An Automated Toolbox to Predict Single Subject Atrophy in Presymptomatic *Granulin* Mutation Carriers

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Abstract.

Background: Magnetic resonance imaging (MRI) measures may be used as outcome markers in frontotemporal dementia (FTD).

Objectives: To predict MRI cortical thickness (CT) at follow-up at the single subject level, using brain MRI acquired at baseline in preclinical FTD.

Methods: 84 presymptomatic subjects carrying *Granulin* mutations underwent MRI scans at baseline and at follow-up (31.2 ± 16.5 months). Multivariate nonlinear mixed-effects model was used for estimating individualized CT at follow-up based on baseline MRI data. The automated user-friendly preGRN-MRI script was coded.

Results: Prediction accuracy was high for each considered brain region (i.e., prefrontal region, real CT at follow-up versus predicted CT at follow-up, mean error $\leq 1.87\%$). The sample size required to detect a reduction in decline in a 1-year clinical trial was equal to 52 subjects (power = 0.80, alpha = 0.05).

Conclusion: The preGRN-MRI tool, using baseline MRI measures, was able to predict the expected MRI atrophy at follow-up in presymptomatic subjects carrying GRN mutations with good performances. This tool could be useful in clinical trials, where deviation of CT from the predicted model may be considered an effect of the intervention itself.

Keywords: Frontotemporal dementia, granulin, magnetic resonance imaging, mutation, preclinical, presymptomatic

INTRODUCTION

Frontotemporal dementia (FTD) refers to a heterogeneous group of disorders predominantly affecting the frontal and temporal lobes and characterized by behavioral disturbances, impairment of executive functions, or language deficits [1, 2]. About 40% of FTD patients have a family history of dementia, and about 20% have a clear autosomal dominant inheritance [3]. Among monogenic FTD, mutations in *Granulin* gene *(GRN)* are one of the most frequent genetic determinants [4–6] where symptoms are preceded by a long period of gradual accrual of subtle impairment of cognitive functions, progressive brain imaging abnormalities, and biomarker changes. However, despite the timely characterization of early and proximity markers of disease onset [7, 8], outcome measures to test the efficacy of treatment interventions are not yet validated. Indeed, in *GRN* mutation carriers, a number of potential therapeutic drugs have been designed [9, 10], and it is likely that these drugs may be more effective if administered early in disease course. However, because of the tautologic impossibility to define a clinical outcome for preclinical FTD, our strategic approach is directed towards fluidic or imaging biomarkers as outcome measures.

Circulating progranulin levels have been demonstrated useful to detect the presence of *GRN* haploinsufficiency [11], while serum or cerebrospinal fluid neurofilaments light chain or glial fibrillary acidic protein concentrations may be used to predict early symptoms development [12, 13], but their utility as outcome markers needs to be further established. In preclinical *GRN* mutations carriers, cross-sectional studies have identified significant grey matter atrophy and white matter hyperintensities in mutation carriers up to 10 years before expected symptom onset [7, 14, 15], while longitudinal studies have carefully shown imaging trajectories over time [15–17]. However, none of these markers can be currently used as outcome measures with sufficient accuracy at the single subject level.

Magnetic resonance imaging (MRI) markers are good candidates for the assessment of intervention efficacy, as they may aid to track the delay of disease progression, selectively evaluating effects on specific brain regions. An ideal marker should be able to accurately predict the expected MRI features at follow up, should be reliable and reproducible, and should be consistent across different centers. In other words, a useful outcome MRI marker should be able to forecast a subject's follow-up findings from baseline data. Accordingly, a pharmacological or non-pharmacological intervention may be considered effective when associated with a significant difference from the predicted model, indicating a reduction of expected disease progression. This approach could be used in early experimental medicine studies without placebo/sham treatment, which is particularly useful in view of the neurosurgical intervention required for some proposed *GRN* treatments and the challenges to global recruitment for large placebo-controlled studies.

