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RESEARCH ARTICLE

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Data-driven staging of genetic frontotemporal dementia using multi-modal MRI

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Abstract

Frontotemporal dementia in genetic forms is highly heterogeneous and begins many years to prior symptom onset, complicating disease understanding and treatment development. Unifying methods to stage the disease during both the presymptomatic and symptomatic phases are needed for the development of clinical trials outcomes. Here we used the contrastive trajectory inference (cTI), an unsupervised machine learning algorithm that analyzes temporal patterns in high-dimensional large-scale population datasets to obtain individual scores of disease stage. We used cross-sectional MRI data (gray matter density, T1/T2 ratio as a proxy for myelin content, resting-state functional amplitude, gray matter fractional anisotropy, and mean diffusivity) from 383 gene carriers (269 presymptomatic and 115 symptomatic) and a control group of 253 noncarriers in the Genetic Frontotemporal Dementia Initiative. We compared the cTI-obtained disease scores to the estimated years to onset (age—mean age of onset in relatives), clinical, and neuropsychological test scores. The cTI based disease scores were correlated with all clinical and neuropsychological tests (measuring behavioral symptoms, attention, memory, language, and executive functions), with the highest contribution coming from mean diffusivity. Mean cTI scores were higher in the presymptomatic carriers than controls, indicating that the method may capture subtle pre-dementia cerebral changes, although this change was not replicated in a subset of subjects with complete data. This study provides a proof of concept that cTI can identify data-driven disease stages in a heterogeneous sample combining different mutations and disease stages of genetic FTD using only MRI metrics.

KEYWORDS
disease progression, frontotemporal dementia, magnetic resonance imaging, unsupervised machine learning

1 | INTRODUCTION

Frontotemporal dementia (FTD) is a highly heterogeneous disorder with substantial clinical, genetic, and pathological variations. FTD is caused by frontotemporal lobar degeneration (FTLD) and presents clinically with predominantly behavioral changes [behavioral variant FTD (bvFTD); Rascovsky et al., 2011] or language impairment (primary progressive aphasias; Gorno-Tempini et al., 2011). However, patients with FTLD can also develop symptoms of amyotrophic lateral sclerosis, progressive supranuclear palsy, and corticobasal syndrome. Up to one-third of cases are caused by an autosomal-dominant genetic mutation. The three most common mutations are in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*), which together account for 10–20% of all FTD cases (Rademakers, Neumann, & Mackenzie, 2012). MAPT mutations are associated with tau pathology, while GRN mutations and C9orf72 expansions are associated with TAR DNA-binding protein 43 (TDP-43). The most common clinical presentation in all genetic forms is bvFTD, but all phenotypes can occur (Lashley, Rohrer, Mead, & Revesz, 2015).

The heterogeneity of FTD is a major barrier to the development of treatments. To optimize therapeutic opportunities, we need biomarkers that can accurately track disease progression despite heterogeneity, both in symptomatic FTD and in the long presymptomatic period. There are several disease-modifying treatments under development for genetic FTD variants (Tsai & Boxer, 2016). The near to full penetrance of FTD-causing gene mutations means that asymptomatic carriers could eventually be included in clinical trials, however, trials are impeded by the variation in age at onset and clinical presentation observed within gene mutations given that presymptomatic mutation carriers will develop different phenotypes. In the context of a relatively rare disease, phase 3 trials will need to merge presymptomatic carriers with symptomatic subjects into a single study with unified outcome measures. Potential biomarkers such as neuroimaging measures from structural and functional MRI find differing group-level patterns across clinical (Bisenius, Neumann, & Schroeter, 2016; Lam, Halliday, Irish, Hodges, & Piguet, 2014; Pan et al., 2012; Seeley, Crawford, Zhou, Miller, & Greicius, 2009) and genetic variants, both symptomatically and in presymptomatic gene carriers (Cash et al., 2018; Jiskoot et al., 2019; Meeter, Kaat, Rohrer, & van Swieten, 2017; Panman et al., 2019). However, considerable variability has also been found within genetic groups; and atrophy in no one region captures the disease process in all subjects well (Olney et al., 2020). While neuroimaging remains a key biomarker of FTD, this high variance in biomarkers across FTD variants reduces the utility of these single measures to stage the disease. It is necessary to find unifying ways to stage the disease during both the presymptomatic and symptomatic phases.

Few studies have investigated disease staging of genetic FTD. Group-level patterns have been found in gray and white matter by regressing against the estimated years to onset (Jiskoot et al., 2018; Rohrer et al., 2015). Data-driven models of disease staging typically order a select number of biomarkers, assuming a single disease trajectory for all subjects, such as a recent model of GRN mutation carriers (Panman et al., 2021). A study combining disease progression modeling and clustering found data-driven subtypes that corresponded with genetic FTD mutations and their temporal progression patterns. This study used lobar gray matter volumes only (Young et al., 2018).

The contrastive trajectory inference (cTI) is a recent unsupervised machine learning algorithm for staging and subtyping disease. This model uses multi-dimensional data to uncover underlying temporal patterns in a diseased population, and subsequently orders and scores individuals along sub-trajectories of disease progression. When applied to gene expression data from individuals with Alzheimer's and Huntington's diseases, cTI-identified individual disease scores were significantly associated with clinical and neuropathological disease severity (Iturria-Medina, Khan, Adewale, & Shirazi, 2020).

In this study, we applied the cTI to multi-modal neuroimaging features from presymptomatic and symptomatic carriers of FTD-causing mutations. We focused on neuroimaging given its key role in the diagnosis of FTD in the absence of approved molecular biomarkers. We compared the cTI obtained disease scores to existing measures of disease severity and clinical performance as a proof of concept of cTI scores for staging disease in a heterogeneous dataset of genetic FTD.

