

## Neurobiology of Aging

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# Structural brain splitting is a hallmark of *Granulin*-related frontotemporal dementia

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## ARTICLE INFO

### Article history:

Received 6 October 2021  
 Revised 17 February 2022  
 Accepted 19 February 2022  
 Available online 26 February 2022

### Keywords:

Graph theory  
 Structural MRI  
 Frontotemporal dementia  
 Granulin  
 Programulin  
 Mutation

## ABSTRACT

Frontotemporal dementia associated with *granulin* (*GRN*) mutations presents asymmetric brain atrophy. We applied a Minimum Spanning Tree plus an Efficiency Cost Optimization approach to cortical thickness data in order to test whether graph theory measures could identify global or local impairment of connectivity in the presymptomatic phase of pathology, where other techniques failed in demonstrating changes.

We included 52 symptomatic *GRN* mutation carriers (SC), 161 presymptomatic *GRN* mutation carriers (PSC) and 341 non-carriers relatives from the Genetic Frontotemporal dementia research Initiative cohort. Group differences of global, nodal and edge connectivity in (Minimum Spanning Tree plus an Efficiency Cost Optimization) graph were tested via Structural Equation Models.

Global graph perturbation was selectively impaired in SC compared to non-carriers, with no changes in PSC. At the local level, only SC exhibited perturbation of frontotemporal nodes, but edge connectivity revealed a characteristic pattern of interhemispheric disconnection, involving homologous parietal regions, in PSC.

Our results suggest that *GRN*-related frontotemporal dementia resembles a disconnection syndrome, with interhemispheric disconnection between parietal regions in presymptomatic phases that progresses to frontotemporal areas as symptoms emerge.

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## 1. Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder anatomically characterized by frontal and temporal atrophy. The most prominent symptoms of FTD are represented by behavioral and personality changes, executive dysfunctions or language impairment (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). About a third of patients with FTD have an autosomal dominant family history (Rohrer et al., 2009) and mutations in the *Granulin* (*GRN*) gene, whose list is enriched with more than 110 pathogenic variants (Greaves and Rohrer, 2019), are recognized as a leading cause of genetic FTD, accounting for 5%–20% of familiar and 1%–5% of sporadic FTD patients (Moore et al., 2020).

In spite of the highly phenotypical heterogeneity, most *GRN* mutation carriers receive a clinical diagnosis of behavioral variant FTD (bvFTD), or non-fluent variant of Primary Progressive Aphasia (nfvPPA), with a minority presenting as Corticobasal Syndrome (Giunta et al., 2021). These clinical phenotypes correspond to imaging findings, with an asymmetric pattern of atrophy, including frontotemporal, striatal and parietal involvement (Cash et al., 2018; Du et al., 2007; Gazzina et al., 2018; Hartikainen et al., 2012; Kim et al., 2007; Rohrer et al., 2010).

In contrast, only subtle structural changes have been reported in the presymptomatic phases, that become noticeable only close to expected onset of symptoms (Borrego-Écija et al., 2021; Cash et al., 2018; Gazzina et al., 2018; Rohrer et al., 2015). The absence of evident clinical signs in presymptomatic subjects, despite initial neuropathological changes, has been explained mainly by functional maintenance of brain connections, a mechanism that is important in healthy ageing but is crucial in subjects at risk for dementia (Rittman et al., 2019; Tsvetanov et al., 2021).

However, different statistical approaches to imaging data might reveal dynamic *GRN* disease signatures over the disease course, from presymptomatic to symptomatic stages. In this context, graph theory has been increasingly applied due to its ability to go beyond local changes, defining brain networks and testing either local and global properties of their architecture (Mårtensson et al., 2018; Sporns, 2018). Structural connectivity is defined by the set

of physical connections linking brain areas at a given time, and can be assessed globally, that is, looking at large-scale properties of the whole cerebral cortex, or locally at the regional level. Anatomical connections are relatively static at shorter time scales (seconds to minutes) but can be dynamic at longer time scales (hours to days) such as during learning, ageing and pathology. While local connectivity estimates inputs and outputs of single brain regions, global connectivity is critical for the maintenance of functional segregation and functional integration: efficient large-scale networks exhibit small-world attributes with short path lengths and high clustering coefficients (Sporns et al., 2004).

Among quantitative measures of cortical atrophy, cortical thickness has increased power in detecting subtle changes compared to voxel-based volumetric techniques. In addition, the development of brain atlases based on sulcal and gyral anatomy has led to the application of graph theory to unveil subtle changes in either healthy brain (Apostolova and Thompson, 2007; Gonzalez-Burgos et al., 2021; Richmond et al., 2021), and neurological and psychiatric disorders (Bethlehem et al., 2017; Pereira et al., 2015; Voevodskaya et al., 2018; Yun et al., 2020).

