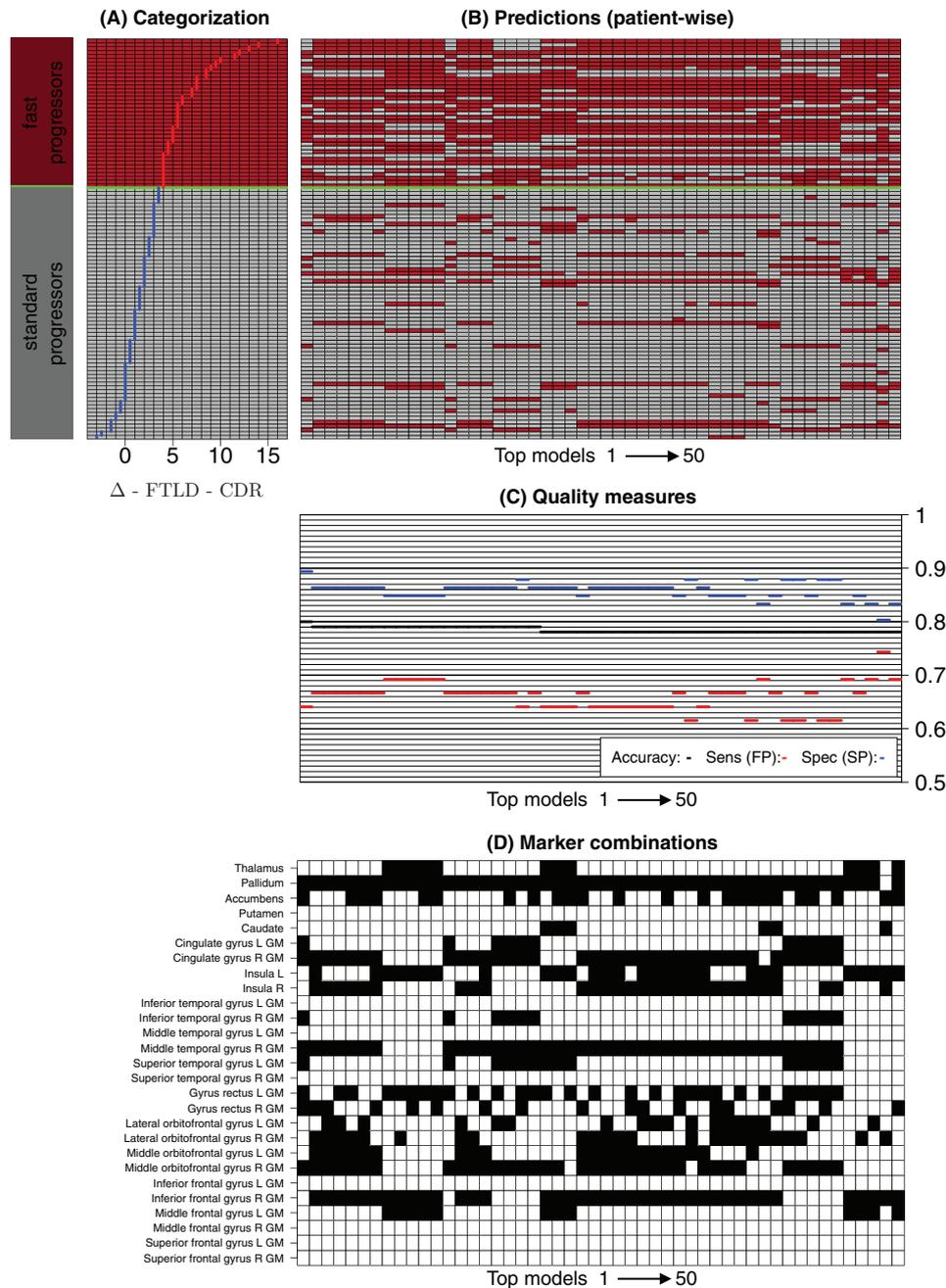
We used supervised machine learning techniques to perform an exhaustive screening for potential marker profiles and revealed different brain areas that may have a significant role in predicting