2 | METHODS

2.1 | Dataset

This study used data release 3 from the Genetic FTD Initiative (GENFI; http://www.genfi.org.uk/). GENFI is a large international study gathering longitudinal data on individuals with genetic FTD (C9orf72 expansion, GRN, or MAPT mutations) and their first-degree relatives, which include an equal proportion of asymptomatic carriers and noncarriers. GENFI aims to develop markers which can identify FTD in its earliest stages as well as track disease progression.

We used multimodal MRI (volumetric T1 and T2, resting-state functional MRI, and diffusion-weighted imaging) as well as demographic, clinical, and neuropsychological data from the third data release of GENFI2, comprising 690 participants recruited from 23 sites in Canada and Europe. All participants were genotyped at their local site and underwent a standardized clinical assessment which consisted of a medical history, family history, and physical examination (Rohrer et al., 2015). Symptomatic status was based on this

assessment, according to established diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Mutation carriers were defined a presymptomatic when clinical criteria were not fulfilled.

2.2 | Image acquisition and processing

MRI scans were acquired using 3 T scanners, or 1.5 T at sites where 3 T was not available. Protocols were designed to harmonize across scanners and sites as much as possible (Rohrer et al., 2015).

T1: Volumetric T1-weighted MRI were acquired for 643 subjects. Acquisition parameters (median and ranges) included slice thickness 1.1 mm (1–1.2 mm), repetition time 2,000 ms (6.6–2,400), echo time 2.9 ms (2.2–9 ms), flip angle 8 (8–11), and number of slices 208 (140–208). Images were processed following the steps described in Iturria-Medina, Carbonell, Sotero, Chouinard-Decorte, and Evans (2017). In summary, images were segmented into gray matter, white matter, and cerebrospinal fluid probabilistic maps using SPM12. The gray matter maps were normalized to MNI space using DARTEL (Ashburner, 2007) and modulated to preserve the total amount of signal.

T2: Volumetric T2-weighted MRI were acquired for all available subjects ($n = 530$). Acquisition parameters (median and ranges) included: repetition time 3,200 ms (2,200–3,200 ms), echo time 401 mm (75–403 mm), slice thickness 1.1 mm (1–1.2 mm), flip angle 120 (90–120), and the number of slices 176 (156–196). All T2 images were normalized to MNI space using the parameters acquired for the T1 image with the closest acquisition date, using SPM12. T1/T2 ratios were calculated by dividing the T2 image from the T1 image with the closest acquisition date.

Resting-state functional MRI: Resting-state fMRI data were acquired for all available subjects ($n = 619$) using an echo-planar imaging sequence. Acquisition parameters (median and ranges) included: slice thickness 3.5 mm (2.7–3.5 mm), repetition time 2,500 ms (2,200–3,000 ms), echo time 30 ms (30–50 ms), flip angle 80 (80–90), and number of timepoints 200 (140–200). Images were processed following steps outlined in (Iturria-Medina et al., 2017) using tools from SPM12, FSL, and the REST toolbox. Preprocessing steps included motion correction, slice timing correction, normalization to MNI space using the parameters acquired for the T1 image with the closest acquisition date, and signal filtering to keep only low frequency fluctuations (0.01–0.08 Hz). Maps of fractional amplitude of low frequency fluctuations (fALFF) were calculated, to have a regional indicator of the brain's functional integrity (Zou et al., 2008).

Diffusion-weighted MRI: Diffusion-weighted images were acquired for all subjects who had the standard GENFI protocol ($n = 483$) which consisted of two sequences, with either four or five b0 images (no diffusion sensitization) and 64 diffusion-weighted images ($b = 1{,}000$ s/mm^2). The second sequence was used when available. Additional acquisition parameters (median and ranges) included: slice thickness 2.5 mm (2–3 mm), repetition time 7,300 ms (3,742–10,300 ms), and echo time 90 ms (36–100 ms). Images were preprocessed using Mrtrix3 software (Tournier et al., 2019). Preprocessing steps included denoising, Gibbs ringing correction, eddy current distortions correction, and bias field correction. Diffusion tensor measures of fractional anisotropy (FA) and mean diffusivity (MD) were calculated using FSL. Images were normalized to MNI space using the parameters acquired for the T1 image with the closest acquisition date using SPM12. All subsequent analyses of FA and MD refer to gray matter.

2.3 | Quality control and data preprocessing

All modalities underwent visual inspection, and images of poor quality were excluded. Imaging data from 637 subjects were used in the subsequent analysis. All imaging data were processed using the NeuroPM-box (Iturria-Medina et al., 2021; available at neuropm-lab.com/neuropm-box.html) "organizing input for MCM" tool, consisting of regional gray matter parcellation of each image, outlier detection and correction, and imputation of missing modalities. The NeuroPM-box is currently designed for the analysis of gray matter. As such, all modalities in this study are measured in the gray matter. Mean gray matter density, fALFF, T1/T2 ratio, and gray matter FA and MD were calculated for 78 cortical and subcortical regions, based on the Desikan–Killiany–Tourville (DKT) atlas (Klein & Tourville, 2012). All baseline data with missing modalities were imputed using the trimmed scores regression with internal principal component analysis algorithm, implemented in the Missing Data Imputation Toolbox for MATLAB, which considers the relationship between all subjects and variables to obtain imputed data by iteratively fitting PCA models to the data (Folch-Fortuny, Arteaga, & Ferrer, 2016).

2.4 | Data harmonization

We used ComBat to harmonize baseline data of each imaging metric by site and scanner type. ComBat, an empirical Bayesian method of harmonizing multi-site data originally used in genomics (Johnson, Li, & Rabinovic, 2007), has been shown to be robust for multi-site imaging studies with small numbers of participants per site (Fortin et al., 2017, 2018). The biological variability in genetic variants, disease status (noncarrier, presymptomatic carrier, and symptomatic carrier), and the estimated years to symptom onset (EYO) was preserved, as well as age, sex, and years of education.