In the present study, we test how structural brain properties change from presymptomatic to symptomatic phases of *GRN* pathology and whether changes in structural connectivity could explain expected age at symptom onset. We applied a Minimum Spanning Tree plus an Efficiency Cost Optimization to filter a connectivity graph and Multiple Group Structural Equation Models to test global and local nodes, and edges differences of cortical thickness data (Stam et al., 2014) in a large cohort of FTD patients from the international Genetic FTD Initiative (GENFI).

## 2. Methods

### 2.1. Subjects

Data were drawn from the GENFI multicentre cohort study, which consists of 27 research centres across Europe and Canada ([www.genfi.org.uk](http://www.genfi.org.uk)). For the purpose of the present study, we included symptomatic *GRN* carriers, relatives who tested positive

for GRN mutations and relatives who tested negative for all FTD-related mutations. The presence of psychiatric disease or central nervous system pathology in relatives was considered as exclusion criteria. Mutation carriers were classified as either symptomatic or presymptomatic based on clinicians' evaluation.

For each subject we recorded demographical data and a standardized neuropsychological and behavioral assessment.

In keeping with other GENFI reports, the years to expected onset were calculated as the difference between age at assessment and mean age at onset within the family (Moore et al., 2020; Rohrer et al., 2015).

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.

## 2.2. Neuroimaging assessment and processing

Participants underwent magnetic resonance imaging at their local site on scanners from three different manufacturers: Philips Healthcare (Koninklijke Philips NV, Amsterdam, Netherlands), GE Healthcare Life Sciences (General Electric, Boston, MA, USA) and Siemens Healthcare Diagnostics (Siemens, Erlangen, Germany). The protocol, designed to match across scanners as much as possible, included a volumetrical (Magnetization Prepared - RAPid Gradient Echo, MPRAGE) T1-weighted scan, as previously published (Rohrer et al., 2015).

Each scan was processed using the standardized cortical thickness pipeline of the Computational Anatomy Toolbox (CAT V.12.5, <http://www.neuro.uni-jena.de/cat/>) as extension to SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>, V.7219) running on MATLAB (Math-Works, Natick, MA, USA, version R2015a). Cortical thickness maps were then parcelled into 68 regions of interest (ROIs), 34 for each hemisphere, according to the Desikan atlas in order to obtain the mean cortical thickness (expressed in millimetres) for each region (see **Supplementary Table 1**) (Desikan et al., 2006). Before network and statistical analyses, data were nonparanormal transformed by smooth functions to help relax the assumption of normality (Liu et al., 2009); subsequently, Gaussianized cortical thickness data were adjusted for age, sex and site of acquisition, and the residual values used as input data.

## 2.3. Network and statistical analyses

**Brain connectivity.** The connectivity matrices were built using Pearson's correlations between the 68 ROIs on the aforementioned residuals. These matrices were weighted (i.e., all edges are represented, without an *a priori* definition of a threshold, which allows assessing both strong and weak connections). Then, we performed a modularity analysis on the weighted graphs of each group to assess the presence of smaller communities of regions (modules) and to get a first visualization of the connectivity matrices. Communities were obtained after applying a Louvain algorithm (Blondel et al., 2008).

**Graph construction.** Graph construction was performed starting from the weighted correlation matrices of the 68 ROIs, combining a Minimum Spanning Tree (MST) and an Efficiency Cost Optimization (ECO) approach. MST is a unique acyclic subgraph that connects  $N$  nodes (i.e., 68 ROIs) with  $(N-1)$  edges (i.e., 67 connections =  $1-\text{abs}(\text{correlations})$ ), and maximizing synchronization between brain areas (i.e., minimizing edge connections), representing unambiguous solution to describe complex brain networks. Among existing methods for MST search, we applied the efficient Prim's algorithm (Cormen et al., 2001). The use of MST avoids methodological issue relative to arbitrary threshold values on the correlation

matrices (fixed cut-off, fixed average degree, fixed edge density, or variable threshold over a range of values) respect to classical graph analytical approaches (Otte et al., 2015; Tewarie et al., 2015). If the brain network can be interpreted as a kind of transport network, a MST might represent the critical backbone of information flow in weighted networks (i.e., contains with high probability all the shortest paths in the network), and intrinsically might provide an accurate representation of subtle and critical topological perturbations, at local scale (Van Mieghem and Magdalena, 2005). On the other hand, MST sparseness (number of edges = number of ROIs - 1) could raise issues at global scale, and recent graph theoretical proposals suggest augmented graph construction, adding connections to MST backbone. We use ECO approach to add new edges; the ECO graph construction uses a topological criterion for selecting a threshold based on a trade-off between local and global efficiency of the graph structure, which is particularly relevant to the brain (Bullmore and Sporns, 2012; De Vico Fallani et al., 2017). The threshold extracts a graph with  $N$  nodes (i.e., 68 ROIs) and  $(3/2)^*N$  edges (i.e.,  $(3/2)^*68$  ROIs), maximizing global efficiency (i.e., the mean of  $1/\text{all shortest paths between nodes of the graph}$ ) and the local efficiency (i.e., the mean of  $1/\text{all shortest paths between nodes of each graph modules}$ ). The MST+ECO graph is then derived as graph union of MST and ECO solution ( $G = \text{MST} \cup \text{ECO}$ ).

