

Education modulates brain maintenance in presymptomatic frontotemporal dementia

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ABSTRACT

Objective Cognitively engaging lifestyles have been associated with reduced risk of conversion to dementia. Multiple mechanisms have been advocated, including increased brain volumes (ie, brain reserve) and reduced disease progression (ie, brain maintenance). In cross-sectional studies of presymptomatic frontotemporal dementia (FTD), higher education has been related to increased grey matter volume. Here, we examine the effect of education on grey matter loss over time.

Methods Two-hundred twenty-nine subjects at-risk of carrying a pathogenic mutation leading to FTD underwent longitudinal cognitive assessment and T1-weighted MRI at baseline and at 1 year follow-up. The first principal component score of the graph-Laplacian Principal Component Analysis on 112 grey matter region-of-interest volumes was used to summarise the grey matter volume (GMV). The effects of education on cognitive performances and GMV at baseline and on the change between 1 year follow-up and baseline (slope) were tested by Structural Equation Modelling.

Results Highly educated at-risk subjects had better cognition and higher grey matter volume at baseline; moreover, higher educational attainment was associated with slower loss of grey matter over time in mutation carriers.

Conclusions This longitudinal study demonstrates that even in presence of ongoing pathological processes, education may facilitate both brain reserve and brain maintenance in the presymptomatic phase of genetic FTD.

(*GRN*) and *chromosome 9 open reading frame 72 (C9orf72)* genes are proven major causes of genetic FTD, accounting for 10% to 20% of all FTD cases.³

There is wide variation in the age at onset within genes and within families with the same mutation, and possible disease modifiers have been recently reported. Identification of disease modifiers is key to correctly select subjects, reduce heterogeneity and increase statistical power of analysis of clinical trials, to stage presymptomatic disease and to enable long-term care planning in at-risk subjects.

Genetic variations within *Transmembrane Protein 106B (TMEM106B)* have been suggested to modulate disease onset in frontotemporal lobar degeneration due to transactive response (TAR) DNA binding protein 43 proteinopathy,^{4,5} and more recently, *glial cell line-derived neurotrophic factor (GDNF) Family Receptor Alpha 2 (GFRA2)* polymorphism and *C6orf10/LOC101929163* locus have been further implied in affecting the onset in *GRN* and *C9orf72* mutation carriers, respectively.^{6,7}

Along with non-modifiable genetic determinants, modifiable factors that modulate brain structure and function have been identified. For example, educational attainment contributes to resilience against brain damage in neurodegenerative disorders including Alzheimer's disease and FTD,^{8,9} in symptomatic and presymptomatic disease stages. In particular, it has been shown that higher educational achievements are associated with greater grey matter volumes in presymptomatic subjects carrying pathogenic FTD mutations.¹⁰ These findings corroborated previous studies in healthy individuals, in which life exposures, such as educational and occupational attainments and engagement in leisure and social activities, have been associated with decreased risk of developing dementia^{11,12} and with greater brain volumes.^{13,14}

These results argue that education, a proxy measure of brain reserve, may postpone FTD symptom onset; however, these findings cannot give any information on the role of educational attainment in counteracting the effect of the

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterised by executive dysfunction, personality changes and language impairment, along with atrophy of frontal and temporal lobes.^{1,2} FTD has a strong genetic background with autosomal dominant inheritance in around a third of patients. Mutations in *Microtubule-Associated Protein Tau (MAPT)*, *Granulin*



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pathogenic mutation on brain changes over time, that is actively coping with pathology progression.¹⁵ This concept, called brain maintenance, cannot be measured through cross-sectional data, but requires longitudinal studies.¹⁶ Indeed, if lifetime exposures, such as education, influence brain maintenance in at-risk subjects, this would have to be carefully evaluated in defining clinical trials' designs and outcomes and it might itself be considered an interventional approach.

In the present study, we aimed at evaluating the effect of educational attainment on longitudinal grey matter changes and cognitive performances in a large cohort of at-risk subjects from the Genetic FTD Initiative (GENFI) study.