2.5 | cTI method

The contrastive Trajectory Inference algorithm [cTI; Iturria-Medina et al. (2020) implemented in the user-friendly open-access *NeuroPM-box* software (Iturria-Medina et al., 2021)] is an unsupervised machine learning method to analyze temporal patterns in multi-dimensional populational datasets. Data can first be adjusted for confounding variables using robust additive linear regression modeling with pair-wise interactions. The cTI method then consists of unsupervised feature

selection (for high dimensional datasets), dimensionality reduction via contrastive principal component analysis, and subject ordering to obtain individual disease scores [described in detail in Iturria-Medina et al. (2020)].

Contrastive principal component analysis (cPCA; Abid, Zhang, Bagaria, & Zou, 2018) is an unsupervised method of data exploration and visualization which identifies patterns in a target population (i.e., a diseased population) by controlling against patterns in a background population (a control group). By adjusting for patterns identified in the background population, such as aging effects or noise, cPCA has been found to be more sensitive to disease progression, by identifying trends in the population of interest that may be missed using standard methods of dimensionality reduction (i.e., PCA). The model then automatically chooses the contrasted principal component space which best optimizes the enriched trends in the target population. Each subject's position in the contrasted principal component space, therefore, reflects their disease state, with further distance from the background indicating more advanced disease.

Subjects are ordered and assigned an individual "pseudo-time" score according to their proximity to the background, standardized to be between 0 and 1. Low scores indicate proximity to the background population while high scores indicate proximity to the most advanced disease state. In the context of neurodegeneration, the pseudo-time score can be interpreted as a personalized index of disease stage (from the continuum of young subjects that are decades away from symptoms up to the more advanced dementia cases).

The cTI also estimates the specific contribution of each feature on the obtained disease scores. Individual weights of each feature reflect how much that feature contributed to the contrasted principal component space from which the subject ordering and disease scores were obtained. A larger weight value, therefore, indicates a greater influence on the cTI-obtained disease scores.

2.6 | cTI analysis

In this analysis, we considered baseline data from five MRI-derived biomarkers in the gray matter (gray matter density, fALFF, T1/T2 ratio, FA, and MD). The cTI was run using all features due to the relatively small number of included features (5 modalities $\times$ 78 brain regions $=$ 390 features). Data were first linearly adjusted by age, sex, and years of education. Parameters of the linear regression were obtained in noncarriers only, to obtain estimates of healthy aging. Parameters were then applied to all subjects. All noncarriers were used as the background population. As opposed to including all gene mutation carriers in the target population, we choose to include symptomatic carriers only. Therefore, the symptomatic subjects only were used in the data exploration and visualization via cPCA, in contrast to the noncarriers, and the corresponding transformations of the data to the disease-associated space (contrastive principal component space) were then applied to all subjects. We used symptomatic subjects as the target population due to their more advanced disease state which should allow for better determination of the disease-associated patterns by the cTI (as only subtle changes are expected in the presymptomatic participants), and due to the much larger number of presymptomatic carriers compared to symptomatic (many of whom are young and likely far from symptom onset) which would likely bias the model towards early presymptomatic cases, increasing the difficulty of finding underlying disease-associated trends. The cTI was run using the combination of all five-imaging metrics, as well as each metric individually.

2.7 | Post-hoc statistical analysis

We compared the cTI obtained disease scores to the EYO, clinical assessment, and neuropsychological test scores using Pearson's correlation. Tests included the Mini-Mental State Examination (MMSE) for cognition, the Cambridge Behavioural Inventory Revised version (CBI-R) for behavioral symptoms, and a neuropsychological battery measuring cognition, attention, memory, language, and executive function (Digit Span forward and backward from the Wechsler Memory Scale-Revised, a Digit Symbol Task, Parts A and B of the Trail Making Test, the short version of the Boston Naming Test, Category Fluency (animals), Letter Fluency and the Wechsler Abbreviated Scale of Intelligence Block Design task). Z scores were calculated for all neuropsychological tests based on language-specific norms (Rohrer et al., 2015). Differences in disease status were tested using one-way ANOVAs. Post hoc pairwise differences between groups were analyzed using Tukey's test. All analyses were conducted using MATLAB (version 2019b) and R (version 4.0.3).

2.8 | Sensitivity analysis

To assess the impact of missing data and the subsequent imputation of this missing data on the analyses, the cTI was run, with all five modalities in combination, using only those individuals with all imaging modalities at their baseline visit ($n = 282$) and the above analyses repeated in this subgroup.

3 | RESULTS

We analyzed cross-sectional data from 637 participants who had at least one useable T1 scan, including 269 presymptomatic carriers, 115 symptomatic carriers, and 253 noncarriers (see Table 1 for demographic characteristics). Of the presymptomatic carriers, 92 had a C9orf72 expansion, 129 had a GRN mutation, and 48 had a MAPT mutation. Of the symptomatic subjects, 56 had a C9orf72 expansion, 40 had a GRN mutation, and 19 had a MAPT mutation. Eighty had a diagnosis of bvFTD, 20 had a primary progressive aphasia (15 non-fluent variant, 1 semantic variant, 4 non-specified), 4 had amyotrophic lateral sclerosis (ALS), 5 had FTD-ALS, 2 had corticobasal syndrome, 1 had progressive supranuclear palsy, and 3 had non-specified dementia.