**Multiple group Structural Equation Models (SEM).** Multiple group analyses via SEM were performed using as input the nonparanormal residual data and the MST+ECO graph extracted from non-carriers group as reference graph, in order to test differences in the strength of global thickness expressed in terms of total graph perturbation, and local size and connectivity perturbation at the nodal and the edge level, respectively. SEM is a general statistical framework including covariance (correlation) analysis, multivariate linear regression, path analysis, and if a measurement model is defined, confirmatory factor analysis and multiple group analysis can be performed for group comparisons. Here, we use correlation analysis modelling of MST+ECO graph connections. We performed multiple group SEM considering:

- 1) The *mean difference* model, where covariance matrices are equal in each group, and the group perturbation influences the nodes of the MST+ECO graph; that is, the link (group  $\rightarrow$  ROI) is measured by the regression coefficient (beta) of each ROI on the dummy variable (0/1) of the group comparison. This coefficient is equivalent to the pairwise group mean differences of ROI mean values, and represents the local size perturbation at nodal level.
- 2) The *covariance difference* model, where the MST+ECO graph covariances are kept separated in each group, and the group perturbation influences the edges of the MST+ECO graph; that is, the link (ROI (j)  $\leftrightarrow$  ROI (k)) is measured by the pairwise group differences of the covariance (correlation) coefficients between the ROIs, and represents the local size perturbation at edge level.
- 3) The *SEM Mahalanobis Distance (D)*, defined as the sum of the mean differences of ROI input data between two groups, after adjusting for the ROI model-implied covariances.  $D$  represents the size of global thickness expressed in terms of total graph size perturbation, and its positive or negative sign determines graph activation or inhibition. Similarly, the sign of node size or edge connectivity in previous model 1) or 2) determines local (node or edge) activation or inhibition.

SEM results were considered significant for  $p$ -values  $< 0.05$  after False Discovery Rate (FDR) correction for multiple comparisons.

**Statistical analysis.** We tested the linear correlation between an indirect measure of brain asymmetry and age at expected symp-

**Table 1**

Demographical, clinical and neuropsychological variables.

Variable	NC(n = 341)	PSC(n = 161)	SC(n = 52)	p <sup>a</sup>
Age, years	46.8±13.4	47.2±12.3	63.0±7.2	<0.001
Sex, female	58.1	64.0	53.8	n.s. <sup>b</sup>
Education, years	14.1±3.6	14.4±3.5	11.7±3.7	<0.001
Age at onset, years	-	-	60.0±7.5	-
Expected age at onset, years	-	-12.8±12.8	-	-
<i>Neuropsychological assessment</i>				
Mini-SEA - Total	26.6±2.7	26.7±2.6	19.6±5.2	<0.001
Digit Span - Forward	7.8±2.1	7.6±2.0	4.6±2.7	<0.001
Digit Span - Backward	6.5±2.2	6.4±2.0	2.9±2.2	<0.001
Digit Symbol Task	57.5±14.3	56.8±13.9	22.7±16.5	<0.001
Trail Making Test Part A	28.3±15.4	28.3±10.5	84.2±45.8	<0.001
Trail Making Test Part B	71.1±44.8	67.5±38.4	232.2±92.5	<0.001
Verbal Fluency - Letters	40.3±13.0	42.1±13.9	15.2±13.1	<0.001
Verbal Fluency - Animals	23.5±6.3	24.7±5.8	10.8±6.1	<0.001
Boston Naming Test	27.7±2.3	27.8±2.4	18.7±8.3	<0.001
Block Design	48.3±15.4	48.2±14.1	14.7±15.5	<0.001

Results are expressed as mean ± standard deviation or percentage.

All significant results are due to differences between SC and non-symptomatic groups (Bonferroni post-hoc comparisons).

Key: mini-SEA, mini-social cognition &amp; emotional assessment; NC, non-carriers; PSC, presymptomatic carriers; SC, symptomatic carriers.

