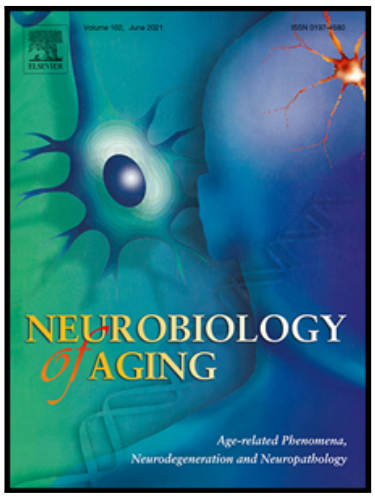
Journal Pre-proof



Structural brain splitting is a hallmark of Granulin-related Frontotemporal Dementia

Stefano Gazzina , Mario Grassi , Enrico Premi , Antonella Alberici , Alberto Benussi , Silvana Archetti , Roberto Gasparotti , Martina Bocchetta , David M. Cash , Emily G. Todd , Georgia Peakman , Rhian S. Convery , John C. van Swieten , Lize C. Jiskoot , Harro Seelaar , Raquel Sanchez-Valle , Fermin Moreno , Robert Laforce Jr , Caroline Graff , Matthis Synofzik , Daniela Galimberti , James B. Rowe , Mario Masellis , Maria Carmela Tartaglia , Elizabeth Finger , Rik Vandenberghe , Alexandre de Mendonça , Fabrizio Tagliavini , Chris R. Butler , Isabel Santana , Alexander Gerhard , Isabelle Le Ber , Florence Pasquier , Simon Ducharme , Johannes Levin , Adrian Danek , Sandro Sorbi , Markus Otto , Jonathan D. Rohrer , on behalf of the Genetic Frontotemporal dementia Initiative (GENFI)

PII: S0197-4580(22)00030-6
DOI: https://doi.org/10.1016/j.neurobiolaging.2022.02.009
Reference: NBA 11322

To appear in: *Neurobiology of Aging*

Received date: 6 October 2021
Revised date: 17 February 2022
Accepted date: 19 February 2022

Please cite this article as: Stefano Gazzina , Mario Grassi , Enrico Premi , Antonella Alberici , Alberto Benussi , Silvana Archetti , Roberto Gasparotti , Martina Bocchetta , David M. Cash , Emily G. Todd , Georgia Peakman , Rhian S. Convery , John C. van Swieten , Lize C. Jiskoot , Harro Seelaar , Raquel Sanchez-Valle , Fermin Moreno , Robert Laforce Jr , Caroline Graff , Matthis Synofzik , Daniela Galimberti , James B. Rowe , Mario Masellis , Maria Carmela Tartaglia , Elizabeth Finger , Rik Vandenberghe , Alexandre de Mendonça , Fabrizio Tagliavini , Chris R. Butler , Isabel Santana , Alexander Gerhard , Isabelle Le Ber , Florence Pasquier , Simon Ducharme , Johannes Levin , Adrian Danek , Sandro Sorbi , Markus Otto , Jonathan D. Rohrer , on behalf of the Genetic Frontotemporal dementia Initiative (GENFI), Structural brain splitting is a hallmark of Granulin-related Frontotemporal Dementia, *Neurobiology of Aging* (2022), doi: https://doi.org/10.1016/j.neurobiolaging.2022.02.009

during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Structural brain splitting is a hallmark of *Granulin*-related Frontotemporal Dementia

Stefano Gazzina,[1] Mario Grassi,[2] Enrico Premi,[3] Antonella Alberici,[4] Alberto Benussi,[4,5] Silvana Archetti,[6] Roberto Gasparotti,[7] Martina Bocchetta,[8] David M. Cash,[8] Emily G. Todd,[8] Georgia Peakman,[8] Rhian S. Convery,[8] John C. van Swieten,[9] Lize C. Jiskoot,[9] Harro Seelaar,[9] Raquel Sanchez-Valle,[10] Fermin Moreno,[11] Robert Laforce Jr,[12] Caroline Graff,[13] Matthis Synofzik,[14] Daniela Galimberti,[15,16] James B. Rowe,[17] Mario Masellis,[18] Maria Carmela Tartaglia,[19] Elizabeth Finger,[20] Rik Vandenberghe,[21,22,23] Alexandre de Mendonça,[24] Fabrizio Tagliavini,[25] Chris R. Butler,[26] Isabel Santana,[27] Alexander Gerhard,[28,29] Isabelle Le Ber,[30,31,32,33] Florence Pasquier,[34] Simon Ducharme,[35] Johannes Levin,[36,37,38] Adrian Danek,[39] Sandro Sorbi,[40,41] Markus Otto,[39] Jonathan D. Rohrer,[9] Barbara Borroni[4] on behalf of the Genetic Frontotemporal dementia Initiative (GENFI)^

1. Neurophysiology Unit, ASST Spedali Civili Hospital, Brescia, Italy

2. Department of Brain and Behavioral Science, Medical and Genomic Statistics Unit, University of Pavia, Pavia, Italy

3. Stroke Unit, Neurology Unit, ASST Spedali Civili Hospital, Brescia, Italy

4. Neurology Unit, ASST Spedali Civili Hospital, Brescia, Italy

5. Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

6. Biotechnology Laboratory, Department of Diagnostics, Spedali Civili Hospital, Brescia, Italy

7. Neuroradiology Unit, University of Brescia, Brescia, Italy

8. Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London

9. Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands

10. Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, University of Barcelona, Barcelona, Spain

11. Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain

12. Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Facultéde Médecine, Université Laval, QC, Canada

13. Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden

14. Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tubingen, Tubingen, Germany

15. Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milan, Italy

16. University of Milan, Centro Dino Ferrari, Milan, Italy

17. Department of Clinical Neurosciences and Cambridge University Hospitals NHS Trust, University of Cambridge, Cambridge, UK

18. Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada

19. Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada

20. Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario Canada

21. Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium

22. Neurology Service, University Hospitals Leuven, Leuven, Belgium

23. Leuven Brain Institute, KU Leuven, Leuven, Belgium

24. Faculty of Medicine, University of Lisbon, Lisbon, Portugal

25. Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy

26. Nueld Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK

27. University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

28. Division of Neuroscience & Experimental Psychology, Faculty of Medicine, Biology and Health, University of Manchester, Manchester, UK