TABLE 1 Demographics of included subjects

	Presymptomatic	Symptomatic	Noncarriers
N	269	115	253
Mutation[a]			
C9orf72	92 (34.2)	56 (48.7)	87 (34.4)
GRN	129 (48.0)	40 (34.8)	126 (49.8)
MAPT	48 (17.8)	19 (16.5)	40 (15.8)
Age (years)[b]	44.9 ± 11.9 (20.1–75.5)	63.0 ± 8.6 (32.9–78.7)	46.8 ± 13.7 (18.6–85.7)
Sex (female)[c]	170 (63.2)	50 (43.5)	142 (56.1)
Education (years)[b]	14.3 ± 3.3	11.9 ± 4.1	14.0 ± 3.5
CBI-R[b]	5.1 ± 9.1	61.2 ± 32.0	3.9 ± 6.3
MMSE[b]	29.3 ± 1.2	22.5 ± 6.3	29.4 ± 1.1
EYO[b]	−13.8 ± 11.5	3.4 ± 6.8	NA

Note: Diagnoses in symptomatic subjects: 79 bvFTD (41 C9orf72, 20 GRN, and 19 MAPT), 5 FTD-ALS (all C9orf72), 4 ALS (C9orf72), 15 nonfluent variant PPA (2 C9orf72, 13 GRN), 1 semantic variant PPA (C9orf72), 2 corticobasal syndrome (GRN), 4 dementia—not otherwise specified (GRN), and 1 progressive supranuclear palsy (C9orf72). Data are *n* (%) or mean ± standard deviation (range).

Abbreviations: ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CBI-R, Cambridge Behavioural Inventory Revised version; EYO, estimated years to symptom onset; MMSE, Mini-Mental State Examination; PPA, primary progressive aphasia.

[a]Genetic mutation status in noncarriers refers to the mutation carried in family members.

[b]$p < .001$ (one-way ANOVA), significant differences between symptomatic and presymptomatic, as well as noncarriers ($p < .001$, Tukey tests).

[c]$p < .001$ (chi-square), the difference in distribution across groups.

3.1 | cTI-identified disease scores

The cTI identified disease scores, obtained using all imaging metrics in combination, were significantly correlated with MMSE ($r = -.273$, $p < .001$, Figure 1a), CBI-R ($r = .516$, $p < .001$, Figure 1b), and each neuropsychological test (all $|r|$ .276–.468, $p < .001$, Figure 2) for all gene mutation carriers. A higher disease score was associated with greater impairment on all tests and clinical scales. Correlations were not significant in presymptomatic carriers only ($p > .05$, Table 2), while in the symptomatic group, only the MMSE was significantly correlated with disease scores ($p < .05$, Table 2). Correlations between cTI scores in the full group (including noncarriers) were similar to those in the gene mutation carriers (all $p < .001$, Table 2).

Significant differences in disease scores were found for disease status ($F = 270.9$, $p < .001$), with symptomatic subjects having higher disease scores than both asymptomatic carriers and noncarriers and asymptomatic carriers having higher disease scores than noncarriers ($p < .001$, Figure 1c). Differences were not driven by a single genetic group. Disease scores were also significantly correlated with the EYO for all gene mutation carriers, with a higher disease score associated with a shorter expected time to symptom onset ($r = .334$, $p < .001$, Figure 1d). See Table 2 for all correlations. Figure 3 shows the association between disease scores and age, by disease status.

3.2 | Feature contributions

We summed the feature weights across modalities and regions to determine the total contribution of each modality (Figure 4) and the total contribution of each brain region (Figure 5) to the obtained disease scores. DTI metrics provide the highest contribution (MD followed by FA), while fALFF provides the lowest. Gray matter density and T1/T2 ratio had similar contributions. Total regional contributions indicate the highest values for frontal, temporal, and subcortical regions.

3.3 | Individual modalities

When obtained using each imaging metric individually, the cTI identified disease scores in all gene mutation carriers were significantly correlated with MMSE (Table 3; gray matter density: $r = -.368$, fALFF: $r = -.355$, $p < .001$), CBI-R (Table 3; gray matter density: $r = .391$, fALFF: $r = .377$, T1/T2 ratio: $r = .373$, $p < .001$), and all neuropsychological tests for all modalities (Table 3; gray matter density: $|r| = .281$–$.447$, fALFF: $|r| = .277$–$.442$, $p < .001$), with a higher disease score being associated with greater impairment on all tests. Significant differences in disease scores were found for disease status, with symptomatic subjects having higher disease scores than both asymptomatic carriers and noncarriers ($p < .001$). Differences between asymptomatic carriers and noncarriers were not significant (fALFF, $p = .15$; FA, $p = .1$; T1/T2 ratio, $p = .07$; MD, $p = .06$; gray matter density, $p = .97$). A significant correlation was found with the EYO for all modalities (Table 3; $|r| = .192$–$.349$, $p < .005$) except MD ($r = .090$, $p = .0792$), with a higher disease score associated with a shorter time to symptom onset among gene carriers.