<sup>a</sup>One-way ANOVA unless otherwise specified (<sup>b</sup>Chi-square).

tom onset in the pre-symptomatic group. To this purpose, we used interhemispheric cortical thickness,  $x = (\text{left ROI} * \text{right ROI})/2$  as input data for scoring a severity index (SI) defined as mean value of  $x$  data with statistically significant edge perturbation in the covariance difference model (corrected  $p$ -values  $< 0.05$ ).

**Software.** Connectivity analysis and community search were performed with MathLab v.R2021b (<http://www.braph.org/>). MST+ECO graph construction and multiple group SEM were performed in R v.4.1.1 (<https://cran.r-project.org/>) using packages *igraph* (Csardi and Nepusz, 2006) and *SEMgraph* (Palluzzi and Grassi, 2021).

### 3. Results

#### 3.1. Participants

A total of 341 non-carriers (NC), 161 presymptomatic GRN carriers (PSC) and 52 symptomatic GRN carriers (SC) were included. Of the 52 SC, 24 subjects presented with bvFTD, 21 with PPA and 6 with less common clinical presentations (2 corticobasal syndromes, 2 Alzheimer disease-like, 1 with psychiatric symptoms, 1 Parkinson disease-like).

Non-carriers and presymptomatic carriers had similar age and sex distribution, while symptomatic carriers were older and less educated compared to the other groups. Cognitive and behavioral scores were comparable between non-symptomatic groups, while symptomatic carriers performed worse in each considered test. Results are shown in **Table 1**.

#### 3.2. Correlation matrices in NC, PSC and SC groups

The weighted correlation matrices of the 68 ROIs are shown in **Fig. 1**. The pattern of correlation matrices was comparable in NC (panel A) and PSC (panel B), whilst it was visually different in SC (panel C).

Correlation matrices were then grouped according to communities, that is brain regions co-varying in their morphological properties and that are structurally and functionally connected (Alexander-Bloch et al., 2013). The list of the ROIs belonging to each community is reported in **Supplementary Table 2**.

While NC and PSC exhibited again a similar correlation pattern with three distinct communities, namely occipito-temporo-parietal, fronto-temporo-parietal and limbic communities (see **Fig. 1**, panels D and E), SC had a “chessboard-like” pattern, with loss of interhemispheric connectivity and independent clustering of the left and right brain regions (panel F). In fact, in SC we recognized only two communities, one with ROIs belonging to the left hemisphere (panel F, community 1) and the other with ROIs belonging to the right hemisphere (panel F, community 2).

Finally, filter graphs of the correlation matrices from MST+ECO solution in NC, PSC and SC are shown in **Fig. 2**, clearly depicting loss of interhemispheric connectivity in SC. The graph extracted from NC group was used as reference graph for multiple group comparison via SEM (see below).