In the present work, we used a multivariate nonlinear mixed effects model to predict brain MRI data at follow-up in presymptomatic subjects carrying pathogenetic *GRN* mutations from the Genetic FTD Initiative (GENFI) cohort. Such multivariate nonlinear mixed effects models have been used to estimate individualized longitudinal trajectories of neuroimaging data, but few studies examined neurodegenerative disorders [18]. We computed and coded an automated user-friendly script in which the simple and straightforward entry of raw baseline MRI T1-weighted data resulted in an accurate prediction of follow-up MRI data at a given time point and at the single subject level.

METHODS

Participants

Data for this study were drawn from the GENFI multicenter cohort study (data freeze 5), which consists of 22 research centers across Europe and Canada (http://www.genfi.org.uk). We included subjects carrying null mutations in the *GRN* gene at their presymptomatic stage, and for whom both baseline and follow-up MRI was available.

A standardized clinical assessment was performed for each subject, including the Digit Symbol Task, parts A and B of the Trail Making Test, the Wechsler Abbreviated Scale of Intelligence Block Design task, the short version of the Boston Naming Test and Letter and Category fluences [7].

Local ethics committees approved the study at each site and all participants provided written informed consent; the study was conducted according to the Declaration of Helsinki.

Study design

This study was aimed at predicting follow-up brain MRI data at a given time point and at single subject
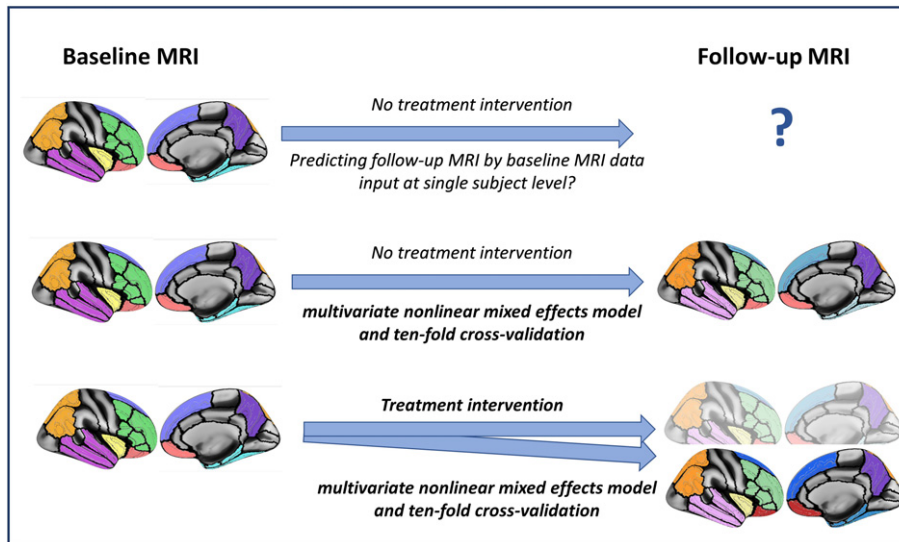
Fig. 1. Study design. The cartoon depicts the rationale of the present study. Predicting follow-up MRI data by baseline MRI data input at single subject level may represent a helpful outcome marker of treatment response (first row). To this, we applied multivariate nonlinear mixed effects model and ten-fold cross-validation to predict follow-up MRI at single subject level at a given time point (second row). When treatment intervention is administered, efficacy may be proven by any deviation from the expected MRI scan (third row).

level with the baseline MRI data serving as inputs to the model. We propose that if a treatment intervention is carried out, any deviation from the predicted model may be considered an effect of the intervention itself (see Fig. 1).

There were five steps to the study: 1) we extracted cortical thickness maps with a widely used automated brain atlas from baseline and follow-up MRI scans (see below, MRI acquisition and pre-processing section); 2) we run a multivariate nonlinear mixed effects model and an expectation-maximization algorithm for estimating individualized longitudinal trajectories of neuroimaging data (see below, Statistical approach section); 3) we then run a montecarlo simulation (5000 runs) leaving ten random subject out to assess results reliability in predicting follow-up MRI cortical regions from baseline MRI cortical thickness at a single subject level, and we assessed the mean percent error for each considered brain region; 4) we coded a user friendly toolbox, the preGRN-MRI, to predict MRI at follow-up; 5) we considered baseline MRI data of another cohort of presymptomatic *GRN* mutations carriers from the GENFI study, not included in the previous analysis, and we assessed the mean percent error in this second dataset to further prove the reliability of the method.