29. Departments of Geriatric Medicine and Nuclear Medicine, Essen University Hospital, Essen, Germany

30. Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

31. Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

32. Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

33. Reference Network for Rare Neurological Diseases (ERN-RND)

34. University of Lille, Inserm, Lille, France

35. Department of Psychiatry, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

36. Department of Neurology, Ludwig-Maximilians-University, Munich, Germany.

37. German Center for Neurodegenerative Diseases (DZNE), Munich, Germany.

38. Munich Cluster for Systems Neurology (SyNergy), Munich, Germany.

39. Department of Neurology, University of Ulm, Ulm, Germany

40. Department of Neurofarba, University of Florence, Italy

41. IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

^ see appendix for consortium authors

Corresponding author:
Barbara Borroni, MD
Clinica Neurologica, Università degli Studi di Brescia
P.le Spedali Civili 1, 25123, Brescia, Italy
Phone: 0039 0303995632
Email: bborroni@inwind.it

Title character count: 113
Number of references: 43
Number of tables: 2
Number of figures: 3
Abstract word count: 170
Main text word count: 4082

Highlights

- Connectivity graph of cortical thickness detects the earliest brain changes
- *Granulin* disease resembles a disconnection syndrome from the earliest phases
- Interhemispheric disconnection starts in the parietal regions in early disease stage
- Interhemispheric disconnection progresses to frontotemporal areas at symptoms onset

ABSTRACT

Frontotemporal dementia (FTD) associated with *granulin (GRN)* mutations presents asymmetric brain atrophy. We applied a Minimum Spanning Tree plus an Efficiency Cost Optimization (MST+ ECO) 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 (NC) from the Genetic Frontotemporal dementia research Initiative cohort. Group differences of global, nodal and edge connectivity in (MST+ ECO) graph were tested via Structural Equation Models.

Global graph perturbation was selectively impaired in SC compared to NC, 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 FTD resembles a disconnection syndrome, with interhemispheric disconnection between parietal regions in presymptomatic phases that progresses to frontotemporal areas as symptoms emerge.

Keywords: graph theory; structural MRI; frontotemporal dementia; granulin; progranulin; mutation

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 behavioural 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., 2020a).

In spite of the highly phenotypical heterogeneity, most *GRN* mutation carriers receive a clinical diagnosis of behavioural variant FTD (bvFTD), or non-fluent variant of Primary Progressive Aphasia (nfvPPA), with a minority presenting as Corticobasal Syndrome (CBS) (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, *i.e.*, 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). 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 behavioural 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., 2020b; 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, Massachusetts, 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 (MathWorks, Natick, Massachusetts, 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-abs(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). 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/[all shortest paths between nodes of the graph]) and the local efficiency (i.e., the mean of 1/[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=MST U 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 NC 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; i.e., the link (group -> 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; i.e., the link (ROI (j)<-> 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 symptom onset in the pre-symptomatic group. To this purpose, we used interhemispheric cortical thickness, x= (left ROI * 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 & 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 behavioural 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 **Figure 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, i.e. 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 **Figure 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 **Figure 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 behaviour 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).**

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 Figure 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.

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 behaviour 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, *i.e.*, PPA vs. bvFTD, are yet to be determined.

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

ACKNOWLEDGEMENTS

We 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.

DISCLOSURES

The authors report no conflicts of interest.

FUNDING

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'.

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.

Appendix – GENFI consortium

- **Sónia Afonso** Instituto Ciencias Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal
- **Maria Rosario Almeida** Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- Sarah Anderl-Straub Department of Neurology, University of Ulm, Ulm, Germany
- **Christin Andersson** Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
- **Anna Antonell** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic Barcelona, Spain
- **Andrea Arighi** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Mircea Balasa** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Myriam Barandiaran** Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Nuria Bargalló** Imaging Diagnostic Center, Hospital Clínic, Barcelona, Spain
- **Robart Bartha** Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada; Centre for Functional and Metabolic Mapping, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada
- **Benjamin Bender** Department of Diagnostic and Interventional Neuroradiology, University of Tübingen, Tübingen, Germany
- **Maxime Bertoux** Inserm 1172, Lille, France
- **Anne Bertrand** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France

- **Valentina Bessi** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Sandra Black** Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
- **Sergi Borrego-Ecija** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Arabella Bouzigues** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Jose Bras** Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA
- **Alexis Brice** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Rose Bruffaerts** Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
- **Agnès Camuzat** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Marta Cañada** CITA Alzheimer, San Sebastian, Gipuzkoa, Spain
- **Valentina Cantoni** Centre for Neurodegenerative Disorders, University of Brescia, Brescia, Italy
- **Paola Caroppo** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Miguel Castelo-Branco** Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- **Olivier Colliot** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Thomas Cope** Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK
- **Vincent Deramecourt** Univ Lille, France
- **Giuseppe Di Fede** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Alina Díez** Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Diana Duro** Faculty of Medicine, University of Coimbra, Coimbra, Portugal
- **Chiara Fenoglio** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Camilla Ferrari** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Catarina B. Ferreira** Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Nick Fox** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Morris Freedman** Baycrest Health Sciences, Rotman Research Institute, University of Toronto, Toronto, Canada
- **Giorgio Fumagalli** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Aurélie Funkiewiez** Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Alazne Gabilondo** Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Serge Gauthier** Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Department of Neurology & Neurosurgery, McGill University, Montreal, Québec, Canada
- **Giorgio Giaccone** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Ana Gorostidi** Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Caroline Greaves** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Rita Guerreiro** Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA
- **Carolin Heller** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Tobias Hoegen** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Begoña Indakoetxea** Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Vesna Jelic** Division of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden
- **Hans-Otto Karnath** Division of Neuropsychology, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany

- **Ron Keren** The University Health Network, Toronto Rehabilitation Institute, Toronto, Canada
- **Gregory Kuchcinski** Univ Lille, France
- **Tobias Langheinrich** Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
- **Thibaud Lebouvier** Univ Lille, France
- **Maria João Leitão** Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal
- **Albert Lladó** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Gemma Lombardi** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Jolina Lombardi** Department of Neurology, University of Ulm, Ulm
- **Sandra Loosli** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Carolina Maruta** Laboratory of Language Research, Centro de Estudos Egas Moniz, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Simon Mead** MRC Prion Unit, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Lieke Meeter** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Gabriel Miltenberger** Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Rick van Minkelen** Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, Netherlands
- **Sara Mitchell** Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada
- **Katrina Moore** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Benedetta Nacmias** Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
- **Annabel Nelson** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Jennifer Nicholas** Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
- **Linn Öijerstedt** Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden
- **Jaume Olives** Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain
- **Sebastien Ourselin** School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK
- **Jessica Panman** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Janne M. Papma** Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands
- **Yolande Pijnenburg** Amsterdam University Medical Centre, Amsterdam VUmc, Amsterdam, Netherlands
- **Cristina Polito** Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Florence, Italy
- **Sara Prioni** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Catharina Prix** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Rosa Rademakers** Department of Neurosciences, Mayo Clinic, Jacksonville, Florida, USA
- **Veronica Redaelli** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Daisy Rinaldi** Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Tim Rittman** Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
- **Ekaterina Rogaeva** Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada
- **Adeline Rollin** CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France
- **Pedro Rosa-Neto** Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Québec, Canada
- **Giacomina Rossi** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Martin Rossor** Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Beatriz Santiago** Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal

- **Dario Saracino** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Sabrina Sayah** Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France
- **Elio Scarpini** Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy
- **Sonja Schönecker** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Rachelle Shafei** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Christen Shoesmith** Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
- **Imogen Swift** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Miguel Tábuas-Pereira** Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal
- **Mikel Tainta** Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain
- **Ricardo Taipa** Neuropathology Unit and Department of Neurology, Centro Hospitalar do Porto - Hospital de Santo António, Oporto, Portugal
- **David Tang-Wai** The University Health Network, Krembil Research Institute, Toronto, Canada
- **David L Thomas** Neuroimaging Analysis Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK
- **Paul Thompson** Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK
- **Hakan Thonberg** Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden
- **Carolyn Timberlake** Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
- **Pietro Tiraboschi** Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy
- **Philip Van Damme** Neurology Service, University Hospitals Leuven, Belgium; Laboratory for Neurobiology, VIB-KU Leuven Centre for Brain Research, Leuven, Belgium
- **Mathieu Vandenbulcke** Geriatric Psychiatry Service, University Hospitals Leuven, Belgium; Neuropsychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium
- **Michele Veldsman** Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
- **Ana Verdelho** Department of Neurosciences and Mental Health, Centro Hospitalar Lisboa Norte - Hospital de Santa Maria & Faculty of Medicine, University of Lisbon, Lisbon, Portugal
- **Jorge Villanua** OSATEK, University of Donostia, San Sebastian, Gipuzkoa, Spain
- **Jason Warren** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Carlo Wilke** Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany; Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
- **Ione Woollacott** Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK
- **Elisabeth Wlasich** Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany
- **Henrik Zetterberg** Dementia Research Institute, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK
- **Miren Zulaica** Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain

REFERENCES

Alexander-Bloch, A., Giedd, J.N., Bullmore, E., 2013. Imaging structural co-variance between human brain regions. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn3465

Apostolova, L.G., Thompson, P.M., 2007. Brain Mapping as a Tool to Study Neurodegeneration. Neurotherapeutics 4. https://doi.org/10.1016/j.nurt.2007.05.009

Baik, K., Yang, J.J., Jung, J.H., Lee, Y.H., Chung, S.J., Yoo, H.S., Sohn, Y.H., Lee, P.H., Lee, J.M., Ye, B.S., 2021. Structural connectivity networks in Alzheimer's disease and Lewy body disease. Brain Behav. 11. https://doi.org/10.1002/brb3.2112

Bethlehem, R.A.I., Romero-Garcia, R., Mak, E., Bullmore, E.T., Baron-Cohen, S., 2017. Structural covariance networks in children with autism or ADHD. Cereb. Cortex 27. https://doi.org/10.1093/cercor/bhx135

Bi, Q., Wang, W., Niu, N., Li, H., Wang, Y., Huang, W., Chen, K., Xu, K., Zhang, J., Chen, Y., Wei, D., Cui, R., Shu, N., Zhang, Z., 2021. Relationship between the disrupted topological efficiency of the structural brain connectome and glucose hypometabolism in normal aging. Neuroimage 226. https://doi.org/10.1016/j.neuroimage.2020.117591

Blondel, V.D., Guillaume, J.L., Lambiotte, R., Lefebvre, E., 2008. Fast unfolding of communities in large networks Journal of Statistical Mechanics: Theory and Experiment. https://doi.org/10.1088/1742-5468/2008/10/P10008

Borrego-Écija, S., Sala-Llonch, R., van Swieten, J., Borroni, B., Moreno, F., Masellis, M., Tartaglia, C., Graff, C., Galimberti, D., Laforce, R., Rowe, J.B., Finger, E., Vandenberghe, R., Tagliavini, F., de Mendonça, A., Santana, I., Synofzik, M., Ducharme, S., Levin, J., Danek, A., Gerhard, A., Otto, M., Butler, C., Frisoni, G., Sorbi, S., Heller, C., Bocchetta, M., Cash, D.M., Convery, R.S., Moore, K.M., Rohrer, J.D., Sanchez-Valle, R., Rossor, M.N., Fox, N.C., Woollacott, I.O.C., Shafei, R., Greaves, C., Neason, M., Guerreiro, R., Bras, J., Thomas, D.L., Nicholas, J., Mead, S., Meeter, L., Panman, J., Papma, J., van Minkelen, R., Pijnenburg, Y., Indakoetxea, B., Gabilondo, A., TaintaMD, M., de Arriba, M., Gorostidi, A., Zulaica, M., Villanua, J., Diaz, Z., Olives, J., Lladó, A., Balasa, M., Antonell, A., Bargallo, N., Premi, E., Cosseddu, M., Gazzina, S., Padovani, A., Gasparotti, R., Archetti, S., Black, S., Mitchell, S., Rogaeva, E., Freedman, M., Keren, R., Tang-Wai, D., Öijerstedt, L., Andersson, C., Jelic, V., Thonberg, H., Arighi, A., Fenoglio, C., Scarpini MD, E., Fumagalli, G., Cope, T., Timberlake, C., Rittman, T., Shoesmith, C., Bartha, R., Rademakers, R., Wilke, C., Bender, B., Bruffaerts, R., Vandamme, P., Vandenbulcke, M., Maruta, C., Ferreira, C.B., Miltenberger, G., Verdelho, A., Afonso, S., Taipa, R., Caroppo, P., Di Fede, G., Giaccone, G., Prioni, S., Redaelli, V., Rossi, G., Tiraboschi, P., Duro, D., Rosario Almeida, M., Castelo-Branco, M., João Leitão, M., Tabuas-Pereira, M., Santiago, B., Gauthier, S., Rosa-Neto, P., Veldsman, M., Flanagan, T., Prix, C., Hoegen, T., Wlasich, E., Loosli, S., Schonecker, S., Semler, E., Anderl-Straub, S., 2021. Disease-related cortical thinning in presymptomatic granulin mutation carriers. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2020.102540

Bullmore, E., Sporns, O., 2009.. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 186–198. 10.1038/nrn2575

Cash, D.M., Bocchetta, M., Thomas, D.L., Dick, K.M., van Swieten, J.C., Borroni, B., Galimberti, D., Masellis, M., Tartaglia, M.C., Rowe, J.B., Graff, C., Tagliavini, F., Frisoni, G.B., Laforce, R., Finger, E., de Mendonça, A., Sorbi, S., Rossor, M.N., Ourselin, S., Rohrer, J.D., 2018. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2017.10.008

Chen, Q., Baran, T.M., Turnbull, A., Zhang, Z., Rebok, G.W., Lin, F.V., 2021. Increased segregation of structural brain networks underpins enhanced broad cognitive abilities of cognitive training. Hum. Brain Mapp. 42. https://doi.org/10.1002/hbm.25428

Cormen, T.H., Leiserson, C.E., Rivest, R.L., Stein, C., 2001. Introduction to Algorithms *2*nd Edn. Cambridge, MA: MIT Press

Csardi, G., Nepusz, T.,2006. The igraph software package for complex network research. Inter Journal Complex Syst. 1695 1–9.