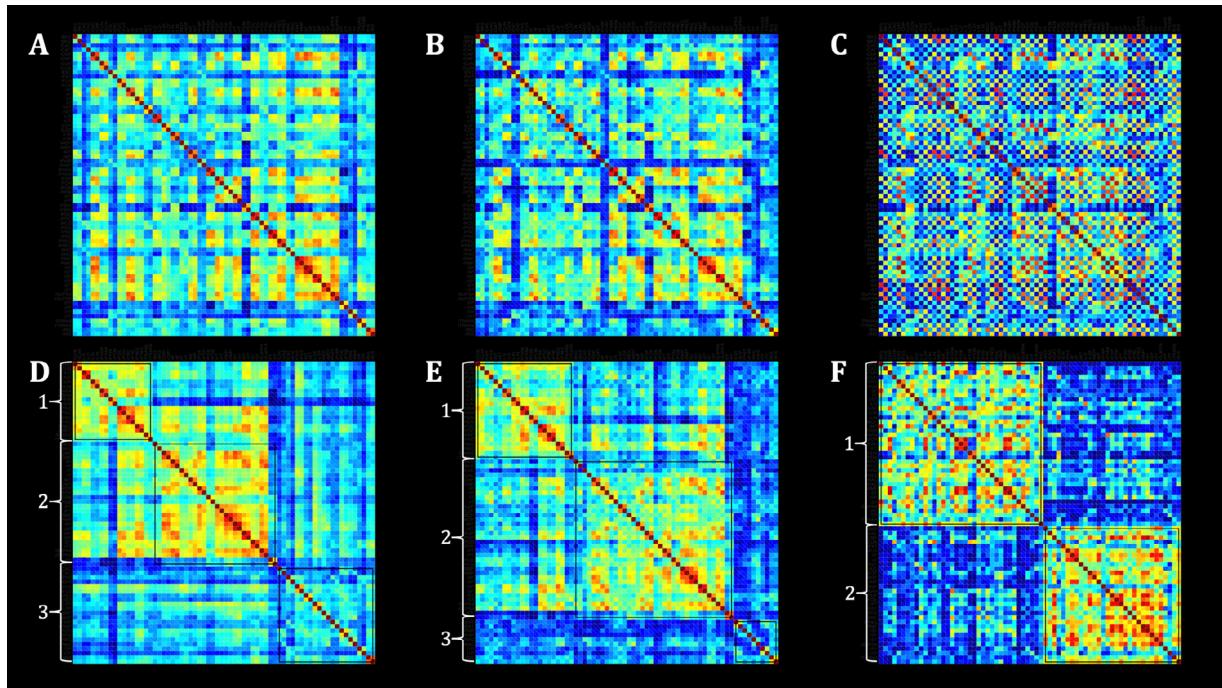
#### 3.3. Global and nodal thickness

When we considered total graph perturbation (D), SC exhibited a significant impairment compared to NC ( $T = -6.71$ ,  $p < 0.001$ ) and PSC ( $-5.24$ ,  $p < 0.001$ ), whilst PSC showed similar perturbation, comparable to NC ( $T = 1.52$ ,  $p > 0.05$ ).

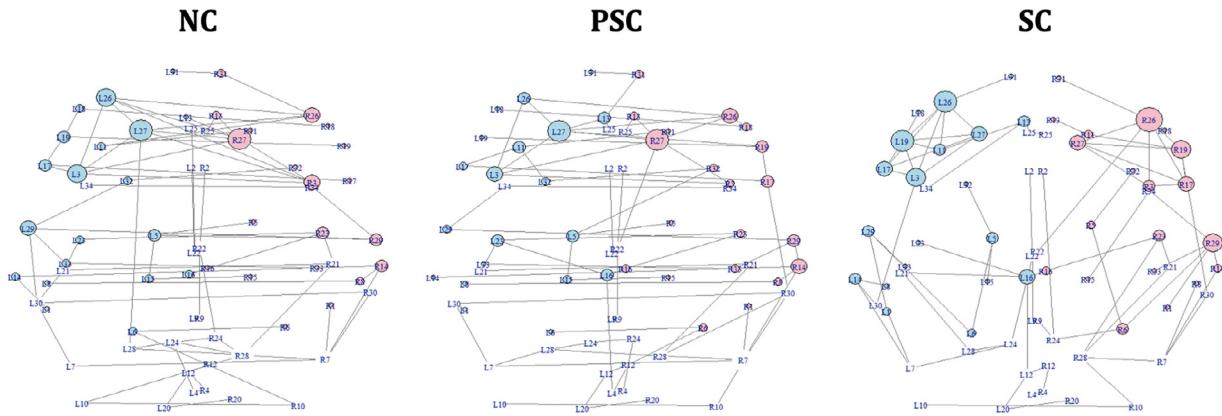
When we considered nodal perturbation, as expected, SC exhibited an extensive impairment in frontal, temporal, parietal and cingulate regions as compared to the other groups (see **Table 2**). Notably, no significant differences in nodal perturbation between PSC compared to NC at the pre-established threshold were detected.

#### 3.4. Edge connectivity between groups

SC had the most widespread impairment of edge connectivity compared to NC or PSC. As shown in **Table 3**, SC showed significant perturbation of interhemispheric connectivity (negative values between homologous regions) along with increased connectivity between intrahemispheric regions (i.e., positive values between frontal and temporal regions of the same hemisphere). Notably, a similar but less extensive behavior was found in PSC compared to NC: impaired connectivity between homologous temporo-parietal regions (namely inferior parietal lobule and supramarginal gyrus) and strengthening of connectivity between the same regions of the same hemisphere (see **Table 3**).



**Fig. 1. Correlation matrices in non-carriers (NC), presymptomatic carriers (PSC) and symptomatic carriers (SC).** The panels in the first and the second row show the correlation matrices of each group (panel A and D – NC, panel B and E – PSC, panel C and F – SC) before and after reordering nodes into communities. Blue color indicates low correlation, while red color indicates high correlation. While NC and PSC exhibited similar correlation patterns, notably three communities of bilateral hemispheric regions (occipito-temporo-parietal, fronto-temporo-parietal and limbic), SC exhibited a “chessboard-like” pattern, with one community constituted by left brain regions and one by right brain regions. The order of the regions of interest (ROIs) in the connectivity matrix and a list of the ROIs belonging to each community are reported in Supplementary Materials. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 2. Structural graphs in non-carriers (NC), presymptomatic carriers (PSC) and symptomatic carriers (SC).** Corresponding nodes and edges of each group. Larger the nodes, higher the number of edges spreading from them. While NC and PSC show preservation of intra and interhemispheric connectivity, SC revealed significant pauperization of intrahemispheric connectivity. Blue dots correspond to left brain nodes, while red dots correspond to right brain nodes. IDs and the corresponding name of each region are reported in Supplementary Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

### 3.5. Correlation between severity index (SI) and expected age at symptoms onset (EYO)

In PSC, a significant inverse linear correlation between the SI, computed as mean value of the left and right ROIs with significant edge perturbation, and EYO was found ( $r = -0.45$ ,  $p < 0.05$ ), the greater the SI the closer the EYO (see **Supplementary Fig. 1**).