The preGRN-MRI toolbox, the user guide, and the related example dataset are available upon reasonable request.

MRI acquisition and pre-processing

Participants were scanned at their local site on 3 Tesla scanners from two different manufacturers, either Philips Healthcare or Siemens Healthcare Diagnostics. The acquisition protocol, designed to match across scanners as much as possible, included a volumetric T1-weighted MRI scan, as previously published [7]. Baseline and follow-up scans were processed using the standardized longitudinal cortical thickness pipeline of the Computational Anatomy Toolbox (CAT v12.6, http://www.neuro.uni-jena.de/cat/), extension to SPM12 V.7219 running on MATLAB R2017a). The quality assurance framework implemented in CAT was applied on a scale from A to F (A excellent to F unacceptable/failed), and we only retained scans with an overall quality ranging from A (excellent) to C (satisfactory).

Baseline and follow-up cortical thickness maps were parceled into 68 cortical regions, according to the Desikan-Killiany atlas [19]. Mean cortical thickness of each region was estimated in the native space. Then, mean values were mediated according to their belonging to brain macro-areas: lateral frontal cortex (caudal middle frontal, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal), orbitofrontal cortex (lateral orbitofrontal, medial orbitofrontal, frontal pole), superior frontal cortex (superior frontal), insula (insula), lateral temporal

cortex (inferior temporal, middle temporal, superior temporal), medial temporal cortex (entorhinal, fusiform, parahippocampal, temporal pole), lateral parietal cortex (inferior parietal, superior parietal) and precuneus (precuneus).

Statistical approach

In this work, we used a multivariate nonlinear mixed effects model developed by Bilgel et al. [18] for estimating the trajectories of biomarkers from longitudinal data in different brain areas. As a hierarchical model, each subject was fitted on its regression, with fitting parameters applied a second-order fitting. At this point, whole-group parameters were used to extrapolate a general trend, considering subjects' age and time spans.

The progression of MRI cortical thickness for each subject S_{ij} was assumed to be as follows:

$$S_{ij} = \alpha_i t_{ij} + \beta_i$$

where α_i is the rate of MRI cortical thickness progression, t_{ij} is the age of the subject i at time j, and β_i is the baseline MRI cortical thickness. Then the K biomarker measurements form a vector $\mathbf{y}_{ij}$ for subject i at time j is modeled by:

$$\mathbf{y}_{ij} = \mathbf{a}\,S_{ij} + \mathbf{b} + \boldsymbol{\epsilon}_{ij}$$

where a and b are vector and $\boldsymbol{\epsilon}_{ij} \sim N(0,\ R)$ is the observation noise assumed to be independent and identically distributed across subjects.

This is a mixed effects model that incorporates the fixed effects a and b, the individual random effects α_i and β_i. The model is nonlinear in the parameters.

To solve for the parameters, we applied an expectation-maximization (EM) algorithm [20], an iterative method that estimates parameters in statistical models, depending on unobserved latent variables. The algorithm alternates between an expectation (E) step, evaluating the expectation of the log-likelihood using the current estimate for the parameters, and a maximization (M) step, which computes the parameters maximizing the function found in the E step.

To assess how the results of the statistical analysis may be generalizable to an independent data set, and to estimate how accurately the predictive model performs, we used a ten-fold cross-validation. The cross-validation method works by partitioning the data into two subsets: a training set and a testing set. The first set is used to calculate the models, while the second set is used to test the model with a set of data not used to calculate the parameters of the models.

To minimize the variability, multiple rounds of cross validation were performed using different sets randomly selected by the original dataset. The validation results were averaged to estimate the performance. In our case, we used a ten-fold cross-validation where in each run we randomly select 10 subjects as testing set and the other subjects were used to estimate the parameters of the models.

The mean error between the predicted cortical thickness of each region and then expected (real) cortical thickness of each region [100*(predicted value – expected value)/predicted value] was calculated.