De Vico Fallani, F., Latora, V., Chavez, M., 2017. A Topological Criterion for Filtering Information in Complex Brain Networks. PLoS Comput. Biol. 13. https://doi.org/10.1371/journal.pcbi.1005305

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31. https://doi.org/10.1016/j.neuroimage.2006.01.021

Du, A.T., Schuff, N., Kramer, J.H., Rosen, H.J., Gorno-Tempini, M.L., Rankin, K., Miller, B.L., Weiner, M.W., 2007. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 130. https://doi.org/10.1093/brain/awm016

Fortanier, E., Grapperon, A.M., Le Troter, A., Verschueren, A., Ridley, B., Guye, M., Attarian, S., Ranjeva, J.P., Zaaraoui, W., 2019. Structural Connectivity Alterations in Amyotrophic Lateral Sclerosis: A Graph Theory Based Imaging Study. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.01044

Gazzina, S., Benussi, A., Premi, E., Paternicò, D., Cristillo, V., Dell'Era, V., Cosseddu, M., Archetti, S., Alberici, A., Gasparotti, R., Padovani, A., Borroni, B., 2018. Neuroanatomical Correlates of Transcranial Magnetic Stimulation in Presymptomatic Granulin Mutation Carriers. Brain Topogr. 31, 488–497. https://doi.org/10.1007/s10548-017-0612-9

Giunta, M., Solje, E., Gardoni, F., Borroni, B., Benussi, A., 2021. Experimental disease-modifying agents for frontotemporal lobar degeneration. J. Exp. Pharmacol. https://doi.org/10.2147/JEP.S262352

Gonzalez-Burgos, L., Pereira, J.B., Mohanty, R., Barroso, J., Westman, E., Ferreira, D., 2021. Cortical Networks Underpinning Compensation of Verbal Fluency in Normal Aging. Cereb. Cortex 31. https://doi.org/10.1093/cercor/bhab052

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. Neurology. https://doi.org/10.1212/WNL.0b013e31821103e6

Greaves, C. V., Rohrer, J.D., 2019. An update on genetic frontotemporal dementia. J. Neurol. https://doi.org/10.1007/s00415-019-09363-4

Hartikainen, P., Räsänen, J., Julkunen, V., Niskanen, E., Hallikainen, M., Kivipelto, M., Vanninen, R., Remes, A.M., Soininen, H., 2012. Cortical thickness in frontotemporal dementia, mild cognitive impairment, and alzheimer's disease. J. Alzheimer's Dis. 30. https://doi.org/10.3233/JAD-2012-112060

Huang, Q., Ren, S., Zhang, T., Li, J., Jiang, D., Xiao, J., Hua, F., Xie, F., Guan, Y., 2021. Aging-related Modular Architectural Reorganization of the Metabolic Brain Network. Brain Connect. https://doi.org/10.1089/brain.2021.0054

Kim, E.J., Rabinovici, G.D., Seeley, W.W., Halabi, C., Shu, H., Weiner, M.W., DeArmond, S.J., Trojanowski, J.Q., Gorno-Tempini, M.L., Miller, B.L., Rosen, H.J., 2007. Patterns of MRI atrophy in tau positive and ubiquitin positive frontotemporal lobar degeneration. J. Neurol. Neurosurg. Psychiatry 78. https://doi.org/10.1136/jnnp.2006.114231

Li, W., Zhao, H., Qing, Z., Nedelska, Z., Wu, S., Lu, J., Wu, W., Yin, Z., Hort, J., Xu, Y., Zhang, B., 2021. Disrupted Network Topology Contributed to Spatial Navigation Impairment in Patients With Mild Cognitive Impairment. Front. Aging Neurosci. 13. https://doi.org/10.3389/fnagi.2021.630677

Liu, H., Lafferty, J., Wasserman, L., 2009. The Nonparanormal: Semiparametric Estimation of High Dimensional Undirected Graphs. Journal of Machine Learning Research 2009; 10(809: 2295-2328.

Mårtensson, G., Pereira, J.B., Mecocci, P., Vellas, B., Tsolaki, M., Kłoszewska, I., Soininen, H., Lovestone, S., Simmons, A., Volpe, G., Westman, E., 2018. Stability of graph theoretical measures in structural brain networks in Alzheimer's disease. Sci. Rep. 8. https://doi.org/10.1038/s41598-018-29927-0

Minkova, L., Habich, A., Peter, J., Kaller, C.P., Eickhoff, S.B., Klöppel, S., 2017. Gray matter asymmetries in aging and neurodegeneration: A review and meta-analysis. Hum. Brain Mapp. 38. https://doi.org/10.1002/hbm.23772