## 4. Discussion

The advances in graph theory and network neuroscience offer a unique opportunity to understand human brain and its structural

properties (Sporns, 2018; Vecchio et al., 2017), that evolve during normal ageing and accelerate in neurodegenerative disorders (Baik et al., 2021; Bi et al., 2021; Fortanier et al., 2019; Huang et al., 2021; Suo et al., 2021). With both ageing and disease, changes in cognitive performance correlate with changes in connectivity (Chen et al., 2021; Gonzalez-Burgos et al., 2021; Li et al., 2021; Nigro et al., 2021).

In the current study, we applied an MST approach with additional edges from an ECO solution. MST+ECO allow to represent weighted networks in a unique simplified (and optimized) way, which allows unbiased comparison of networks. In addition, node and edge perturbation of the healthy filter graph is evaluated by pairwise comparison of study groups with SEM.

**Table 2**Structural equation model estimates of nodal size (mean differences) comparison between groups (*p*-values < 0.05, FDR-corrected).

SC vs. NC <sup>a</sup>	Estimates	Lower CI	Upper CI	SC vs. PSC <sup>a</sup>	Estimates	Lower CI	Upper CI
L bank of the superior temporal sulcus	-0.19	-0.28	-0.09	<b>L lateral orbitofrontal</b>	-0.34	-0.47	-0.22
<b>L lateral orbitofrontal</b>	-0.33	-0.43	-0.25	L medial orbitofrontal	-0.23	-0.36	-0.10
L medial orbitofrontal	-0.20	-0.30	-0.11	<b>L middle temporal gyrus</b>	-0.33	-0.45	-0.21
<b>L middle temporal gyrus</b>	-0.34	-0.42	-0.25	L paracentral	-0.27	-0.40	-0.13
L paracentral	-0.23	-0.32	-0.13	<b>L pars opercularis</b>	-0.41	-0.53	-0.29
<b>L pars opercularis</b>	-0.38	-0.46	-0.29	<b>L pars orbitalis</b>	-0.34	-0.46	-0.21
<b>L pars orbitalis</b>	-0.34	-0.43	-0.25	<b>L pars triangularis</b>	-0.39	-0.51	-0.27
<b>L pars triangularis</b>	-0.35	-0.44	-0.27	L postcentral	-0.22	-0.34	-0.10
L caudal anterior cingulate	-0.21	-0.30	-0.11	<b>L posterior cingulate cortex</b>	-0.31	-0.43	-0.19
L postcentral	-0.17	-0.26	-0.08	<b>L precentral</b>	-0.36	-0.48	-0.24
L posterior cingulate cortex	-0.29	-0.38	-0.20	L precuneus	-0.27	-0.38	-0.16
<b>L precentral</b>	-0.32	-0.41	-0.23	<b>L rostral middle frontal gyrus</b>	-0.36	-0.48	-0.24
L precuneus	-0.26	-0.34	-0.18	<b>L superior frontal gyrus</b>	-0.38	-0.49	-0.28
<b>L rostral middle frontal gyrus</b>	-0.37	-0.46	-0.29	L superior temporal gyrus	-0.25	-0.37	-0.13
<b>L superior frontal gyrus</b>	-0.35	-0.42	-0.27	<b>L caudal middle frontal gyrus</b>	-0.40	-0.51	-0.29
L superior parietal lobule	-0.20	-0.29	-0.10	<b>L supramarginal gyrus</b>	-0.36	-0.47	-0.25
L superior temporal gyrus	-0.25	-0.34	-0.16	L temporal pole	-0.24	-0.37	-0.11
<b>L caudal middle frontal gyrus</b>	-0.34	-0.43	-0.26	L entorhinal	-0.24	-0.36	-0.11
<b>L supramarginal gyrus</b>	-0.34	-0.42	-0.26	<b>L inferior parietal lobule</b>	-0.34	-0.46	-0.23
L frontal pole	-0.20	-0.30	-0.19	L inferior temporal gyrus	-0.25	-0.37	-0.12
L temporal pole	-0.26	-0.35	-0.16	R lateral orbitofrontal	-0.26	-0.39	-0.14
L insula	-0.21	-0.30	-0.11	R middle temporal gyrus	-0.29	-0.40	-0.17
L entorhinal	-0.18	-0.28	-0.09	R paracentral	-0.25	-0.38	-0.12
<b>L inferior parietal lobule</b>	-0.34	-0.43	-0.25	<b>R pars opercularis</b>	-0.39	-0.52	-0.27
L inferior temporal gyrus	-0.25	-0.34	-0.15	R pars orbitalis	-0.25	-0.38	-0.12
R lateral orbitofrontal	-0.27	-0.36	-0.17	<b>R pars triangularis</b>	-0.32	-0.45	-0.20
R middle temporal gyrus	-0.29	-0.38	-0.20	R caudal anterior cingulate	-0.24	-0.37	-0.11
R paracentral	-0.22	-0.31	-0.12	R posterior cingulate cortex	-0.29	-0.41	-0.17
<b>R pars opercularis</b>	-0.35	-0.44	-0.25	<b>R precentral</b>	-0.32	-0.44	-0.19
R pars orbitalis	-0.29	-0.38	-0.19	R precuneus	-0.25	-0.38	-0.13
<b>R pars triangularis</b>	-0.33	-0.42	-0.23	R rostral middle frontal gyrus	-0.29	-0.41	-0.17
R caudal anterior cingulate	-0.23	-0.33	-0.14	<b>R superior frontal gyrus</b>	-0.33	-0.45	-0.22
R postcentral	-0.17	-0.26	-0.07	R superior parietal lobule	-0.21	-0.32	-0.10
R posterior cingulate cortex	-0.25	-0.34	-0.16	<b>R caudal middle frontal gyrus</b>	-0.40	-0.53	-0.28
R precentral	-0.27	-0.36	-0.18	R inferior parietal lobule	-0.23	-0.33	-0.12
R precuneus	-0.22	-0.32	-0.13				
<b>R rostral middle frontal gyrus</b>	-0.32	-0.41	-0.23				
<b>R superior frontal gyrus</b>	-0.32	-0.41	-0.24				
R superior parietal lobule	-0.20	-0.27	-0.12				
R superior temporal gyrus	-0.19	-0.28	-0.09				
<b>R caudal middle frontal gyrus</b>	-0.35	-0.44	-0.26				
R supramarginal gyrus	-0.21	-0.30	-0.12				
R insula	-0.17	-0.26	-0.08				
R entorhinal	-0.19	-0.29	-0.09				
R inferior parietal lobule	-0.24	-0.32	-0.16				
R inferior temporal gyrus	-0.23	-0.32	-0.14				
R isthmus cingulate cortex	-0.18	-0.28	-0.09				

