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RESEARCH ARTICLE

Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia

Kamen A. Tsvetanov^{1,2,†} | Stefano Gazzina^{1,3,†} | P. Simon Jones¹ | John van Swieten³ | Barbara Borroni⁴ | Raquel Sanchez-Valle⁵ | Fermin Moreno^{6,7} | Robert Laforce Jr⁸ | Caroline Graff^{9,10} | Matthis Synofzik^{11,12} | Daniela Galimberti^{13,14} | Mario Masellis¹⁵ | Maria Carmela Tartaglia¹⁶ | Elizabeth Finger¹⁷ | Rik Vandenberghe^{18,19} | Alexandre de Mendonça²⁰ | Fabrizio Tagliavini²¹ | Isabel Santana^{22,23,24} | Simon Ducharme^{25,26} | Chris Butler²⁷ | Alexander Gerhard^{28,29} | Adrian Danek³⁰ | Johannes Levin³¹ | Markus Otto³² | Giovanni Frisoni^{33,34} | Roberta Ghidoni³⁵ | Sandro Sorbi^{36,37} | Jonathan D. Rohrer³⁸ | James B. Rowe^{1,2} | the Genetic FTD Initiative, GENFI¹

¹ Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

² Cambridge Centre for Ageing and Neuroscience (Cam-CAN), University of Cambridge and MRC Cognition and Brain Sciences Unit, Cambridge, UK

³ Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands

⁴ Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

⁵ Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain

⁶ Cognitive Disorders Unit, Department of Neurology, Hospital Universitario Donostia, San Sebastian, Gipuzkoa, Spain

⁷ Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain

⁸ Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, Québec, Canada

⁹ Department NVS, Center for Alzheimer Research, Division of Neurogenetics, Karolinska Institutet, Stockholm, Sweden

¹⁰ Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital-Solna, Stockholm, Sweden

¹¹ Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research & Center of Neurology, University of Tübingen, Germany

¹² German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany

¹³ Centro Dino Ferrari, University of Milan, Milan, Italy

¹⁴ Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy

¹⁵ LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada

¹⁶ Tanz Centre for Research in Neurodegenerative Disease, Toronto Western Hospital, Toronto, Ontario, Canada

¹⁷ Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

¹⁸ Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium

¹⁹ Neurology Service, University Hospitals Leuven, Leuven, Belgium

²⁰ Laboratory of Neurosciences, Faculty of Medicine, Institute of Molecular Medicine University of Lisbon, Lisbon, Portugal

²¹ Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

²² Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

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²³ Faculty of Medicine, University of Coimbra, Coimbra, Portugal

²⁴ Centre of Neurosciences and Cell biology, Universidade de Coimbra, Coimbra, Portugal

²⁵ Department of Psychiatry, McGill University Health Centre/McGill University, Montreal, Canada

²⁶ McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada

²⁷ Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK

²⁸ Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK

²⁹ Departments of Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Germany

³⁰ Neurologische Klinik und Poliklinik, German Center for Neurodegenerative Diseases (DZNE), Ludwig-Maximilians-Universität, Munich, Munich, Germany

³¹ German Center for Neurodegenerative Diseases, Munich Cluster for Systems Neurology (Synergy), Munich, Germany

³² Department of Neurology, University Hospital Ulm, Ulm, Germany

³³ Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

³⁴ Memory Clinic and LANVIE-Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland

³⁵ Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

³⁶ Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

³⁷ Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Fondazione Don Carlo Gnocchi", Florence, Italy

³⁸ Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Correspondence

Kamen A. Tsvetanov, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

Email: kat35@cam.ac.uk

[†] Joint first authorship.

[‡] See Appendix for a list of GENFI consortium members.

Abstract

Introduction: The presymptomatic phase of neurodegenerative disease can last many years, with sustained cognitive function despite progressive atrophy. We investigate this phenomenon in familial frontotemporal dementia (FTD).

Methods: We studied 121 presymptomatic FTD mutation carriers and 134 family members without mutations, using multivariate data-driven approach to link cognitive performance with both structural and functional magnetic resonance imaging. Atrophy and brain network connectivity were compared between groups, in relation to the time from expected symptom onset.

Results: There were group differences in brain structure and function, in the absence of differences in cognitive performance. Specifically, we identified behaviorally relevant structural and functional network differences. Structure-function relationships were similar in both groups, but coupling between functional connectivity and cognition was stronger for carriers than for non-carriers, and increased with proximity to the expected onset of disease.