**FIGURE 2** Brain volumes. The figure provides an overview on the declines of brain volumes (ml) of the analyzed gyri for the patient groups slow progressors (blue,  $\Delta$ -FTLD-CDR < 4) and fast progressors (red,  $\Delta$ -FTLD-CDR  $\geq$  4). Each panel shows a specific gyrus or a pair of gyri. For paired gyri a line indicates the correspondence of the left and right hemisphere. The brain volumes were screened for statistically significant median differences between the group of fast progressors and slow progressors by applying two-sided Wilcoxon rank-sum. Significant results were indicated by an asterisk ( $P = 0.05$ , Bonferroni correction  $n = 27$ ). CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration

disease progression: pallidum, middle temporal gyrus, inferior frontal gyrus, cingulate gyrus, middle orbitofrontal gyrus, and insula. These areas have been identified by comprehensive quantitative meta-analytical techniques as hotspots of the disease<sup>20</sup> and have already been described as playing a crucial role in this disease entity: The inferior frontal gyrus and orbitofrontal gyrus play a major role in social and emotional behavior.<sup>21,22</sup> The pallidum is a subcortical structure of the brain, a component of the basal ganglia that appears to fulfill interest-

ing tasks in reward and motivation.<sup>23</sup> Miller et al. found that the pallidum is important for reward-seeking behavior and that this is a major component of bvFTD regarding overeating and craving sweet food,<sup>25</sup> hypersexuality<sup>26</sup> or drug abuse.<sup>27</sup> The insula strongly correlates with a range of functions, particularly empathy,<sup>28</sup> and contains a high portion of so-called von Economo neurons,<sup>29</sup> which play a major role in social cognition.<sup>30</sup> The insula seems to be affected in very early stages of bvFTD.<sup>31</sup> Josephs et al.<sup>32</sup> investigated distinct anatomic variants of



**FIGURE 3** Results of multivariate screening. The figure provides an overview on the results of the screening experiments with multivariate profiles (subsets) of brain volumes. All combinations from one up to 10 gyri ( $> 1.6 \times 10^7$  experiments) were evaluated in LOOCV experiments and ranked according to the accuracy achieved by 1-NN classifiers. The top 50 marker combinations according to accuracy are shown. A, Overview on the  $\Delta$ -FTLD-CDR scores of the individual patients. The scores are sorted and a green line indicates the border between the groups of fast progressors (red) and slow progressors (gray). The columns of (B-D) are sorted according to the accuracy of the top 50 marker combinations. The leftmost columns provide the results for the marker combination with the highest accuracy. B, Predictions for the individual patients. The patients (rows) are sorted according to their  $\Delta$ -FTLD-CDR scores (A). The overall accuracies as well as the sensitivities (fast progressors) and specificities (slow progressors) are given in (C). The corresponding brain volume combinations (black) are given in the columns of (D). 1-NN, nearest neighbor; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; LOOCV, leave-one-out cross-validation

FTD and found that personality change and inappropriate behaviors have been the most frequent features of a cohort with right temporal lobe atrophy.

In our sample, genetic status did not seem to have an impact and only 14 out of our 105 patients were identified as having bvFTD with

definite FTLD pathology due to presence of a known pathogenic mutation. But information about genetic status in our sample was incomplete: genetic testing was performed depending on the consent of the participants only in 78 cases; 27 patients chose to withhold from genetic testing. It might be interesting to validate our results using

a bigger and fully investigated genetic cohort following the example of the international GENFI (Genetic Frontotemporal Initiative) study,<sup>33</sup> as we know that in genetic FTD certain phenotypic signatures of the genes can be identified.<sup>34</sup> Furthermore, it has recently been shown that asymptomatic C9orf72 (chromosome 9 open reading frame 72) mutation carriers already have faster cortical thinning and surface loss throughout adulthood in brain regions that show atrophy in FTD.<sup>35</sup>

The reality of clinical trials as multicentric studies makes it necessary to handle imaging data of different MRI scanners. Although we have used a harmonized, standard MRI protocol, in a next step it would be helpful and important to have a closer look at potential effects of different scanners. In the present study, we also have not taken account of sex differences in our groups. Before this supervised machine learning technique can be applied in clinical trials, this must be addressed in an increased cohort size, especially to validate our results and to proof generalization. This method then could be a powerful tool in clinical trials as these MRI stratification clusters enable us to classify participating patients prior to treatment and could be used to capture disease progression rates under treatment by comparing the predicted to the actual disease trajectories.