Finally, we performed a power analysis using G*Power [21], to investigate the minimum number of subjects necessary have a good reliability and power as defined by Cohen [22]. To this, we used the noncentrality parameter L calculated as:

$$L = f^2(n - k - 1)$$

where n is the number of subjects, k the number of regressor and f^2 defined as:

$$f^2 = \frac{R^2}{1 - R^2}$$

that is the ratio of the proportion of variance accounted for relative to the proportion of variance unaccounted for.

Data availability statement

The data used to support the findings of this study were derived from the Genetic Frontotemporal Dementia Initiative (GENFI, http://genfi.org.uk/). They are available on request from the Principal Investigator of the GENFI consortium (Dr Jonathan Rohrer, University College London, E-mail: genfi@ucl.ac.uk.).

RESULTS

Participants

We firstly considered 84 presymptomatic subjects carrying *GRN* mutations. The mean age was 47.8 (standard deviation, SD = 11.4), 60.7% were female ($n = 51$), with 15.04 (SD = 3.4) years of formal schooling. Neuropsychological assessment (mean score ± standard deviation) is reported in Supplementary Table 1. The mean interval between MRI scans was 31.2 months from the baseline MRI scan (SD = 16.5, range = 9.6–71.3 months). MRI quality ranking was excellent/good for both baseline and

Table 1
Cortical thickness of each brain region in presymptomatic GRN mutation carriers

Brain ROIs	First cohort ($n = 84$)				Second cohort ($n = 6$)			
	baseline MRI	follow-up MRI	p	mean error %*	baseline MRI	follow-up MRI	p	mean error %*
lateral frontal L	2.76 ± 0.13	2.76 ± 0.12	0.71	1.84 ± 0.36	2.88 ± 0.09	2.85 ± 0.11	0.52	1.19 ± 0.35
lateral frontal R	2.76 ± 0.12	2.76 ± 0.17	0.36	1.87 ± 0.49	2.85 ± 0.12	2.84 ± 0.10	0.87	0.53 ± 0.13
orbitofrontal L	2.65 ± 0.17	2.67 ± 0.16	0.84	4.07 ± 0.94	2.82 ± 0.18	2.77 ± 0.16	0.63	1.84 ± 0.26
orbitofrontal R	2.64 ± 0.17	2.67 ± 0.20	0.06	3.69 ± 0.88	2.86 ± 0.124	2.86 ± 0.17	1.00	1.95 ± 0.37
superior frontal L	**2.88 ± 0.14**	**2.83 ± 0.18**	**<0.001**	2.59 ± 0.53	3.04 ± 0.09	3.03 ± 0.11	0.87	1.37 ± 0.27
superior frontal R	**2.87 ± 0.14**	**2.82 ± 0.17**	**<0.001**	2.84 ± 0.59	3.04 ± 0.11	3.02 ± 0.11	0.63	0.96 ± 0.19
medial temporal L	3.16 ± 0.26	3.20 ± 0.25	0.10	5.92 ± 1.18	3.51 ± 0.23	3.61 ± 0.20	0.42	4.61 ± 0.87
medial temporal R	3.18 ± 0.29	3.22 ± 0.3	0.08	6.89 ± 1.37	3.61 ± 0.08	3.54 ± 0.08	0.20	2.11 ± 0.49
lateral temporal L	2.90 ± 0.16	2.93 ± 0.14	0.014	2.68 ± 0.49	2.98 ± 0.10	2.94 ± 0.11	0.42	1.29 ± 0.33
lateral temporal R	2.93 ± 0.15	2.97 ± 0.20	0.008	2.54 ± 0.62	2.99 ± 0.14	2.98 ± 0.15	0.75	0.87 ± 0.14
lateral parietal L	2.46 ± 0.12	2.46 ± 0.10	0.86	2.23 ± 0.51	2.53 ± 0.07	2.53 ± 0.10	0.75	1.11 ± 0.15
lateral parietal R	2.45 ± 0.14	2.47 ± 0.16	0.16	2.66 ± 0.61	2.52 ± 0.07	2.50 ± 0.10	0.87	1.21 ± 0.19
precuneus	2.48 ± 0.13	2.45 ± 0.14	0.02	2.41 ± 0.56	2.60 ± 0.09	2.61 ± 0.08	0.87	1.51 ± 0.27
insula L	3.49 ± 0.22	3.51 ± 0.20	0.14	4.44 ± 0.82	3.69 ± 0.11	3.63 ± 0.16	0.42	2.40 ± 0.69
insula R	3.47 ± 0.22	3.5 ± 0.26	0.04	4.75 ± 1.06	3.70 ± 0.25	3.76 ± 0.18	0.42	2.84 ± 0.61