Discussion: Our findings suggest that the maintenance of functional network connectivity enables carriers to maintain cognitive performance.

KEYWORDS

frontotemporal dementia (FTD), functional magnetic resonance imaging (fMRI), network connectivity, presymptomatic

1 | INTRODUCTION

Across the adult healthy lifespan, the structural and functional properties of brain networks are coupled, and both are predictive of cognitive ability.^{1,2} The connections between structure, function, and performance have been influential in developing current models of aging and neurodegeneration.³⁻⁵ However, this work contrasts with

the emerging evidence of neuropathological and structural changes many years before the onset of symptoms of Alzheimer's disease (AD) and frontotemporal dementia (FTD).⁶⁻⁸ Genetic FTD with highly penetrant gene mutations provides the opportunity to examine the precursors of symptomatic disease. Three main genes account for 10% to 20% of FTD cases: chromosome 9 open reading frame 72 (*C9orf72*), granulin (*GRN*), and microtubule-associated protein tau

(MAPT). These genes vary in their phenotypic expression and in the age at onset.⁹ Despite pleiotropy¹⁰ and environmental and secondary genetic moderation^{11,12} all three mutations cause significant structural brain changes in key regions over a decade before the expected age at disease onset,^{7,13} confirmed by longitudinal studies.^{14,15}

The divergence between early structural change and late cognitive decline provokes the question: how do presymptomatic mutation carriers stay so well in the face of progressive atrophy? We propose that the answer lies in the maintenance of network dynamics and functional organisation.¹⁶ Across the lifespan, functional brain network connectivity predicts cognitive status,¹⁷ and this connectivity-cognition relationship becomes stronger with age.¹⁸⁻²⁰

Our overarching hypothesis is that for those at genetic risk of dementia, the maintenance of network connectivity prevents the manifestation of symptoms despite progressive structural changes. A challenge is that neither the anatomical and functional substrates of cognition nor the targets of neurodegenerative disease are mediated by single brain regions: They are distributed across multi-level and interactive networks. We therefore used a multivariate data-driven approach to identify differences in the multidimensional brain-behavior relationship between presymptomatic carriers and non-carriers of mutations in FTD genes. We identified key brain networks²¹ from a large independent population-based age-matched data set.²²

We tested three key hypotheses: (1) presymptomatic carriers differ from non-carriers in brain structure and brain function, but not in cognitive function, (2) brain structure and function correlate with performance in both groups, but functional network indices are stronger predictors of cognition in carriers, and (3) the dependence on network integrity for maintaining cognitive functioning increases as carriers approach the onset of symptoms.

2 | METHODS

2.1 | Participants

Thirteen research sites across Europe and Canada recruited participants as part of an international multicenter partnership, the Genetic Frontotemporal Initiative (GENFI). A total of 313 participants had usable structural and resting state functional magnetic resonance imaging (fMRI) data.^{7,13} The study was approved by the institutional review boards for each site, and participants providing written informed consent. Inclusion criteria included anyone over the age of 18 who is symptomatic or an asymptomatic first-degree relative. Five participants were excluded due to excessive head motion (see below), resulting in 308 data sets for further analysis.

Participants were genotyped based on whether they carried a pathogenic mutation in *MAPT*, *GRN*, and *C9orf72*. Mutation carriers were classified as either symptomatic or presymptomatic based on clinician evaluation. Participants were only classified as symptomatic if the clinician judged that symptoms were present, consistent with

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed systematically the literature using Web of Science, preprint repositories (eg, BioRxiv) and research citing key articles. The connections between structure, function, and performance have been influential in developing current models of aging and neurodegeneration. We discuss these citations in light of emerging evidence of contrasting views that neuropathological changes occur many years before the onset of symptoms of Alzheimer's disease and frontotemporal dementia.
2. Interpretation: Our results suggest that the maintenance of brain functional network integrity enables presymptomatic carriers of frontotemporal dementia mutations to remain cognitively well despite progressive brain atrophy.
3. Future directions: The novel methods and results will inform the design of pre-symptomatic disease-modifying therapy trials and guide strategies to maintain cognitive function with age and age-related neurodegenerative diseases.