METHODS

Participants

Data for this study were drawn from the GENFI multicentre cohort study, which consists of 27 research centres across Europe and Canada (www.genfi.org.uk). For the purpose of the present study, we included subjects at-risk of carrying mutations in *C9orf72*, *MAPT* and *GRN*, as having the proband with monogenic FTD¹⁷ and for whom both baseline and 1 year follow-up MRI was available. Conversion to symptomatic stage at follow-up visit or the presence of psychiatric disease or central nervous system pathology, including expansive or vascular lesions, were considered exclusion criteria.

Between January 2012 and December 2017, 229 at-risk subjects fulfilled inclusion/exclusion criteria, namely 116 mutation carriers (*C9orf72* n=31, *GRN* n=65, *MAPT* n=20) and 113 mutation non-carriers.

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.

For each subject we recorded demographical data, including years of formal schooling (education), past medical history and a standardised clinical and neuropsychological assessment, as previously published.¹⁷ We considered education as reserve proxy and Mini-Mental examination (MMSE) raw scores as measure of cognitive status.

Furthermore, we considered age, sex and *TMEM106B* genotype (see¹⁰ for details), as variables of interest in the statistical model.

MRI processing

Participants were scanned at their local site on scanners from three different manufacturers (Philips Healthcare, GE Healthcare Life Sciences, Siemens Healthcare Diagnostics). Magnetic field strength was 3T for 221 scans (96.5%) and 1.5T for eight scans (3.5%). The protocol, designed to match across scanners as much as possible, included a volumetric T1-weighted MRI scan, as previously published.¹⁷

Baseline and follow-up scans were processed using the standardised longitudinal voxel-based morphometry pipeline of the Computational Anatomy Toolbox (CAT V.12.1, extension to SPM12 V.7219 running on MATLAB R2015a) (<http://www.neuro.uni-jena.de/cat/>).

Baseline and follow-up grey matter volume (GMV) maps were parcellated into 112 cortical and subcortical regions (excluding the cerebellum because of some subjects with incomplete coverage of the inferior cerebellar hemispheres¹⁸) according to the maximum probability tissue labels derived from the "MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labelling" (<https://my.vanderbilt.edu/masi/workshops/>). This atlas was created from MRI scans belonging to the OASIS project (www.oasis-brains.org/) and labels were provided by Neuromorphometrics, Inc. (www.neuromorphometrics.com/).

Tissue volumes were estimated in the native space, before any spatial normalisation. Thus, region of interests (ROIs) values, representing the GMV contained in each ROI (expressed in millilitres, mL), were further corrected for the total intracranial volume (TIV). Estimates of TIV, total GMV, total white matter volume (WMV) and total cerebrospinal fluid volume (CSFV) were also computed to assess macroscopical differences. Total GMV, total WMV and total CSFV were expressed as percentage of TIV.

Statistical analysis

To overcome the complexity of MRI data, graph-Laplacian Principal Component Analysis (gLPCA) was applied to obtain a low dimensional representation of grey matter parcellation at baseline and at follow-up,¹⁰ which incorporated graph structure. gLPCA has several advantages compared with principal component analysis: (i) it is modelled on the representation of the data, (ii) it can be easily calculated, presenting a compact closed-form solution and (iii) it allows noise removal. The first principal component score (PC1) was used to summarise GMV at each time point. A correlation threshold higher than 0.6 was used to define PC1, which was constituted by 100 ROIs belonging to frontal, cingulate, temporal and parietal regions.

Successively, a two-group structural equation modelling (SEM) was fitted on longitudinal data.

SEM is a multivariate regression technique that models the covariance structure of a set of observed and latent (random effects) variables, and is based on a subset of possible paths connecting those variables, incorporating directional information (regression coefficients) and bi-directional information (covariance).