L, left; R, right; ROIs, region of Interest expressed in millimeters; significant *p*-values in bold face, baseline MRI scores versus follow-up MRI cortical thickness scores ($p < 0.004$ corrected for multiple comparisons). Results are expressed as mean $\pm$ standard deviation. *mean error between real cortical thickness at follow-up and predicted cortical thickness at follow-up.

follow-up scans (baseline: 82% B, 18% B-; follow-up: 80% B, 20% B-).

Baseline and follow-up cortical thickness values are reported in Table 1 (first cohort). We found significant differences between baseline and follow-up in the superior frontal region, bilaterally. These areas presented more severe cortical thinning at follow-up compared to baseline (one-way mixed ANOVA, with baseline versus follow-up MRI as within-subjects factors). No other significant differences between baseline and follow-up cortical regions were found.

Model fitting

The prediction analysis takes baseline cortical regions as input, considering age and time between the two MRI scans as regressors, and the model was then fitted. As reported in Fig. 2 and Table 1 (first cohort), overall prediction accuracy was high for each considered brain region, with low mean error. The best prediction was obtained considering lateral prefrontal regions, bilaterally (real cortical thickness at follow-up versus predicted cortical thickness at follow-up, mean error $\leq 1.87\%$), while the worst was for medial temporal region, bilaterally (mean error $= 5.82\%$ and 6.89%). Thus, for each subject, we obtained overall high accuracy in predicting brain imaging outcome.

We then coded a user-friendly automated preGRN-MRI toolbox to predict cortical thickness of each region at follow-up at the single subject level.
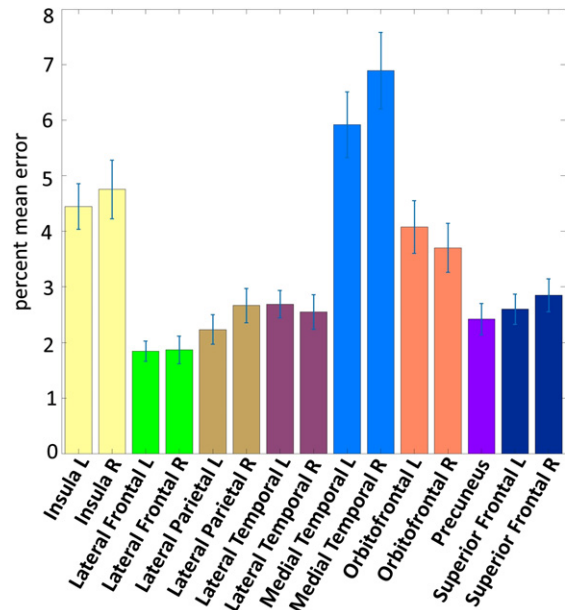

Fig. 2. Mean percent error of multivariate nonlinear mixed effects model in predicting follow-up cortical regions by baseline MRI data in first cohort of presymptomatic *Granulin (GRN)* mutation carriers. L, left; R, right. The results are expressed as mean error $\pm$ standard deviation.