a diagnosis of a degenerative disorder, and progressive in nature. An additional group of controls, termed non-carriers, comprised mutation-negative family members. In this study, we focus on non-carriers (NC, N = 134) and presymptomatic carriers (PSC, N = 121). Participants and site investigators were blinded to the research genotyping, although a minority of participants had undergone predictive testing outwith the GENFI study. See Table 1 for demographic information and Table 2 for behavioral, cognitive, and neuropsychological information of both groups. In keeping with other GENFI reports, the years to expected onset (EYO) were calculated as the difference between age at assessment and mean age at onset within the family.⁷

2.2 | Neurocognitive assessment

Each participant completed a standard clinical assessment consisting of medical history, family history, functional status, and physical examination, in complement with collateral history from a family member or a close friend. In the current study, 13 behavioral measures of cognitive function were correlated with neuroimaging measures. These included the Uniform Data Set²³: the Logical Memory subtest of the Wechsler Memory Scale-Revised with Immediate and Delayed Recall scores, Digit Span forwards and backwards from the Wechsler Memory Scale-Revised, a Digit Symbol Task, Parts A and B of the Trail Making Test, the short version of the Boston Naming Test, and Category Fluency (animals). Additional tests included Letter Fluency,

TABLE 1 Demographics of participants included in the analysis, grouped by genetic status as non-carriers (NCs) and presymptomatic carriers (PSCs)

	Gene status group		Statistical tests ^a	
	NC	PSC	X ² or F-test	P-value
N	134	121		
Mutated gene, n (%)			0.86	0.649
MAPT	17 (12.7)	19 (15.7)		
GRN	77 (57.5)	63 (52.1)		
C9Orf72	40 (29.9)	39 (32.2)		
Gender, n (%)			0.01	0.908
Male	53 (39.6)	47 (38.8)		
Handedness, n (%)			0.06	0.806
Right-handed	122 (91)	107 (88.4)		
Age (y)			2.68	0.103
Mean/SD	49/14	46/11		
Range [Min/Max]	19/86	20/70		
Expected years to onset			0.23	0.631
Mean/SD	-10/12	-11/11		
Range [Min/Max]	-25/10	-25/10		
Education (y)			0.05	0.826
Mean/SD	14/3	14/3		
Range [Min/Max]	5/24	5/22		

^aStatistical test to indicate whether demographics vary between NC and PSC groups.

Wechsler Abbreviated Scale of Intelligence Block Design task, and the Mini-Mental State Examination. Latency measures for the Trail Making Test were inverted so that higher values across all tests reflect better performance.

2.3 | Neuroimaging assessment

Figure 1 provides a schematic representation of imaging data processing pipeline and the analysis strategy for linking brain-behavior data. MRI data were acquired using 3T scanners and 1.5T where no 3T scanning was available from various vendors, with optimized scanning protocols to maximize synchronization across scanners and sites.^{7,13} A three-dimensional (3D) structural MRI was acquired for each participant using T1-weighted magnetic prepared rapid gradient echo (MPRAGE) sequence over at least 283 s (283 to 462 s) and had a median isotropic resolution of 1.1 mm (1 to 1.3 mm), repetition time of 2000 ms (6.6 to 2400), echo time of 2.9 ms (2.6 to 3.5 ms), inversion time of 8 ms (8 to 9 ms), and field of view 256 × 256 × 208 mm (192 to 256 × 192 to 256 × 192 to 208 mm). The co-registered T1 images were segmented to extract probabilistic maps of six tissue classes: grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), bone, soft tissue, and residual noise. The native-space GM and WM images were submitted to diffeomorphic registration to create equally represented

TABLE 2 Behavioral, cognitive, and neuropsychological estimates in presymptomatic carriers and non-carriers

	Gene status group		Statistical tests ^a	
	NC	PSC	X ²	P-value
Behavioral				
Cambridge Behavioral Inventory—Revised (/180)	3.5 (5.4)	4.7 (10)	0.03	.864
Cognitive				
Mini-Mental State Examination	29.3 (1.1)	29.2 (1.3)	<0.01	.963
Neuropsychological				
Logical Memory—Immediate Recall	15.2 (5.6)	15.7 (5.6)	0.47	.495
Logical Memory—Delayed Recall	14.1 (4.7)	14 (5)	0.97	.356
Digit Span—Forwards	6.4 (1.2)	6.3 (1.3)	0.52	.470
Digit Span—Backwards	4.9 (1.2)	4.8 (1.2)	1.62	.203
Digit Symbol Task	32 (14.1)	35 (14)	0.35	.556
Trail Making Test Part A	28.9 (17.2)	28.9 (11.5)	0.97	.325
Trail Making Test Part B	72.5 (43.7)	72.3 (45.5)	0.02	.895
Verbal Fluency—Letter	42 (12.2)	40.7 (15.1)	0.95	.330
Verbal Fluency—Animal	23.3 (6)	23.7 (5.8)	0.58	.445
Boston Naming Test	28.1 (2.1)	27.6 (2.7)	0.58	.446
Block Design	41.8 (16.1)	42.5 (17.1)	0.17	.683