Significant nodal connectivity comparisons with estimates &gt;0.30 in boldface.

Key: CI, Confidence Interval; L, left; NC, non-carriers; PSC, presymptomatic carriers; R, right; SC, symptomatic carriers.

<sup>a</sup>Only significant findings are reported (*p*-value < 0.05, False Discovery Rate (FDR) corrected for multiple comparisons).

We identified a progressive pattern of structural perturbation from the presymptomatic to the symptomatic stages of GRN-related FTD: in the presymptomatic stages, nodal impairment of frontotemporal regions, reduced communication between homologous temporo-parietal regions and stronger intrahemispheric communication between close regions; in the symptomatic stages, a similar but more extensive behavior with further impairment of global connectivity.

Thus, GRN disease resembles a “split brain” condition, supporting a characteristic nexopathy model (Warren et al., 2013). Indeed, as previously postulated (Warren et al., 2013), in the early stages, GRN disease is characterized by predominant involvement of nodal (shorter-range) connections, with a strong gradient of network damage, leading to relatively focal and strongly asymmetric brain involvement.

Our data extend literature findings in the presymptomatic stages of GRN disease, claiming for an early disease signature characterized by left-right disconnection starting from parietal regions

and then spreading to frontotemporal brain areas when symptoms are overt. Indeed, despite clear asymmetric atrophy patterns in the symptomatic stages of the disease (Saracino et al., 2021), previous studies have reported none or only subtle changes in presymptomatic disease stages (Cash et al., 2018; Panman et al., 2019; Popuri et al., 2018), even in cortical thickness (Borrego-Écija et al., 2021; Gazzina et al., 2018).

Asymmetries of brain function and structure are a common phenomenon in the human brain (Toga and Thompson, 2003), which most likely arises from a complex interplay of genetic and environmental factors. It might be argued that TDP-43 proteinopathy induced by GRN mutations might interact with these existing asymmetries or exacerbate them (Minkova et al., 2017). The factors that will confer more selective vulnerability and will drive right or left clinical phenotype in GRN disease, that is, PPA versus bvFTD, are yet to be determined.