No significant further preprocessing is needed; the user has only to insert the age of the subject at baseline MRI, the values of each considered baseline cortical region, previously computed with the Desikan-Killiany atlas 19, and the age of the subject
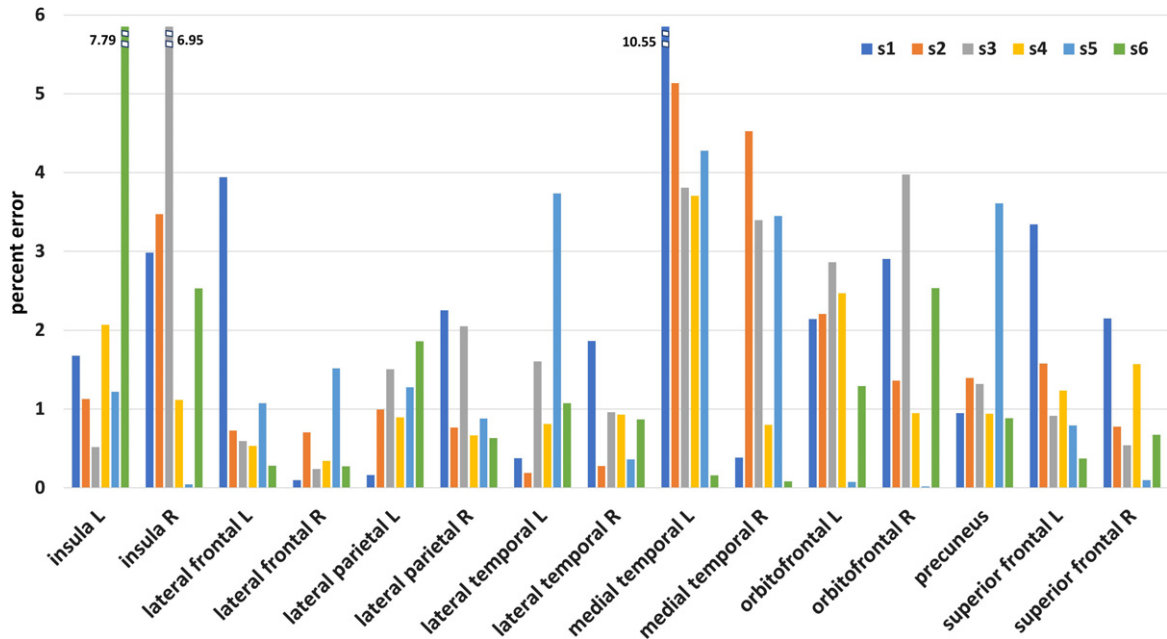
Fig. 3. Percent error of multivariate nonlinear mixed effects model in predicting follow-up cortical regions by baseline MRI data in a new sample of 6 presymptomatic Granulin (GRN) mutation carriers. L, left; R, right. High percentage error values for several subjects (subject 6 for left insula, subject 4 for right insula, subject 1 for left medial temporal region) were reported to maintain consistency in the graphical representation.

at the desired MRI follow-up. The toolbox will assess automatically the predicted brain regions' values at follow-up in the referral presymptomatic subject carrying a *GRN* mutation.

Model validation

We further evaluated the effectiveness of our toolbox, using a new dataset of 6 presymptomatic subjects carrying *GRN* mutations from the GENFI cohort, not included in the previous analyses. The mean age was 47.3 (standard deviation, SD = 11.4), 33% were female ($n = 2$), with 11.4 (SD = 4.3) years of formal schooling. The mean follow-up MRI was 18.2 months (SD = 6.4, range = 12–25 months). MRI quality ranking was excellent/good for both baseline and follow-up scans (baseline: 84% B, 16% B-; follow-up: 85% B, 15% B-). This second (validation) cohort presented a different pattern of cortical thickness, as demonstrated by the between-cohort comparisons (1st versus 2nd cohort at baseline and at follow-up), with statistically significant differences between the two cohort at baseline as well as at follow-up (frontal, temporal, parietal and insula regions, bilaterally) (Supplementary Table 2).

We re-run the analyses using the previously coded preGRN-MRI toolbox. The mean percent error was

comparable, as reported in Fig. 3 and Table 1 (second cohort).

Sample size estimates

The sample size required to detect a reduction in decline of overall cortical thickness in a 1-year clinical trial was equal to 52 subjects (power = 0.80, alpha = 0.05).

DISCUSSION

Our study demonstrated that a novel user-friendly toolbox, preGRN-MRI, can accurately predict cortical thickness changes at follow-up MRI, at the single subject level over a timescale compatible for clinical trials. Thus, preGRN-MRI toolbox might be proposed as a useful device to track neuroimaging changes in early phase clinical trials, as any deviation of cortical thickness from the predicted model could be considered an effect of the intervention itself. It avoids complicated processing by the end users, by providing them with an easy-to-use, automated pipelined toolbox. It also produces comprehensive and interpretable results for model evaluation toward better understanding FTD, and better design of trials.