Although multivariate classification models at first might be unprofitable for clinical routine, we believe that this method enables a gain in information that could also help caregivers deal with this disease. It has been shown that caregiver stress and burden impede nursing care of FTD patients significantly as many patients don't live in care facilities. A study by Diehl-Schmid et al.<sup>36</sup> demonstrated that information by trained staff is one of the most important and helpful interventions for caregivers to cope with this disease. Information about disease progression rates could help families be better prepared for future challenges.

Besides the limited number of patients, a further limitation of our study might be the definition of patient groups in fast and slow progressors using a  $\Delta$ -FTLD-CDR value that was rather data driven. Up to now there is no clinical consensus that this upper third is the definition of fast progressors although this seems to be clinical reasonable.

In summary, this study provides a potential approach to predict individual disease progression rates in bvFTD by combining brain volumes through advanced statistical classification models. As MR investigations are part of standard diagnostic procedures, this might be a feasible and relevant tool for clinicians who are confronted with questions of disease progression in a regular manner.

## ACKNOWLEDGMENTS

The study was supported by grants from the German Federal Ministry of Education and Research (project: FTLDc 01G11007A), the EU Joint Program—Neurodegenerative Disease Research (JPND) network, Genfi-Prox (01ED1512 to M.O. and 01ED2008B to M.S.), the Thierry Latran Foundation and German Research Foundation/DFG (SFB1279; SCHR 774/5-1), Boehringer Ingelheim Ulm University Bio-

Center (D.5009). Jens Wiltfang is supported by an Illídio Pinho professorship in iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal. The authors kindly thank all participants and their relatives for their participation in our study.

## HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the local Ethics Committees (proposal number at the central study center at University of Ulm, 39/11, March 8, 2011). On-site monitoring was conducted regularly for all patient data. Every participant or his/her legal representative signed written informed consent

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## AUTHOR CONTRIBUTIONS

Data acquisition: Sarah Anderl-Straub, Jolina Lombardi, Elisa Semler, Ingo Uttner, Janine Diehl-Schmid, Matthias Synofzik, Adrian Danek, Klaus Fassbender, Klaus Fliessbach, Holger Jahn, Johannes Kornhuber, Martin Lauer, Johannes Prudlo, Anja Schneider, Jens Wiltfang, Matthias L. Schroeter, Hellmuth Obrig, Markus Otto. Study concept and design: Sarah Anderl-Straub, Ingo Uttner, Jan Kassubek, Janine Diehl-Schmid, Adrian Danek, Klaus Fassbender, Klaus Fliessbach, Holger Jahn, Johannes Kornhuber, Bernhard Landwehrmeyer, Martin Lauer, Johannes Prudlo, Anja Schneider, Jens Wiltfang, Albert Ludolph, Hans Kestler, Markus Otto. Analysis and interpretation of data: Sarah Anderl-Straub, Ludwig Lausser, Jolina Lombardi, Elisa Semler, Jan Kassubek, Matthias Synofzik, Hans-Jürgen Huppertz, Alexander Volk, Matthias L. Schroeter, Helmuth Obrig, Hans A. Kestler, Markus Otto. *Drafting the manuscript*: Sarah Anderl-Straub, Ludwig Lausser, Markus Otto. Critical revision of the manuscript for important intellectual content: Jolina Lombardi, Elisa Semler, Ingo Uttner, Janine Diehl-Schmid, Matthias Synofzik, Klaus Fliessbach, Hans-Jürgen Huppertz, Alexander Volk, Matthias L. Schroeter, Markus Otto

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Anderl-Straub S, Lausser L, Lombardi J, et al., Predicting disease progression in behavioral variant frontotemporal dementia. *Alzheimer's Dement*. 2021;13:e12262. <https://doi.org/10.1002/dad2.12262>

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