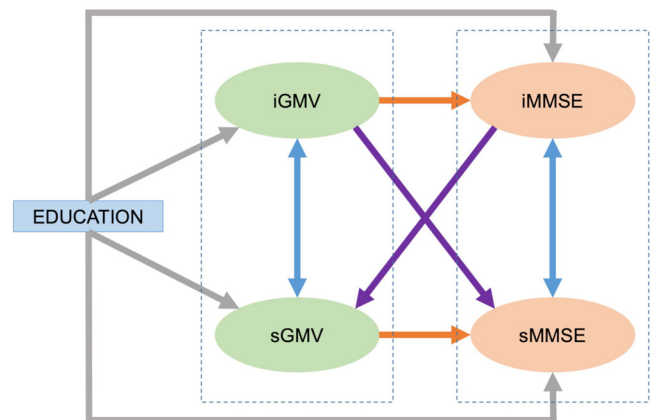


Figure 1 Model design of structural equation model. The explanatory variable is enclosed in the blue box, while response variables in green (grey matter volume) and pink (Mini-Mental examination test) circles. For convenience the indicator variables, covariates and error terms are not displayed. An arrow from one variable to another indicates that the first variable has a causal influence on the latter. Grey arrows indicate the tested effect of education on cognitive performances and grey matter volumes; orange arrows indicate the tested effect of grey matter volumes on cognitive performances at each time point; purple arrows indicate the tested effects of baseline measures on slopes' measures; blue arrows indicate the tested interaction effects between slopes and baseline measures (see Methods for details). GMV, grey matter volume; i, intercept; s, slope; MMSE, Mini-Mental State examination.

The study design was reported in [figure 1](#). We considered mutation carriers and mutation non-carriers separately. In the two groups, the effect of education was evaluated on: (a) cognitive performances (as measured by MMSE) at baseline, (b) GMV (as measured by PC1) at baseline, (c) the slope of cognitive performances between 1 year follow-up and baseline and (d) the slope of GMV between 1 year follow-up and baseline. Moreover, we evaluated the effect of: (e) GMV at baseline on the cognitive performances at baseline, (f) GMV at baseline on the slope of cognitive performances, (g) the slope of GMV on the slope of cognitive performances and (h) the cognitive performances at baseline on the slope of GMV. Finally, we evaluated the covariance between: (i) the baseline and the slope of cognitive performances and (j) the baseline and the slope of GMV.

Regression effects were adjusted by observed covariates, namely age and sex; in view of previous evidence for *TMEM106B* polymorphism effect on GMV in presymptomatic mutation carriers,¹⁰ we also considered *TMEM106B* genotype (rs1990622 T/T, T/C, C/C, recorded using additive coding 0,1,2), as covariate.

We did not include random effects (latent covariates), such as family's pedigree and Country, on the basis of an initial exploratory analysis that indicated no significant effects of these variables.

Baseline and follow-up demographical, cognitive and volumetrical variables were compared across groups using independent t-test or paired sample t-test for continuous variables and Fisher's exact tests for dichotomous variables. Exploratory Random Effect Models was performed by "lme4" R package. SEM analysis was performed via "lavaan" R package, using full information maximum likelihood method for simultaneously estimating SEM parameters and imputing MMSE score and *TMEM106B* genotype random missing values. In addition, for quality control, MMSE score and *TMEM106B* genotype missing values were imputed with non-parametric random forest imputation procedure of the "missForest" R package, and imputed data matrix was successively used for SEM analysis. Two-group SEM analysis was performed by an overall likelihood ratio test (LRT) of two SEM models: model (1) with unequal regression coefficients, and residual (co)variances in the two groups versus model (0) with equal regression coefficients, and residual (co)variances. Finally, a model (2) was fitted considering the group as covariate and adding the interaction terms education*group and *TMEM**group, for evaluating the statistical significance of the regression coefficient differences between the two-groups. P values less than 0.05 were considered significant.

RESULTS

Demographical characteristics of at-risk asymptomatic subjects, that is, mutation carriers and mutation non-carriers, are reported in [table 1](#). Non-carriers were older than carriers (p=0.036); no other significant differences were found in sex, years of schooling, MMSE at baseline and brain volumes at baseline between groups. No significant group-wise differences were found in MMSE and brain volumes changes at 1 year follow-up in either carriers or non-carriers.

SEM fitting results are shown in [table 2](#) and [figure 2](#). Overall, the two-group models' difference was statistically significant (LRT=34.3, df=20, p value=0.019).