We considered MRI T1-weighted structural imaging and a widely used atlas [19] to easily compute the data analysis, and to use preGRN-MRI toolbox in any centre with comparable findings, independently of MRI scan or acquisition process [23, 24]. Indeed, in both the first and in the second cohorts the best prediction was obtained by considering the lateral frontal cortex (mean error <1.88% and <1.20%, respectively) but other regions scored adequately, suggesting the possibility to compute a compound score to increase predictive performances.

These results show that the nonlinear mixed effect model has good reliability and good generalizability. The proposed framework simplifies the estimation of parameters, and accurately estimates the trajectory parameters taking into account inter-individual differences: as hierarchical model, the first level regression of the subjects and the subsequent second level analysis provided a regression over time independent from the single subjects. From this point of view, this can be considered as an experimental "single subject" measure along all times. The high reproducibility was further demonstrated by a second dataset from the GENFI cohort (even including subjects with different cortical thickness pattern), with comparable findings.

Future clinical trials in presymptomatic subjects carrying GRN mutations may benefit from preGRN-MRI toolbox to capture variations in response to a treatment intervention. Up to now, no reliable outcome marker in the preclinical stages of FTD is yet available. The present model fitting may be expanded to other monogenic forms of FTD in their preclinical or symptomatic stages. Indeed, we may argue that the model parameters may differ in C9orf72 or MAPT mutations, as these are characterized by different disease trajectories and the involvement of selective brain areas [7], in both presymptomatic and symptomatic disease stages.

A number of ongoing pharmacological trials aim to postpone or revert disease onset in monogenic FTD. GRN mutations impair transcription of the gene, leading to levels of progranulin in the serum and cerebrospinal fluid that are >50% lower than normal from birth [4, 5]. Therefore, therapeutic approaches may range from either increasing transcription from the normal allele or modulating post-translational mechanisms [25]. Clinical trials have already tested amiodarone, with the purpose to increase progranulin levels in GRN mutations carriers, with no clear-cut efficacy [26] and pharmacological trials targeting the sortilin (SORT1), a

lysosomal trafficking receptor for progranulin and mediating progranulin endocytosis [27], are ongoing with promising results [28]. Other potential therapeutic strategies are in the pipeline, including the delivery of a healthy GRN gene via an AAV9 vector [29]. Recently, non-pharmacological approaches by using non-invasive brain stimulation technologies have been demonstrated safe and effective in restoring clinical symptoms and brain connectivity in FTD patients [30–32]. Within this context, and prospectively thinking to future intervention strategies, a reliable surrogate marker of disease, such as regional cortical thinning, may be of crucial to assess treatment efficacy in clinical trials. We do not argue against the ultimate necessity for randomized placebo controlled trials, but in view of the low prevalence of known GRN mutation carriers worldwide, and the invasiveness of non-pharmacological approaches in development, early proof of concept studies may benefit from open label studies without placebo, relying on accurate predictive biomarkers to indicate efficacy.

PreGRN-MRI toolbox presents several advantages for this approach. It is automated, together with parameter optimization through nested cross-validation and it is flexible, allowing users to consider different brain regions individually or to compute a comprehensive measure of brain changes.

We acknowledge that this study entails some limitations. First, the prediction model may be improved considering modulators of disease progression, such as cognitive reserve proxy measures [16, 33] or computing cerebral regions in a different way. However, the model used here, implemented by an expectation-maximization algorithm, takes into account unobserved latent variables, i.e., variables that do not change over time, such as TMEM106b genotype [33]. Moreover, testing preGRN-MRI toolbox in future clinical trials may prove its reliability in assessing intervention efficacy. Finally, the same approach might be tested in the other pathogenetic mutations, such as MAPT or C9orf72, to develop a user-friendly toolbox tailored on each monogenic FTD-related disorder.

In conclusion, preGRN-MRI tool, using baseline MRI measures, was able to predict the expected MRI at follow-up in presymptomatic subjects carrying GRN mutations with good performances. In future studies, preGRN-MRI tool might be useful in clinical trials, where deviation of CT from the predicted model may be considered an effect of the intervention itself.

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SUPPLEMENTARY MATERIAL

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