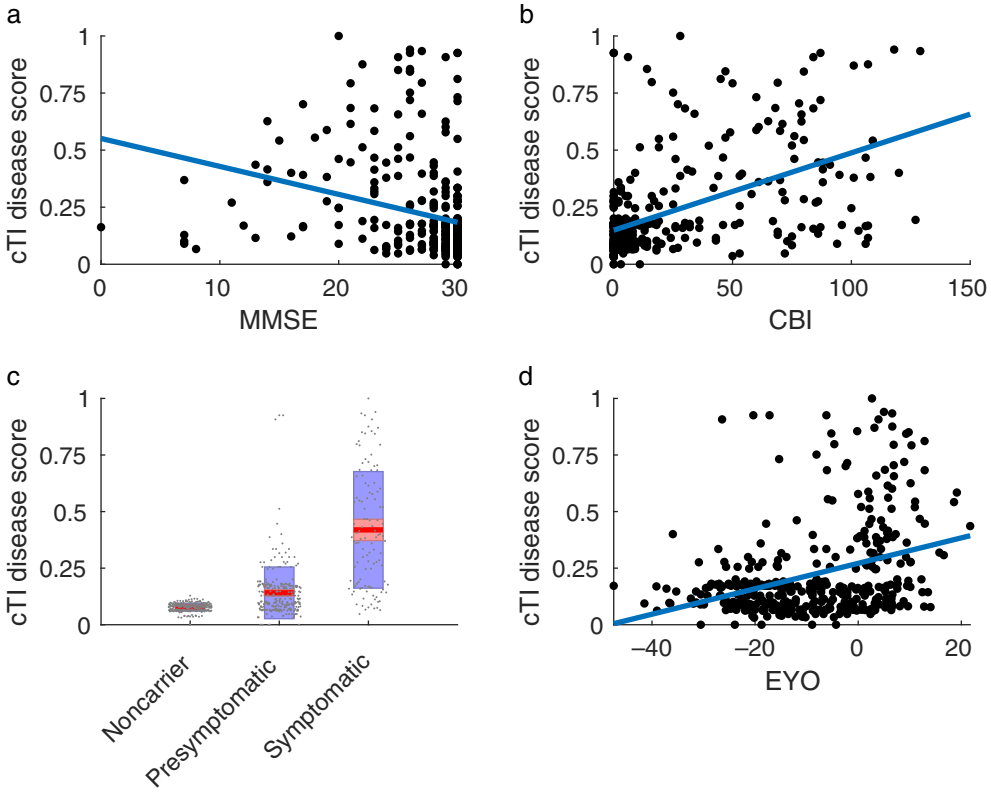

FIGURE 1 Association between cTI identified disease scores and (a) MMSE, (b) CBI-R, (c) Disease status, and (d) EYO. In c, points are laid over a 1.96 SEM (95% confidence interval) in red and at 1 SD in blue. CBI, Cambridge Behavioural Inventory; EYO, estimated years to symptom onset; MMSE, Mini-Mental State Examination

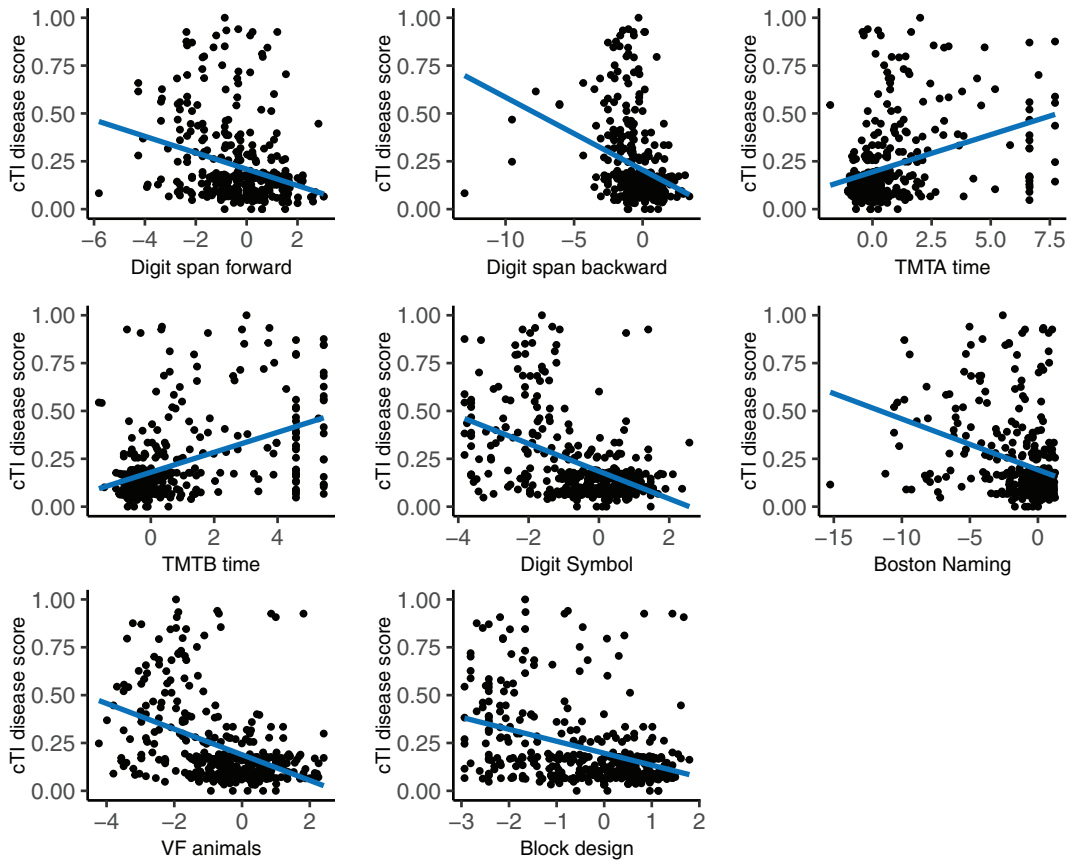

FIGURE 2 Association between cTI identified disease scores and neuropsychological tests. TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; VF, verbal fluency

	Carriers	Presymptomatic	Symptomatic	All
MMSE	−0.273	−0.014	0.237	−0.337
CBI-R	0.516	0.017	0.109	0.573
DS F score	−0.276	0.008	0.087	−0.269
DS B score	−0.292	−0.017	0.091	−0.295
TMTA time	0.357	0.019	−0.072	0.392
TMTB time	0.466	0.061	0.015	0.490
Digit symbol	−0.468	0.025	−0.026	−0.461
Boston naming	−0.334	0.015	0.132	−0.385
VF animals	−0.436	0.043	0.057	−0.424
VF F	−0.406	−0.007	−0.062	−0.387
VF A	−0.386	−0.064	0.023	−0.374
VF S	−0.398	−0.037	−0.021	−0.389
Block design	−0.370	0.090	0.069	−0.371
EYO	0.343	−0.089	0.026	0.298

Abbreviations: CBI-R, Cambridge Behavioural Inventory Revised version; DS B, Digit Span backward; DS F, Digit Span forward; EYO, estimated years to symptom onset; MMSE, Mini-Mental State Examination; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; VF, verbal fluency.