In mutation carriers, significant direct effects of education on cognitive performances (as measured by MMSE) and on GMV at baseline (as measured by PC1, which summarised ROI measures) were found (beta=0.349, 95% CI = 0.047 to 0.650, p=0.023

Table 1 Demographical characteristics and brain volumes of the cohort

Variables	Mutation carriers	Mutation non-carriers	P value*
No of subjects			
All	116	113	–
<i>C9orf72</i> , %	26.7	–	
<i>GRN</i> , %	56.0	–	
<i>MAPT</i> , %	17.2	–	
Sex, female %	60.3	58.4	n.s.†
Education, years	14.4±3.4	14.0±3.2	n.s.
Age at baseline visit, years	45.7±11.2	49.2±14.0	0.036
Age at follow-up visit, years	47.1±11.3	50.6±14.1	0.038
Expected age at onset, years‡	–12.1±11.5	–	–
MMSE, baseline	29.4±1.2	29.4±0.9	n.s.
MMSE, follow-up	29.3±1.1	29.4±1.0	n.s.
TIV baseline, mL	1498±151	1490±123	n.s.
TIV follow-up, mL	1500±141	1492±128	n.s.
Total GMV baseline, %	42.8±3.5	42.7±3.7	n.s.
Total GMV follow-up, %	42.6±3.7	42.6±3.6	n.s.
Total WMV baseline, %	34.0±2.5	33.6±2.5	n.s.
Total WMV follow-up, %	33.7±2.5	33.6±2.7	n.s.
Total CSFV baseline, %	23.1±4.8	23.7±4.8	n.s.
Total CSFV follow-up, %	23.7±4.9	23.9±4.9	n.s.

P refers to mutation carriers versus mutation non-carriers comparisons; no significant differences between baseline versus follow-up MMSE scores and brain volumes in both mutation non-carriers and in mutation carriers were found. Results are expressed as mean±SD, unless otherwise specified.

*Two sample t-test, otherwise specified.

†Fisher's exact test.

‡computed as previously published¹⁷

CSFV, cerebrospinal fluid volume; C9orf72, chromosome 9 open reading frame 72; GMV, grey matter volume; GRN, Granulin; MAPT, Microtubule-Associated Protein Tau; MMSE, Mini-Mental State Examination; TIV, total intracranial volume; WMV, white matter volume; mL, millilitre; n.s., not significant.

and beta=0.284, 95% CI = 0.047 to 0.521, p=0.019, respectively). Moreover, education had a significant inverse effect on GMV slope (beta=–0.270, 95% CI = –0.501 to –0.041, p=0.021), the higher the years of formal schooling the lower the loss of GMV at follow-up.

No significant effect of education on cognitive performances' slope at 1 year follow-up was observed (beta=0.125, 95% CI = –0.174 to 0.423, p=0.413). No direct effect (p>0.05) between baseline and slopes of cognitive performances and GMV was observed, while expected significant negative covariances were confirmed (cov=–0.636, 95% CI = –0.869 to –0.402, p<0.001 and cov=–0.305, 95% CI = –0.444 to –0.166, p<0.001 for cognitive performances and GMV, respectively).

These above effects were similarly present in non-carriers, with the distinctive difference for the null effect of education on GMV slope (beta=–0.020, 95% CI = –0.181 to 0.140, p=0.806). Notably, in mutation non-carriers, the significant direct effect of education on cognitive performances was greater (two-fold) than in mutation carriers (beta=0.548, 95% CI = 0.289 to 0.807, p<0.001). Nevertheless, the two-group beta differences (the two-way interaction effect) was statistically suggestive in the combined group SEM analysis (p=0.088).

In addition, a significant covariate effect of *TMEM106B* genotype was observed in mutation carriers, and it was not shown in mutation non-carriers (the two-way interaction testing was statistically significant: p=0.041), confirming the previous evidence¹⁰ of the modulating effect of *TMEM106B* genotype on