Moreover, in presymptomatic subjects the severity of brain asymmetry significantly correlated with estimated age at symptom

**Table 3**

Structural equation model estimates of edge connectivity (correlation differences) comparison between groups.

SC vs. NC	Estimation	Lower CI	Upper CI	p-value <sup>a</sup>
<b>L - R middle temporal gyrus</b>	-0.38	-0.57	-0.19	0.003
<b>L - R postcentral</b>	-0.51	-0.75	-0.28	<0.001
<b>L - R precentral</b>	-0.55	-0.83	-0.28	0.002
<b>L - R superior temporal gyrus</b>	-0.57	-0.78	-0.35	<0.001
<b>L - R insula</b>	-0.48	-0.74	-0.22	0.004
<b>L - R rostral middle frontal gyrus</b>	-0.41	-0.65	-0.17	0.02
R superior temporal gyrus - R insula	0.49	0.19	0.79	0.02
<b>L - R inferior temporal gyrus</b>	-0.38	-0.64	-0.12	0.04
R postcentral - R precentral	0.46	0.14	0.77	0.04
<b>SC vs. PSC</b>				
<b>L - R postcentral</b>	-0.53	-0.80	-0.26	0.005
<b>L - R precentral</b>	-0.58	-0.89	-0.27	0.007
<b>L - R superior temporal gyrus</b>	-0.54	-0.79	-0.29	0.002
<b>L - R middle temporal gyrus</b>	-0.38	-0.60	-0.16	0.02
<b>L - R rostral middle frontal gyrus</b>	-0.47	-0.74	-0.19	0.02
<b>L - R frontal pole</b>	-0.47	-0.79	-0.16	0.04
R superior temporal gyrus - R insula	0.47	0.16	0.78	0.04
R postcentral - R precentral	0.47	0.15	0.79	0.05
<b>PSC vs. NC</b>				
L supramarginal gyrus - L inferior parietal lobule	0.47	0.27	0.67	<0.001
<b>L - R supramarginal gyrus</b>	-0.48	-0.64	-0.31	<0.001
R supramarginal gyrus - R inferior parietal lobule	0.45	0.26	0.64	<0.001
<b>L - R inferior parietal lobule</b>	-0.43	-0.58	-0.28	<0.001
R precentral - L paracentral	-0.11	-0.17	-0.04	0.03

Significant perturbation of interhemispheric connectivity between homologous regions in boldface.

Key: CI, Confidence Interval; L, left; NC, non-carriers; PSC, presymptomatic carriers; R, right; SC, symptomatic carriers.

<sup>a</sup>Only significant findings are reported (*p*-value < 0.05, False Discovery Rate (FDR) corrected for multiple comparisons).

onset, indirectly supporting the view that brain disconnection syndrome is key to disease development. This result needs to be confirmed in future studies as prediction of estimated age at onset was weaker in *GRN* mutations as compared to other monogenic FTD, likely due to other genetic or environmental modulators that are currently poorly understood (Moore et al., 2020; Premi et al., 2017).

In conclusion, the graph theory approach and multiple group Structural equation models identify a characteristic behavior of structural connectivity in people with *GRN* mutations that, starting from interhemispheric disconnection between homologous posterior regions, leads to an independent and asymmetric brain progression of the disease.

## Contributors

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.

SG planned the study, contributed to interpretation of the results and drafted the initial version of the manuscript; MG carried out network and statistical analyses and contributed to interpretation of the results; EP, FP, MG, AA, AB, SA, RG, MB, DMC, EGT, GP, RSC, JvS, LCJ, RS-V, FM, RL Jr, CG, MS, DG, JBR, MM, MCT, EF, RV, AdeM, FT, CRB, IS, AG, ILB, FP, SD, JL, AD, SS, MO and JDR contributed to the conception of GENFI and acquisition of data and revised the manuscript for content; BB planned the study, contributed to interpretation of the results, drafted the initial version of the manuscript.

## Disclosure statement

The authors report no conflicts of interest.

## Acknowledgements

This work is supported by JPND grant “GENFI-prox” (to MS, JvS, MO, CG, JR, and BB), the Centre d’Investigation Clinique (ICM,

France), the Centre pour l’Acquisition et le Traitement des Images platform (CATI, France), the UK Medical Research Council, and the Canadian Institutes of Health Research as part of a Centres of Excellence in Neurodegeneration grant, a Canadian Institutes of Health Research operating grant, Fundació Marató de TV3, Spain. JBR is supported by the Medical Research Council (SUAG/051 101400) and NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The authors thank our participant volunteers and their families for their participation; the radiographers/technologists and research nurses from all centers involved in this study for their invaluable support in data acquisition.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.neurobiolaging.2022.02.009](https://doi.org/10.1016/j.neurobiolaging.2022.02.009).

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