TABLE 2 Correlation (*r*) between cTI disease scores (all modalities) and each clinical/neuropsychological test for all gene carriers, presymptomatic carriers only, symptomatic carriers only, and the full group (including noncarriers)

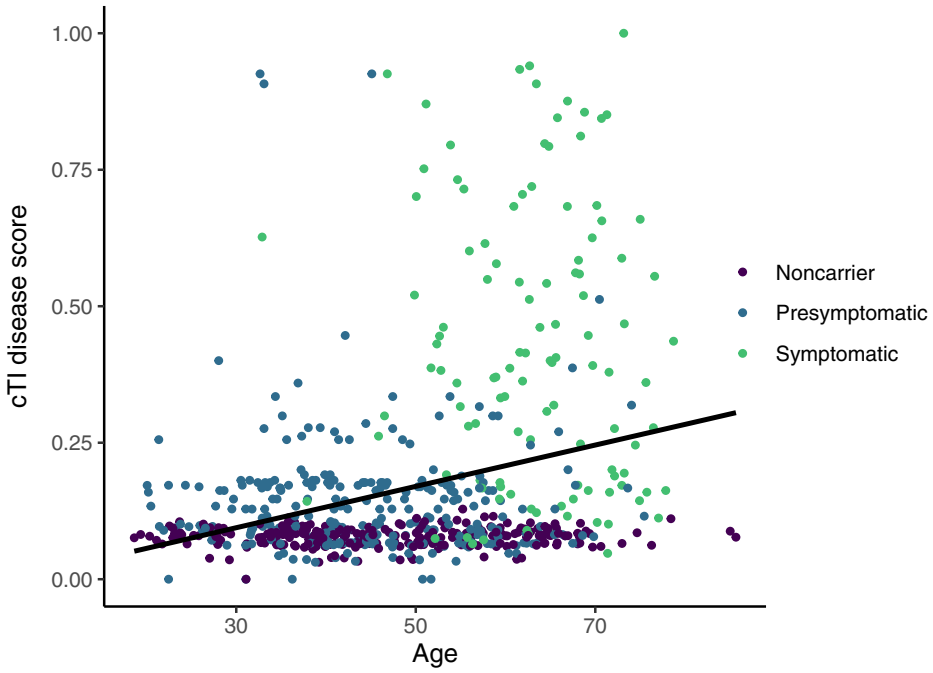

FIGURE 3 Association between cTI identified disease scores and age, by disease status

3.4 | Sensitivity analysis

Overall results of the analysis in the subset of subjects with full baseline imaging are similar to those in the full dataset; cTI disease scores were significantly correlated with all clinical and neuropsychological tests, and with the EYO (Figures S1 and S2). All correlations were equal to or stronger than in the full analysis. Significant differences in disease scores were found for disease status ($F = 318.6$, $p < .001$; Figure S1c). Symptomatic subjects had higher disease scores than both asymptomatic carriers and noncarriers ($p < .001$), but differences between asymptomatic carriers and noncarriers were not significant ($p = .15$). The feature contribution analysis indicated a higher contribution of gray matter density (Figure S3). The ordering of regional contributions were also somewhat altered (Figure S4), but the highest values were again found for frontal, temporal, and subcortical regions.

4 | DISCUSSION

In this study, we show that the cTI, a data-driven staging model, can identify the cross-sectional progression of disease in a heterogeneous sample of genetic FTD using only neuroimaging metrics without

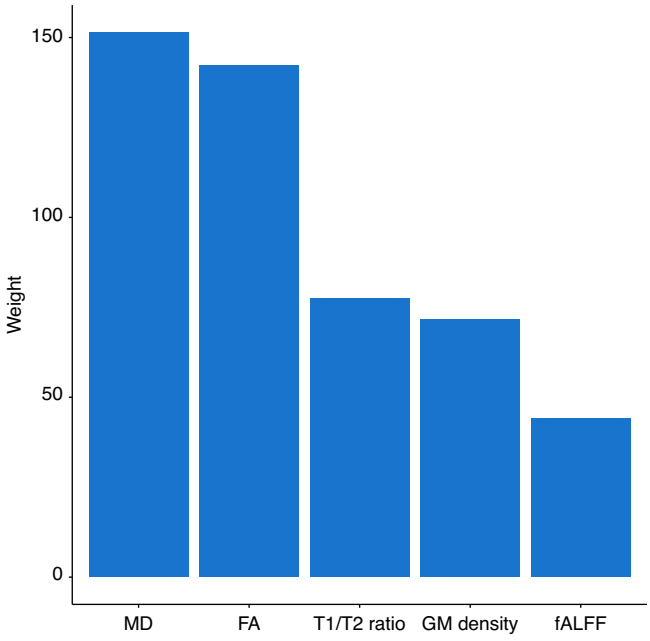

FIGURE 4 Total contribution of each modality to the cTI identified disease scores. FA, fractional anisotropy; fALFF, fractional amplitude of low frequency fluctuations; GM, gray matter; MD, mean diffusivity

clinical information. As a proof of validity, significant correlations were found between the data-driven cTI identified disease scores and the estimated years to symptom onset and to all the tested measures of clinical performance. In addition, higher mean cTI scores were found in presymptomatic carriers compared to noncarriers, suggesting that the staging system may be able to detect subtle pre-dementia changes in mutation carriers. Gray matter DTI measures, particularly MD, provided the largest contribution to the model. Disease scores derived from individual metrics were also significantly correlated with clinical performance. Differences in disease scores between presymptomatic carriers and noncarriers did not reach statistical significance in individual metrics, suggesting a combination of metrics may be important to differentiate presymptomatic carriers from asymptomatic subjects.