Table 2 Structural equation model in mutation carriers and mutation non-carriers

Variable	Mutation carriers				Mutation non-carriers			
	Estimate	SE	z value	P value	Estimate	SE	z value	P value
<i>MMSE, baseline</i>								
GMV baseline	0.074	0.115	0.644	0.520	-0.025	0.110	-0.231	0.817
Sex	-0.003	0.208	-0.014	0.989	-0.058	0.163	-0.355	0.723
Age	-0.160	0.100	-1.599	0.110	0.006	0.076	0.078	0.938
<i>TMEM106B</i>	0.147	0.184	0.797	0.425	0.058	0.129	0.447	0.655
Education	0.349	0.153	2.279	0.023	0.548	0.132	4.145	<0.001
<i>MMSE, slope</i>								
GMV baseline	0.092	0.122	0.748	0.454	0.101	0.153	0.661	0.509
GMV slope	0.141	0.109	1.298	0.194	0.123	0.185	0.668	0.504
Sex	0.117	0.208	0.561	0.575	-0.370	0.207	-1.787	0.074
Age	0.098	0.102	0.961	0.336	-0.200	0.099	-2.013	0.044
<i>TMEM106B</i>	0.086	0.182	0.470	0.639	-0.249	0.162	-1.533	0.125
Education	0.125	0.152	0.818	0.413	-0.307	0.166	-1.849	0.065
<i>GMV, baseline</i>								
Sex	0.104	0.168	0.619	0.536	-0.020	0.140	-0.145	0.884
Age	-0.386	0.072	-5.333	<0.001	-0.428	0.051	-8.424	<0.001
<i>TMEM106B</i>	0.468	0.142	3.287	0.001	0.086	0.110	0.778	0.437
Education	0.284	0.121	2.347	0.019	0.277	0.110	2.515	0.012
<i>GMV, slope</i>								
MMSE baseline	-0.043	0.064	-0.664	0.507	-0.017	0.049	-0.343	0.731
Sex	-0.357	0.160	-2.235	0.025	-0.178	0.098	-1.814	0.070
Age	-0.060	0.070	-0.857	0.392	-0.009	0.036	-0.256	0.798
<i>TMEM106B</i>	-0.072	0.136	-0.582	0.597	0.034	0.078	0.433	0.665
Education	-0.270	0.117	-2.303	0.021	-0.020	0.082	-0.246	0.806
Covariances								
MMSE baseline with MMSE slope	-0.636	0.119	5.340	<0.001	-0.514	0.096	-5.375	<0.001
GMV baseline with GMV slope	-0.305	0.071	4.309	<0.001	-0.186	0.038	-4.860	<0.001

Significant results of educational attainment's effect in boldface.

. GMV, grey matter volume; MMSE, Mini-Mental State examination; z value, estimate/SE.

GMV in presymptomatic FTD (beta=0.468, 95% CI = 0.189 to 0.747, p=0.001 and beta=0.034, 95% CI = -0.119 to 0.186, p=0.665 for mutation carriers and non-carriers, respectively).

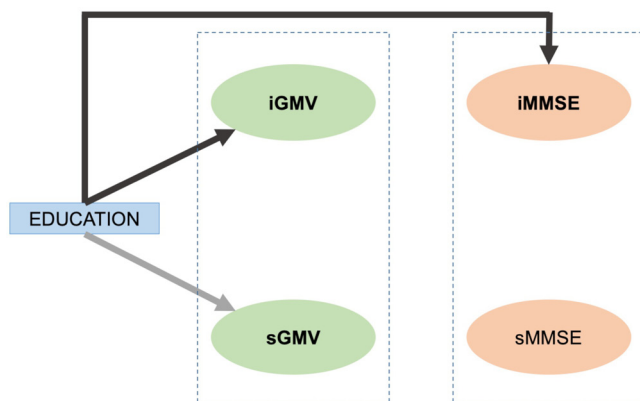


Figure 2 Significant results from the structural equation model. Significant effects in either mutation carriers and non-carriers are depicted by dark grey arrows, while significant effects only in mutation carriers are depicted by light grey arrows (see Results section for details). GMV, grey matter volume; i, intercept; s, slope; MMSE, Mini-Mental State examination.

DISCUSSION

Genetic FTD is preceded by a long period in which, despite the evidence of initial changes in biomarkers and brain structure, behaviour and cognition are spared.^{17–19–21}

Pharmacological and non-pharmacological interventions may provide better clinical outcomes if applied in this phase, when the brain can still cope with pathology processes, and such treatments may eventually delay disease onset.²² Beyond future disease-modifying drugs,²³ the possibility to intervene on environment and other modulating factors is attractive. Some evidence shows that cognitive stimulating environments lead to brain volumetrical advantages and better cognitive performances. These effects are common to physiological^{24–26} and initial pathological ageing,^{27–29} suggesting that neuroplasticity is maintained even in diseased brains, regardless of the specific clinical picture or the underlying pathological process.