^aStatistical test to indicate whether scores vary between NC and PSC groups.

gene-group template images (DARTEL²⁴). The templates for all tissue types were normalized to the Montreal Neurological Institute (MNI) template using a 12-parameter affine transformation. The normalized images were smoothed using an 8-mm Gaussian kernel.

For resting state fMRI measurements, echo-planar imaging (EPI) data were acquired with at least 6 minutes of scanning. Analogous imaging sequences were developed by the GENFI Imaging Core team, and used at each GENFI study site to accommodate different scanner models and field strengths. EPI data were acquired over at least 300 s (interquartile range [IQR] 309 to 440) and had a median repetition time of 2200 ms (2200 to 3000 ms), echo time of 30 ms, in-plane resolution of 2.75 × 2.75 mm (2.75 to 3.31 × 2.75 to 3.31), and slice thickness of 3.3 mm (3.0 to 3.3).

The imaging data were analyzed using Automatic Analysis [AA 4.0²⁵] pipelines and modules, which called relevant functions from Statistical Parametric Mapping (SPM12).²⁶ To quantify the total motion for each participant, the root mean square volume-to-volume displacement was computed using the approach of Jenkinson et al.²⁷ Participants with 3.5 or more standard deviations (SD) above the group mean motion displacement were excluded from further analysis (N = 5). To further ensure that potential group bias in head motion did not affect later analysis of connectivity, we took three further steps:

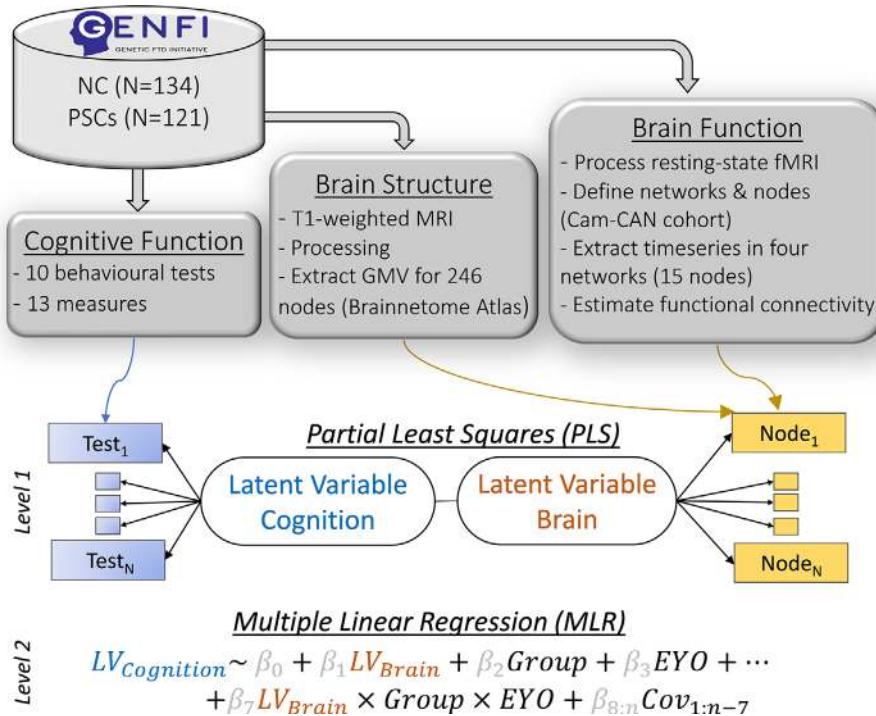


FIGURE 1 Schematic representation of data processing and analysis pipeline to test for brain-behavior differences between presymptomatic carriers (PSCs) and non-carriers (NCs) as a function of expected years to onset (EYO) of symptoms, while controlling for covariates of no interest (Covs). Brain structural measures were based on the mean gray matter volume (GMV) in 246 nodes, as defined in the Brainnetome atlas.³⁵ Brain functional measures were based on the functional connectivity between 15 nodes as part of four large-scale networks, which were defined in an independent cohort of 298 age-matched individuals part of the Cam-CAN data set