This study is a proof of concept that it is possible to generate a data-driven unified staging system across genetic and phenotypical variations that correlate strongly with the most relevant clinical and cognitive measures in FTD. Previous application of the cTI model has shown strong associations between the model-derived disease scores and clinical and neuropathological disease severity in both Alzheimer's and Huntington's diseases, as well as a cohort encompassing the spectrum of both diseases (Iturria-Medina et al., 2020). Our results corroborate the use of cTI-derived disease scores as a marker of neurodegenerative diseases, showing that the individual scores reflect

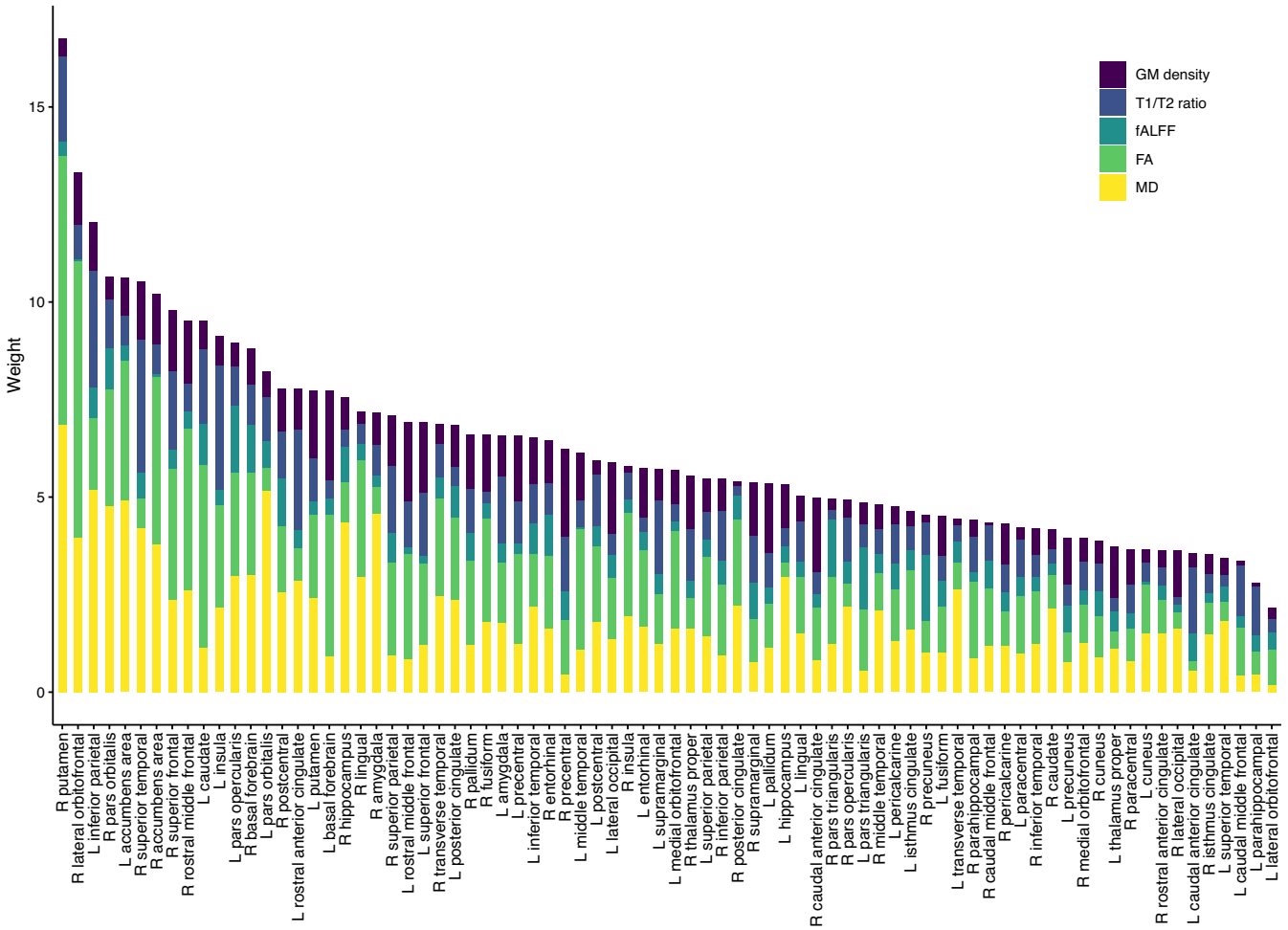

FIGURE 5 Total contribution of each brain region to the cTI identified disease scores. FA, fractional anisotropy; fALFF, fractional amplitude of low frequency fluctuations; GM, gray matter; L, left; MD, mean diffusivity; R, right

TABLE 3 Correlation (*r*) between cTI disease scores for each modality and each clinical/neuropsychological test (in all gene carriers)

	GM density	T1/T2 ratio	fALFF	FA	MD
MMSE	−0.368	−0.188	−0.355	−0.093	−0.24
CBI-R	0.391	0.373	0.377	0.28	0.261
DS F score	−0.306	−0.237	−0.277	−0.107	−0.258
DS B score	−0.281	−0.258	−0.289	−0.177	−0.243
TMTA time	0.358	0.160	0.376	0.210	0.238
TMTB time	0.447	0.275	0.442	0.225	0.265
Digit symbol	−0.442	−0.261	−0.372	−0.264	−0.237
Boston naming	−0.415	−0.244	−0.362	−0.247	−0.216
VF animals	−0.433	−0.296	−0.355	−0.210	−0.239
VF F	−0.358	−0.285	−0.374	−0.248	−0.266
VF A	−0.336	−0.269	−0.322	−0.229	−0.258
VF S	−0.357	−0.236	−0.318	−0.220	−0.269
Block design	−0.360	−0.217	−0.350	−0.211	−0.233
EYO	0.353	0.225	0.286	0.205	0.107