Moore, K.M., Nicholas, J., Grossman, M., McMillan, C.T., Irwin, D.J., Massimo, L., Van Deerlin, V.M., Warren, J.D., Fox, N.C., Rossor, M.N., Mead, S., Bocchetta, M., Boeve, B.F., Knopman, D.S., Graff-Radford, N.R., Forsberg, L.K., Rademakers, R., Wszolek, Z.K., van Swieten, J.C., Jiskoot, L.C., Meeter, L.H., Dopper, E.G., Papma, J.M., Snowden, J.S., Saxon, J., Jones, M., Pickering-Brown, S., Le Ber, I., Camuzat, A., Brice, A., Caroppo, P., Ghidoni, R., Pievani, M., Benussi, L., Binetti, G., Dickerson, B.C., Lucente, D., Krivensky, S., Graff, C., Öijerstedt, L., Fallström, M., Thonberg, H., Ghoshal, N., Morris, J.C., Borroni, B., Benussi, A., Padovani, A., Galimberti, D., Scarpini, E., Fumagalli, G.G., Mackenzie, I.R., Hsiung, G.Y.R., Sengdy, P., Boxer, A.L., Rosen, H., Taylor, J.B., Synofzik, M., Wilke, C., Sulzer, P., Hodges, J.R., Halliday, G., Kwok, J., Sanchez-Valle, R., Lladó, A., Borrego-Ecija, S., Santana, I., Almeida, M.R., Tábuas-Pereira, M., Moreno, F., Barandiaran, M., Indakoetxea, B., Levin, J., Danek, A., Rowe, J.B., Cope, T.E., Otto, M., Anderl-Straub, S., de Mendonça, A., Maruta, C., Masellis, M., Black, S.E., Couratier, P., Lautrette, G., Huey, E.D., Sorbi, S., Nacmias, B., Laforce, R., Tremblay, M.P.L., Vandenberghe, R., Damme, P. Van, Rogalski, E.J., Weintraub, S., Gerhard, A., Onyike, C.U., Ducharme, S., Papageorgiou, S.G., Ng, A.S.L., Brodtmann, A., Finger, E., Guerreiro, R., Bras, J., Rohrer, J.D., Heller, C., Convery, R.S., Woollacott, I.O., Shafei, R.M., Graff-Radford, J., Jones, D.T., Dheel, C.M., Savica, R., Lapid, M.I., Baker, M., Fields, J.A., Gavrilova, R., Domoto-Reilly, K., Poos, J.M., Van der Ende, E.L., Panman, J.L., Donker Kaat, L., Seelaar, H., Richardson, A., Frisoni, G., Mega, A., Fostinelli, S., Chiang, H.H., Alberici, A., Arighi, A., Fenoglio, C., Heuer, H., Miller, B., Karydas, A., Fong, J., João Leitão, M., Santiago, B., Duro, D., Ferreira, Carlos, Gabilondo, A., De Arriba, M., Tainta, M., Zulaica, M., Ferreira, Catarina, Semler, E., Ludolph, A., Landwehrmeyer, B., Volk, A.E., Miltenberger, G., Verdelho, A., Afonso, S., Tartaglia, M.C., Freedman, M., Rogaeva, E., Ferrari, C., Piaceri, I., Bessi, V., Lombardi, G., St-Onge, F., Doré, M.C., Bruffaerts, R., Vandenbulcke, M., Van den Stock, J., Mesulam, M.M., Bigio, E., Koros, C., Papatriantafyllou, J., Kroupis, C., Stefanis, L., Shoesmith, C., Robertson, E., Coppola, G., Da Silva Ramos, E.M., Geschwind, D., 2020b. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol. https://doi.org/10.1016/S1474-4422(19)30394-1

Nigro, S., Tafuri, B., Urso, D., Blasi, R. De, Frisullo, M.E., Barulli, M.R., Capozzo, R., Cedola, A., Gigli, G., Logroscino, G., 2021. Brain structural covariance networks in behavioral variant of frontotemporal dementia. Brain Sci.

11. https://doi.org/10.3390/brainsci11020192
Otte, W.M., van Diessen, E., Paul, S., Ramaswamy, R., Subramanyam Rallabandi, V.P., Stam, C.J., Roy, P., 2015. Aging alterations in whole-brain networks during adulthood mapped with the minimum spanning tree indices: the interplay of density, connectivity cost and life-time trajectory. Neuroimage 109. 10.1016/j.neuroimage.2015.01.011
Palluzzi, F., Grassi, M., 2021. SEMgraph: An R Package for Causal Network Analysis of High-Throughput Data with Structural Equation Models. arXiv:2103.08332 [q-bio.MN]
Panman, J.L., Jiskoot, L.C., Bouts, M.J.R.J., Meeter, L.H.H., van der Ende, E.L., Poos, J.M., Feis, R.A., Kievit, A.J.A., van Minkelen, R., Dopper, E.G.P., Rombouts, S.A.R.B., van Swieten, J.C., Papma, J.M., 2019. Gray and white matter changes in presymptomatic genetic frontotemporal dementia: a longitudinal MRI study. Neurobiol. Aging 76. https://doi.org/10.1016/j.neurobiolaging.2018.12.017
Pereira, J.B., Aarsland, D., Ginestet, C.E., Lebedev, A. V., Wahlund, L.O., Simmons, A., Volpe, G., Westman, E., 2015. Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. Hum. Brain Mapp. 36. https://doi.org/10.1002/hbm.22822
Popuri, K., Dowds, E., Beg, M.F., Balachandar, R., Bhalla, M., Jacova, C., Buller, A., Slack, P., Sengdy, P., Rademakers, R., Wittenberg, D., Feldman, H.H., Mackenzie, I.R., Hsiung, G.Y.R., 2018. Gray matter changes in asymptomatic C9orf72 and GRN mutation carriers. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2018.02.017
Premi, E., Grassi, M,. van Swieten, J., Galimberti, D., Graff, C., Masellis, M., Tartaglia, C., Tagliavini, F., Rowe, J.B., Laforce, R. Jr, Finger, E., Frisoni, G.B., de Mendonça, A., Sorbi, S., Gazzina, S., Cosseddu, M., Archetti, S., Gasparotti, R., Manes, M., Alberici, A., Cardoso, M.J., Bocchetta, M., Cash, D.M., Ourselin, S., Padovani, A., Rohrer, J.D., Borroni, B.; Genetic FTD Initiative (GENFI), 2017. Cognitive reserve and TMEM106B genotype modulate brain damage in presymptomatic frontotemporal dementia: a GENFI study. Brain. https://doi: 10.1093/brain/awx103.
Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G.P., Onyike, C.U., Hillis, A.E., Josephs, K. a, Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.-L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134, 2456–77. https://doi.org/Doi 10.1093/Brain/Awr179
Richmond, S., Beare, R., Johnson, K.A., Allen, N.B., Seal, M.L., Whittle, S., 2021. Towards understanding neurocognitive mechanisms of parenting: Maternal behaviors and structural brain network organization in late childhood. Hum. Brain Mapp. 42. https://doi.org/10.1002/hbm.25334
Rittman, T., Borchert, R., Jones, S., van Swieten, J., Borroni, B., Galimberti, D., Masellis, M., Tartaglia, M.C., Graff, C., Tagliavini, F., Frisoni, G.B., Laforce, R., Finger, E., Mendonça, A., Sorbi, S., Rohrer, J.D., Rowe, J.B., Afonso, S., Almeida, M.R., Anderl-Straub, S., Andersson, C., Antonell, A., Archetti, S., Arighi, A., Balasa, M., Barandiaran, M., Bargalló, N., Bartha, R., Bender, B., Benussi, L., Bessi, V., Binetti, G., Black, S., Bocchetta, M., Borrego-Ecija, S., Bras, J., Bruffaerts, R., Caroppo, P., Cash, D., Castelo-Branco, M., Convery, R., Cope, T., Cosseddu, M., de Arriba, M., Di Fede, G., Díaz, Z., Dick, K.M., Duro, D., Fenoglio, C., Ferrari, C., Ferreira, C.B., Flanagana, T., Fox, N., Freedman, M., Fumagalli, G., Gabilondo, A., Gasparotti, R., Gauthier, S., Gazzina, S., Ghidoni, R., Giaccone, G., Gorostidi, A., Greaves, C., Guerreiro, R., Heller, C., Hoegen, T., Indakoetxea, B., Jelic, V., Jiskoot, L., Karnath, H.O., Keren, R., Leitão, M.J., Lladó, A., Lombardi, G., Loosli, S., Maruta, C., Mead, S., Meeter, L., Miltenberger, G., van Minkelen, R., Mitchell, S., Nacmias, B., Neason, M., Nicholas, J., Öijerstedt, L., Olives, J., Padovani, A., Panman, J., Papma, J., Pievani, M., Pijnenburg, Y., Premi, E., Prioni, S., Prix, C., Rademakers, R., Redaelli, V., Rogaeva, E., Rosa-Neto, P., Rossi, G., Rosser, M., Santiago, B., Scarpini, E., Schönecker, S., Semler, E., Shafei, R., Shoesmith, C., Tábuas-Pereira, M., Tainta, M., Taipa, R., Tang-Wai, D., Thomas, D.L., Thonberg, H., Timberlake, C., Tiraboschi, P., Vandamme, P., Vandenbulcke, M., Veldsman, M., Verdelho, A., Villanua, J., Warren, J., Wilke, C., Woollacott, I., Wlasich, E., Zetterberg, H., Zulaica, M., 2019. Functional network resilience to pathology in presymptomatic genetic frontotemporal dementia. Neurobiol. Aging 77. https://doi.org/10.1016/j.neurobiolaging.2018.12.009
Rohrer, J.D., Guerreiro, R., Vandrovcova, J., Uphill, J., Reiman, D., Beck, J., Isaacs, A.M., Authier, A., Ferrari, R., Fox, N.C., MacKenzie, I.R.A., Warren, J.D., De Silva, R., Holton, J., Revesz, T., Hardy, J., Mead, S., Rossor, M.N., 2009. The heritability and genetics of frontotemporal lobar degeneration. Neurology. https://doi.org/10.1212/WNL.0b013e3181bf997a
Rohrer, J.D., Nicholas, J.M., Cash, D.M., van Swieten, J., Dopper, E., Jiskoot, L., van Minkelen, R., Rombouts, S.A., Cardoso, M.J., Clegg, S., Espak, M., Mead, S., Thomas, D.L., De Vita, E., Masellis, M., Black, S.E., Freedman, M., Keren, R., MacIntosh, B.J., Rogaeva, E., Tang-Wai, D., Tartaglia, M.C., Laforce, R., Tagliavini, F., Tiraboschi, P., Redaelli, V., Prioni, S., Grisoli, M., Borroni, B., Padovani, A., Galimberti, D., Scarpini, E., Arighi, A., Fumagalli, G., Rowe, J.B., Coyle-Gilchrist, I., Graff, C., Fallström, M., Jelic, V., Ståhlbom, A.K., Andersson, C., Thonberg, H., Lilius, L., Frisoni, G.B., Pievani, M., Bocchetta, M., Benussi, L., Ghidoni, R., Finger, E., Sorbi, S., Nacmias, B.,