(1) fMRI data were further postprocessed using whole-brain independent component analysis (ICA) of single subject time-series denoising, with noise components selected and removed automatically using a priori heuristics and the ICA-based algorithm,²⁸ (2) postprocessing of network node time-series (see below), and (3) a subject-specific estimate of head movement for each participant²⁷ included as a covariate in group-level analysis.²⁹

2.4 | Network definition

The location of the key cortical regions in each network was identified by spatial-ICA in an independent data set of 298 age-matched healthy individuals from a large population-based cohort.²² Full details about preprocessing and node definition have been described previously.³⁰ Four networks commonly affected by neurodegenerative diseases including FTD²¹ were identified by spatially matching to pre-existing templates.³¹ The default mode network (DMN) contained five nodes: the ventral anterior cingulate cortex (vACC), dorsal and ventral posterior cingulate cortex (vPCC and dPCC), and right and left inferior parietal lobes (rIPL and lIPL). The salience network (SN) was defined using right and left anterior insular (rAI and lAI) and dorsal anterior cingulate cortex (dACC). The frontoparietal network (FPN) was defined using right and left anterior superior frontal gyrus (raSFG and laSFG) and right and left angular gyrus (rAG and lAG). The dorsal attention network (DAN) was defined using right and left intraparietal sulcus (rIPS

and lIPS). The node time-series were defined as the first principal component resulting from the singular value decomposition of voxels in an 8-mm radius sphere, which was centered on the peak voxel for each node.¹⁸ Visual representation of the spatial distribution of the nodes is shown in Figure 2.

We aimed to further reduce the effects of noise confounds on functional connectivity effects of node time-series using the general linear model (GLM).²⁹ This model included linear trends, expansions of realignment parameters, as well as average signal in WM and CSF, including their derivative and quadratic regressors from the time-courses of each node. The WM and CSF signals were created by using the average signal across all voxels with corresponding tissue probability >0.7 in associated tissue probability maps available in SPM12. A band-pass filter (0.0078 to 0.1 Hz) was implemented by including a discrete cosine transform set in the GLM. Finally, the functional connectivity (FC) between each pair of nodes was computed using Pearson correlation on postprocessed time-series.

2.5 | Statistical analysis

2.5.1 | Group differences in brain structure, function, and cognition

To assess the group differences in neuroimaging and behavioral data set we used multiple linear regression with a well-conditioned shrink-