Abbreviations: CBI-R, Cambridge Behavioural Inventory Revised version; DS B, Digit Span backward; DS F, Digit Span forward; EYO, estimated years to symptom onset; MMSE, Mini-Mental State Examination; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; VF, verbal fluency.

a combination of subtle clinical differences in the presymptomatic stage and disease severity in symptomatic patients. We further show that the model can accurately identify disease stages in a heterogeneous population including the wide variety of clinical presentations and genetic mutations found in genetic FTD, factoring the presymptomatic and symptomatic spectrum. This association is found despite a large number of subjects in the early presymptomatic stage (i.e., more than 30–40 years prior to probable symptom onset). The association was largely driven by differences between presymptomatic and symptomatic stages, as correlations in the individual subgroups were mostly not significant; this is likely due to the fact that most presymptomatic subjects will have normal to very mild impairment on these tests, while symptomatic subjects are impaired. It also may reflect the inability of the clinical and cognitive scales to reflect specific aspects of each individual's subtle clinical decline.

The cTI has previously been applied to gene expression data. Here we show the utility of this model derived using neuroimaging features. The feature contributions analysis indicates that DTI metrics, in particular MD, are the biggest contributors to the model. These measures have rarely been studied in gray matter, although increases in MD have been reported in symptomatic FTD (Whitwell et al., 2010). This finding may warrant further investigation of gray matter microstructural changes. Of note, both DTI metrics indicate strong contributions to the model from similar brain regions. While FA and MD measure different processes, it is likely that multiple interrelated microstructural changes are occurring in the same brain regions.

Our results indicate moderate association between disease scores derived individually from gray matter atrophy, fALFF and T1/T2 ratio, and clinical performance. Gray matter atrophy is the most frequently studied imaging biomarker in FTD, and atrophy has been consistently reported across phenotypes and genetics, symptomatically and presymptomatically (Cash et al., 2018; Rohrer et al., 2015; Staffaroni et al., 2020). T1/T2 ratio and fALFF have been much less frequently studied. Alterations in functional connectivity have been reported in both presymptomatic and symptomatic FTD (Dopper et al., 2014; Lee et al., 2017; Premi et al., 2016). T1/T2 ratio, as a marker of intracortical myelin, has not been investigated in FTD to our knowledge; results here indicate a change in myelin content along with FTD progression. We obtained the highest correlations with clinical measures when using a combination of all modalities, and all modalities providing some level of contribution to the model, indicating an added benefit of combining information from multiple modalities which provide complementary information. Our results suggest that the combination of metrics may be particularly important to differentiate presymptomatic carriers from controls. The regional contributions analysis indicated that along with frontal and temporal regions, subcortical involvement was an important contributor to the model, while the left inferior parietal region also showed a high contribution. Subcortical involvement has also been reported in genetic FTD, while parietal involvement has been reported most commonly in GRN mutations (Rohrer et al., 2015).

The sensitivity analysis suggests that the observed associations between disease scores and the estimated years to symptom onset and to all the tested measures of clinical performance are fairly robust, while the differences between presymptomatic carriers and controls, the contribution of GM density to the disease scores are more sensitive to missing data. These findings should therefore be validated in a larger dataset with more complete data.

The development of data-driven biologically based staging would be useful for clinical trials. This study provides initial evidence supporting the potential usefulness of this type of modeling as a unified measure to track disease progression and monitor treatment effectiveness in a highly heterogeneous population. A main advantage

of the cTI is that it is an unsupervised data-driven model, determined by cross-sectional data, which does not rely on a priori phenotypical information. The clinical variables are not used to train a predictive model, removing concerns of circularity or overfitting. Furthermore, the cTI can incorporate various features from high dimensional data, and data-driven feature selection, eliminating the necessity of choosing select biomarkers or brain regions, seen in existing data-driven models (Panman et al., 2021; Young et al., 2018). It therefore provides unbiased biomarkers based solely on biological metrics. Further work is needed to evaluate the usefulness of this type of measure clinically and as a validated outcome for clinical trials.

A limitation of this study is the modalities used. All neuroimaging features used here are in the gray matter; including DWI metrics from white matter in future models may provide increased benefit to the model, as white matter microstructure changes may be an early feature of FTD (Feis et al., 2018; Jiskoot et al., 2018). Future models would likely also benefit from non-imaging neurodegeneration biomarkers like neurofilament light chain, which has good potential as a prognostic biomarker in clinical FTD (Benussi et al., 2020; Rohrer et al., 2016) and presymptomatic mutation carriers (Meeter et al., 2016; van der Ende et al., 2019). Our model suggests that while single biomarkers may perform reasonably well on their own and have high clinical feasibility, the inclusion of other advanced imaging metrics may increase precision, particularly in presymptomatic subjects, and therefore could be valuable in a clinical trial setting. Ultimately, a select number of biomarkers providing distinct information to the model, such as a combination of imaging and non-imaging metrics, may provide the best staging system. Future work could also analyze each genetic group separately, as larger datasets become available. Finally, we used EYO as a measure of disease severity, which has been shown to be imprecise as a predictor of actual onset (Moore et al., 2020). However, EYO remains the only predictive estimate of time to symptom onset other than age.

In summary, this study provides promising evidence for the development of unifying staging of heterogeneous neurodegenerative disorders using data-driven, unsupervised methods. Neuroimaging features show promise as potential biomarkers of disease progression but would most likely benefit from being combined with complementary clinical and biological information for optimal staging. While further validation work is required, biologically based staging systems are a promising tool to monitor monitoring disease progression and treatment outcomes in future clinical trials of genetic FTD.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used in this study are part of the Genetic Frontotemporal dementia Initiative (GENFI). The senior author (S. Ducharme) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Information on GENFI data availability can be obtained by contacting genfi@ucl.ac.uk.

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APPENDIX

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