Lombardi, G., Polito, C., Warren, J.D., Ourselin, S., Fox, N.C., Rossor, M.N., 2015. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: A cross-sectional analysis. Lancet Neurol. https://doi.org/10.1016/S1474-4422(14)70324-2

Rohrer, J.D., Ridgway, G.R., Modat, M., Ourselin, S., Mead, S., Fox, N.C., Rossor, M.N., Warren, J.D., 2010. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. Neuroimage. https://doi.org/10.1016/j.neuroimage.2009.12.088

Saracino, D., Ferrieux, S., Noguès-Lassiaille, M., Houot, M., Funkiewiez, A., Sellami, L., Deramecourt, V., Pasquier, F., Couratier, P., Pariente, J., Géraudie, A., Epelbaum, S., Wallon, D., Hannequin, D., Martinaud, O., Clot, F., Camuzat, A., Bottani, S., Rinaldi, D., Auriacombe, S., Sarazin, M., Didic, M., Boutoleau-Bretonnière, C., Thauvin-Robinet, C., Lagarde, J., Roué-Jagot, C., Sellal, F., Gabelle, A., Etcharry-Bouyx, F., Morin, A., Coppola, C., Levy, R., Dubois, B., Brice, A., Colliot, O., Gorno-Tempini, M.L., Teichmann, M., Migliaccio, R., Le Ber, I., 2021. Primary Progressive Aphasia Associated With GRN Mutations: New Insights Into the Nonamyloid Logopenic Variant. Neurology 97, e88–e102. https://doi.org/10.1212/WNL.0000000000012174

Sporns, O., 2018. Graph theory methods: Applications in brain networks. Dialogues Clin. Neurosci. 20. https://doi.org/10.31887/DCNS.2018.20.2/OSPORNS

Sporns, O., Chialvo, D.R., Kaiser, M., Hilgetag, C.C., 2004. Organization, development and function of complex brain networks. Trends Cogn. Sci. https://doi.org/10.1016/j.tics.2004.07.008

Stam, C.J., Tewarie, P., Van Dellen, E., van Straaten, E.C.W., Hillebrand, A., Van Mieghem, P., 2014. The trees and the forest: Characterization of complex brain networks with minimum spanning trees. Int. J. Psychophysiol. https://doi.org/10.1016/j.ijpsycho.2014.04.001

Suo, X., Lei, D., Li, N., Li, J., Peng, J., Li, W., Yang, J., Qin, K., Kemp, G.J., Peng, R., Gong, Q., 2021. Topologically convergent and divergent morphological gray matter networks in early-stage Parkinson's disease with and without mild cognitive impairment. Hum. Brain Mapp. https://doi.org/10.1002/hbm.25606

Tewarie, P., Hillebrand, A., Schoonheim, M.M., van Dijk, B.W., Geurts, J.J.G., Barkhof, F., Polman C.H., Stam, C.J., 2014. Functional brain network analysis using minimum spanning trees in multiple sclerosis: an MEG source-space study. Neuroimage 88. 10.1016/j.neuroimage.2013.10.022

Toga, A.W., Thompson, P.M., 2003. Mapping brain asymmetry. Nat. Rev. Neurosci. 4. https://doi.org/10.1038/nrn1009

Tsvetanov, K.A., Gazzina, S., Jones, P.S., van Swieten, J., Borroni, B., Sanchez-Valle, R., Moreno, F., Laforce, R.J., Graff, C., Synofzik, M., Galimberti, D., Masellis, M., Tartaglia, M.C., Finger, E., Vandenberghe, R., de Mendonça, A., Tagliavini, F., Santana, I., Ducharme, S., Butler, C., Gerhard, A., Danek, A., Levin, J., Otto, M., Frisoni, G., Ghidoni, R., Sorbi, S., Rohrer, J.D., Rowe, J.B., 2021. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. Alzheimers. Dement. 17, 500–514. https://doi.org/10.1002/alz.12209