Two alternate hypotheses address this issue. First, that lifestyle acts passively by increasing brain volume, but does not influence on brain loss; second, lifestyle acts by increasing brain maintenance. To test the latter hypothesis longitudinal data is required. These positive effects may diminish as disease progresses to the symptomatic phase. If this second hypotheses were the case, it would be plausible to think of modulating the disease course of dementing disorders by enrichment of lifetime exposures.

In the current longitudinal study, we applied SEM analysis to test these hypotheses in presymptomatic monogenic FTD, evaluating the effect of the educational level on two outcome measures of reserve: cognitive performances and grey matter volumes.

Our results seem to confirm the latter hypothesis, showing that higher education confers higher grey matter volumes and greater brain maintenance over time. Additionally, as previously reported,^{10,30} *TMEM106B* genotype significantly modulates grey matter volume at baseline in mutation carriers.

These findings are in line with previous longitudinal studies demonstrating that reserve proxies are associated with reduced rate of hippocampal atrophy,^{31,32} reduced rate of brain hypometabolism³³ and cerebrospinal fluid biomarkers changes³³ in healthy agers and Alzheimer's disease.

One intriguing aspect of brain maintenance is that it may reflect differences in the accumulation of pathology-related changes.^{34,35} Such demonstration in FTD requires in vivo pathological markers (ie, tau or TDP-43 tracers), which are not currently available.³⁶ This neuroprotective effect may be related to changes at the molecular level, such as increased levels of neurotrophic factors³⁷ and glutamate neurotransmission,³⁸ or at the cellular level, with increased neurogenesis,³⁹ synaptogenesis⁴⁰ and angiogenesis,⁴¹ and might be able to go beyond the underlying pathogenic mechanisms related to the specific mutation (*GRN*, *C9ORF72*, *MAPT*) or to specific proteinopathy (ie, TDP-43 or tau).

Interestingly, as previously reported,¹⁰ years of education had a significant effect on grey matter volume even in mutation non-carriers, supporting the idea of a generalisable beneficial effect of education. Conversely, in the present work, we did not find any effect of education on brain maintenance in mutation non-carriers, but we recognise that this could be likely due to the low variance of grey matter volume within 1 year follow-up in healthy subjects. However, longer follow-up is necessary to draw definitive conclusions.

Regarding cognition, higher education led to better cognitive performances at baseline, but not to significant effects on cognitive decline. This effect was comparable in mutation carriers and mutation non-carriers; of note, in subjects without pathogenic mutations, the beneficial effect of education on cognitive performances was greater than in mutation carriers.

We acknowledge that this study entails some limitations. Despite that education represents an environmental factor, it is often immutable because acquired in childhood/young adulthood. Thus, the present results do not allow to directly conclude that interventional trials could delay disease onset. However, education is known to influence professional attainment, which has been already proven a proxy measure of reserve in FTD.^{9,42} Also, we chose MMSE as a global measure of cognition, acknowledging that MMSE is affected only close to disease onset¹⁷ and that it does not represent the best measure of severity even in symptomatic phases.⁴³ Thus, the effect of more sensitive neuropsychological tests¹⁷ has to be evaluated in future studies, especially to assess changes of cognitive performances over time. Moreover, we could not test the effect of educational attainment in each mutation due to low sample number: larger samples are needed to address this issue. Last, due to the observational nature of the study, data on possible confounders, such as concomitant vascular risk factors, were not available. However, in a recent large-scale Mendelian randomisation study of the related condition, that is amyotrophic lateral sclerosis, the authors confirmed educational attainment to be an important modulator based on genetics.⁴⁴

In conclusion, these findings extend our knowledge of the reserve theory, demonstrating that in presymptomatic FTD the rate of atrophy was influenced by the educational level, with reduced grey matter loss in more educated subjects. Thus, even in presence of an ongoing pathological process, presymptomatic

FTD subjects still maintain a high-performing reserve like in healthy brains, virtually turning back the clock of the disease natural history. The demonstration that differences in early life-style may slow down later disease progression suggests that even in monogenic disorders, outcomes are not wholly determined from birth, and this opens exciting perspectives for eventually delaying symptom onset. Future confirmatory studies assessing the role of other reserve proxies and their effect on longitudinal brain changes in symptomatic monogenic and sporadic FTD are needed.

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