Van Mieghem, P., Magdalena, S.M., 2005. Phase transition in the link weight structure of networks. Phys. Rev. E Stat. Nonlin. Soft Matter Phys. 72:056138. 10.1103/PhysRevE.72.056138

Vecchio, F., Miraglia, F., Maria Rossini, P., 2017. Connectome: Graph theory application in functional brain network architecture. Clin. Neurophysiol. Pract. https://doi.org/10.1016/j.cnp.2017.09.003

Voevodskaya, O., Pereira, J.B., Volpe, G., Lindberg, O., Stomrud, E., van Westen, D., Westman, E., Hansson, O., 2018. Altered structural network organization in cognitively normal individuals with amyloid pathology. Neurobiol. Aging 64. https://doi.org/10.1016/j.neurobiolaging.2017.11.014

Warren, J.D., Rohrer, J.D., Schott, J.M., Fox, N.C., Hardy, J., Rossor, M.N., 2013. Molecular nexopathies: A new paradigm of neurodegenerative disease. Trends Neurosci. https://doi.org/10.1016/j.tins.2013.06.007

Yun, J.Y., Boedhoe, P.S.W., Vriend, C., Jahanshad, N., Abe, Y., Ameis, S.H., Anticevic, A., Arnold, P.D., Batistuzzo, M.C., Benedetti, F., Beucke, J.C., Bollettini, I., Bose, A., Brem, S., Calvo, A., Cheng, Y., Cho, K.I.K., Ciullo, V., Dallaspezia, S., Denys, D., Feusner, J.D., Fouche, J.P., Giménez, M., Gruner, P., Hibar, D.P., Hoexter, M.Q., Hu, H., Huyser, C., Ikari, K., Kathmann, N., Kaufmann, C., Koch, K., Lazaro, L., Lochner, C., Marques, P., Marsh, R., Martínez-Zalacaín, I., Mataix-Cols, D., Menchón, J.M., Minuzzi, L., Morgado, P., Moreira, P., Nakamae, T., Nakao, T., Narayanaswamy, J.C., Nurmi, E.L., O'Neill, J., Piacentini, J., Piras, Fabrizio, Piras, Federica, Janardhan Reddy, Y.C., Sato, J.R., Blair Simpson, H., Soreni, N., Soriano-Mas, C., Spalletta, G., Stevens, M.C., Szeszko, P.R., Tolin, D.F., Venkatasubramanian, G., Walitza, S., Wang, Z., Van Wingen, G.A., Xu, J., Xu, X., Zhao, Q., Thompson, P.M., Stein, D.J., Van Den Heuvel, O.A., Kwon, J.S., 2020. Brain structural covariance networks in obsessive-compulsive disorder: A graph analysis from the ENIGMA consortium. Brain 143. https://doi.org/10.1093/brain/awaa001

Table 1. Demographical, clinical and neuropsychological variables

Variable	NC *(n=341)*	PSC *(n=161)*	SC *(n=52)*	*p**
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.^
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	-	-
Neuropsychological assessment				
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.
*One-way ANOVA unless otherwise specified (^Chi-square).
All significant results are due to differences between SC and non-symptomatic groups (Bonferroni *post-hoc* comparisons).
NC=non-carriers; PSC=presymptomatic carriers; SC=symptomatic carriers; mini-SEA=mini-social cognition & emotional assessment.

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

SC vs NC*	Estimates	Lower CI	Upper CI
L bank of the superior temporal sulcus	-0.19	-0.28	-0.09
L lateral orbitofrontal	-0.33	-0.43	-0.25
L medial orbitofrontal	-0.20	-0.30	-0.11
L middle temporal gyrus	-0.34	-0.42	-0.25
L paracentral	-0.23	-0.32	-0.13
L pars opercularis	-0.38	-0.46	-0.29
L pars orbitalis	-0.34	-0.43	-0.25
L pars triangularis	-0.35	-0.44	-0.27
L caudal anterior cingulate	-0.21	-0.30	-0.11
L postcentral	-0.17	-0.26	-0.08
L posterior cingulate cortex	-0.29	-0.38	-0.20
L precentral	-0.32	-0.41	-0.23
L precuneus	-0.26	-0.34	-0.18
L rostral middle frontal gyrus	-0.37	-0.46	-0.29
L superior frontal gyrus	-0.35	-0.42	-0.27
L superior parietal lobule	-0.20	-0.29	-0.10
L superior temporal gyrus	-0.25	-0.34	-0.16
L caudal middle frontal gyrus	-0.34	-0.43	-0.26
L supramarginal gyrus	-0.34	-0.42	-0.26
L frontal pole	-0.20	-0.30	-0.19
L temporal pole	-0.26	-0.35	-0.16
L insula	-0.21	-0.30	-0.11
L entorhinal	-0.18	-0.28	-0.09
L inferior parietal lobule	-0.34	-0.43	-0.25
L inferior temporal gyrus	-0.25	-0.34	-0.15
R lateral orbitofrontal	-0.27	-0.36	-0.17
R middle temporal gyrus	-0.29	-0.38	-0.20
R paracentral	-0.22	-0.31	-0.12
R pars opercularis	-0.35	-0.44	-0.25
R pars orbitalis	-0.29	-0.38	-0.19
R pars triangularis	-0.33	-0.42	-0.23
R caudal anterior cingulate	-0.23	-0.33	-0.14
R postcentral	-0.17	-0.26	-0.07
R posterior cingulate cortex	-0.25	-0.34	-0.16
R precentral	-0.27	-0.36	-0.18
R precuneus	-0.22	-0.32	-0.13
R rostral middle frontal gyrus	-0.32	-0.41	-0.23
R superior frontal gyrus	-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
R caudal middle frontal gyrus	-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

SC vs PSC*	Estimates	Lower CI	Upper CI
L lateral orbitofrontal	-0.34	-0.47	-0.22
L medial orbitofrontal	-0.23	-0.36	-0.10
L middle temporal gyrus	-0.33	-0.45	-0.21
L paracentral	-0.27	-0.40	-0.13
L pars opercularis	-0.41	-0.53	-0.29
L pars orbitalis	-0.34	-0.46	-0.21
L pars triangularis	-0.39	-0.51	-0.27
L postcentral	-0.22	-0.34	-0.10
L posterior cingulate cortex	-0.31	-0.43	-0.19
L precentral	-0.36	-0.48	-0.24
L precuneus	-0.27	-0.38	-0.16
L rostral middle frontal gyrus	-0.36	-0.48	-0.24
L superior frontal gyrus	-0.38	-0.49	-0.28
L superior temporal gyrus	-0.25	-0.37	-0.13
L caudal middle frontal gyrus	-0.40	-0.51	-0.29
L supramarginal gyrus	-0.36	-0.47	-0.25
L temporal pole	-0.24	-0.37	-0.11
L entorhinal	-0.24	-0.36	-0.11
L inferior parietal lobule	-0.34	-0.46	-0.23
L inferior temporal gyrus	-0.25	-0.37	-0.12
R lateral orbitofrontal	-0.26	-0.39	-0.14
R middle temporal gyrus	-0.29	-0.40	-0.17
R paracentral	-0.25	-0.38	-0.12
R pars opercularis	-0.39	-0.52	-0.27
R pars orbitalis	-0.25	-0.38	-0.12
R pars triangularis	-0.32	-0.45	-0.20
R caudal anterior cingulate	-0.24	-0.37	-0.11
R posterior cingulate cortex	-0.29	-0.41	-0.17
R precentral	-0.32	-0.44	-0.19
R precuneus	-0.25	-0.38	-0.13
R rostral middle frontal gyrus	-0.29	-0.41	-0.17
R superior frontal gyrus	-0.33	-0.45	-0.22
R superior parietal lobule	-0.21	-0.32	-0.10
R caudal middle frontal gyrus	-0.40	-0.53	-0.28
R inferior parietal lobule	-0.23	-0.33	-0.12

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	

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

Significant nodal connectivity comparisons with estimates>0.30 in boldface.

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

Table 3. Structural Equation Model estimates of edge connectivity (correlation differences) comparison between groups.

SC vs NC	Estimation	Lower CI	Upper CI	*p-value**
L - R middle temporal gyrus	-0.38	-0.57	-0.19	0.003
L - R postcentral	-0.51	-0.75	-0.28	<0.001
L - R precentral	-0.55	-0.83	-0.28	0.002
L – R superior temporal gyrus	-0.57	-0.78	-0.35	<0.001
L - R insula	-0.48	-0.74	-0.22	0.004
L - R rostral middle frontal gyrus	-0.41	-0.65	-0.17	0.02
R superior temporal gyrus - R insula	0.49	0.19	0.79	0.02
L - R inferior temporal gyrus	-0.38	-0.64	-0.12	0.04
R postcentral - R precentral	0.46	0.14	0.77	0.04

SC vs PSC	Estimation	Lower CI	Upper CI	*p-value**
L - R postcentral	-0.53	-0.80	-0.26	0.005
L - R precentral	-0.58	-0.89	-0.27	0.007
L – R superior temporal gyrus	-0.54	-0.79	-0.29	0.002
L - R middle temporal gyrus	-0.38	-0.60	-0.16	0.02
L - R rostral middle frontal gyrus	-0.47	-0.74	-0.19	0.02
L - R frontal pole	-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

PSC vs NC	Estimation	Lower CI	Upper CI	*p-value**
L supramarginal gyrus - L inferior parietal lobule	0.47	0.27	0.67	<0.001
L - R supramarginal gyrus	-0.48	-0.64	-0.31	<0.001
R supramarginal gyrus - R inferior parietal lobule	0.45	0.26	0.64	<0.001
L - R inferior parietal lobule	-0.43	-0.58	-0.28	<0.001
R precentral - L paracentral	-0.11	-0.17	-0.04	0.03

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

Significant perturbation of interhemispheric connectivity between homologous regions in boldface.

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

FIGURE LEGENDS

FIGURE 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 colour indicates low correlation, while red colour 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 ROIs in the connectivity matrix and a list of the ROIs belonging to each community are reported in Supplementary Materials.

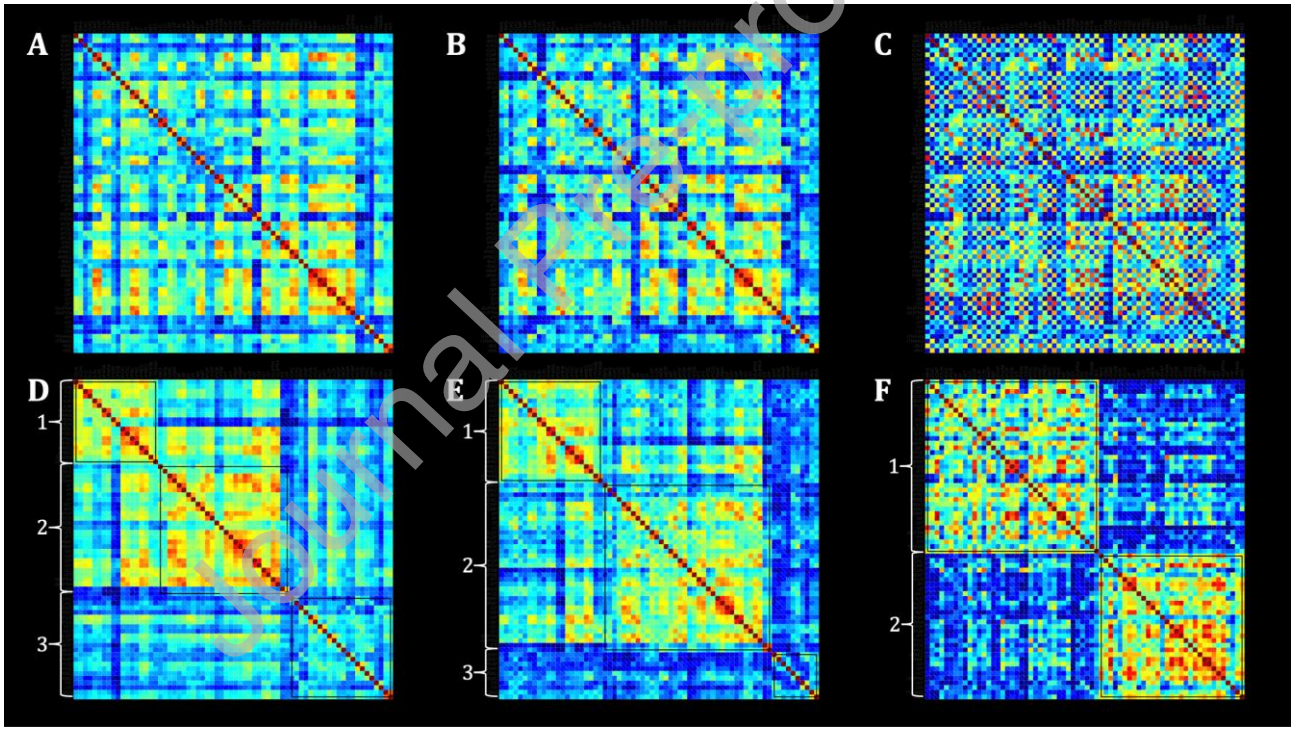


FIGURE 2. Structural graphs in non-carriers (NC), presymptomatic carriers (PSC) and symptomatic carriers (SC).

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.