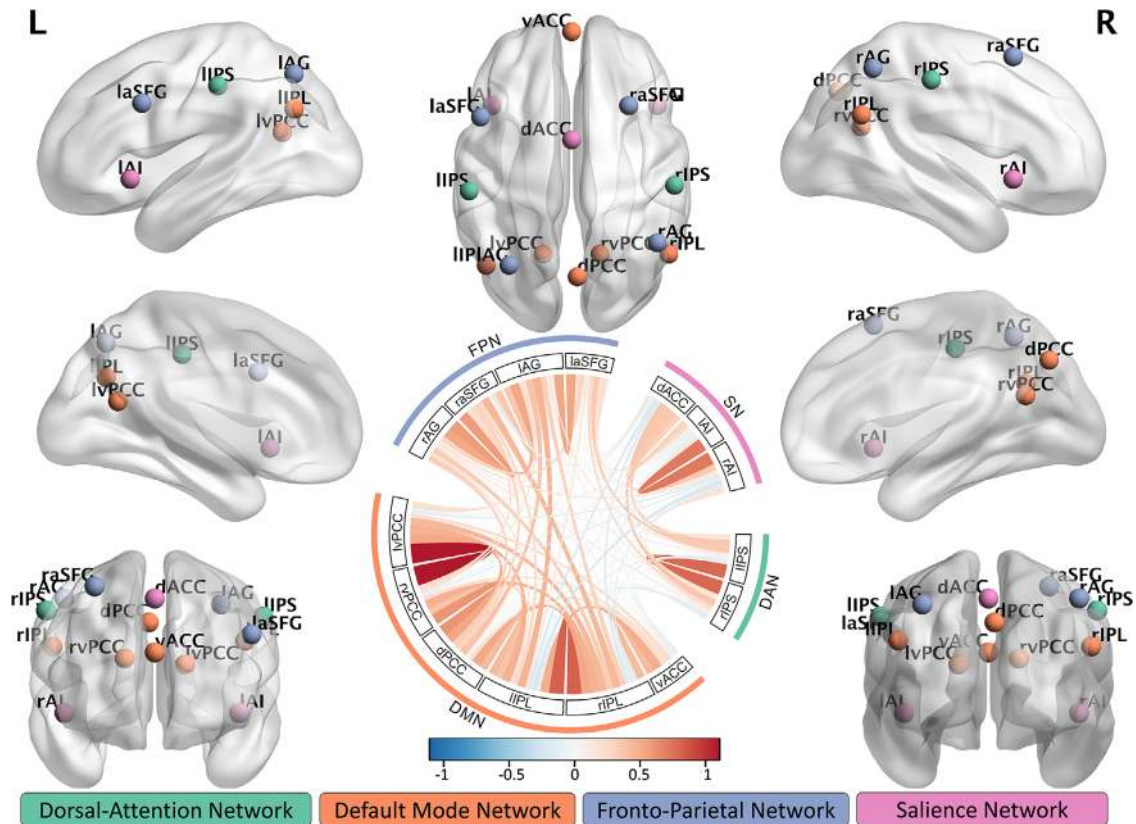


FIGURE 2 Visualization of spatial localization of the nodes part of the four large-scale networks and their mean functional connectivity (circular plot) across all participants in this study. Nodes and networks were defined in an independent cohort of 298 age-matched individuals part of the Cam-CAN data set.³⁰ The default mode network (DMN) contained five nodes: the ventral anterior cingulate cortex (vACC), dorsal and ventral posterior cingulate cortex (vPCC and dPCC), and right and left inferior parietal lobes (rIPL and lIPL). The salience network (SN) was defined using right and left anterior insular (rAI and lAI) and dorsal anterior cingulate cortex (dACC). The frontoparietal network (FPN) was defined using right and left anterior superior frontal gyrus (raSFG and laSFG) and right and left angular gyrus (rAG and lAG). The dorsal attention network (DAN) was defined using right and left intraparietal sulcus (rIPS and lIPS)

age regularization^{32,33} and 10-fold cross-validation.³⁴ In the analysis of brain structure we used as independent variables the mean GM volume (GMV) of the 246 brain nodes in the Brainnetome atlas.³⁵ The Brainnetome atlas was developed to link functional and structural characteristics of the human brain³⁵ and provides a fine-grained whole-brain parcellation with a superior representation of age-related differences in brain structure compared to other cortical parcellation schemes.^{36,37} In the analysis of brain function, we used the functional connectivity between 15 nodes, which were part of the four large-scale functional networks described earlier. In the analysis of cognitive function, the independent variables comprised the performance measures on the 13 neuropsychological tests performed outside of the scanner. In all three analyses the dependent variable was the genetic status (PSC vs NC) including age as a covariate of no interest. GENFI's large-sampled cohort was created using harmonized multi-site neuroimaging data. Although, scanning protocols were optimized to maximize comparability across scanners and sites,^{7,13} different scanning platforms can introduce systematic differences that might confound true effects of interest.³⁸ Therefore, in the analysis of neuroimaging data we included scanner site and head motion as additional covariates of no interest.

2.5.2 | Brain-behavior relationships

For the brain-behavior analysis, we adopted a two-level procedure. In the first-level analysis, we assessed the multidimensional brain-behavior relationships using partial least squares.³⁹ This analysis described the linear relationships between the two multivariate data sets, namely neuroimaging (either GMV or FC) and behavioral performance, by providing pairs of latent variables (Brain-LVs and Cognition-LVs) as linear combinations of the original variables that are optimized to maximize their covariance. Namely, data set 1 consisted of a brain feature set, which could be either GMV (GMV data set) or functional connectivity strength between pairs of regions for each individual (FC data set). Data set 2 included the performance measures on the 13 tests (ie, Cognition data set), as considered in the multiple linear regression analysis of group differences in cognition. Covariates of no interest included head motion, scanner site, gender, and handedness. In addition, we also included average GMV across all 15 nodes as a covariate of no interest in the FC-behavior analysis to ensure that the observed effects are over and above differences in the level of atrophy.

Next, we tested whether the identified behaviorally relevant LVs of brain structure and function were differentially expressed by NC and

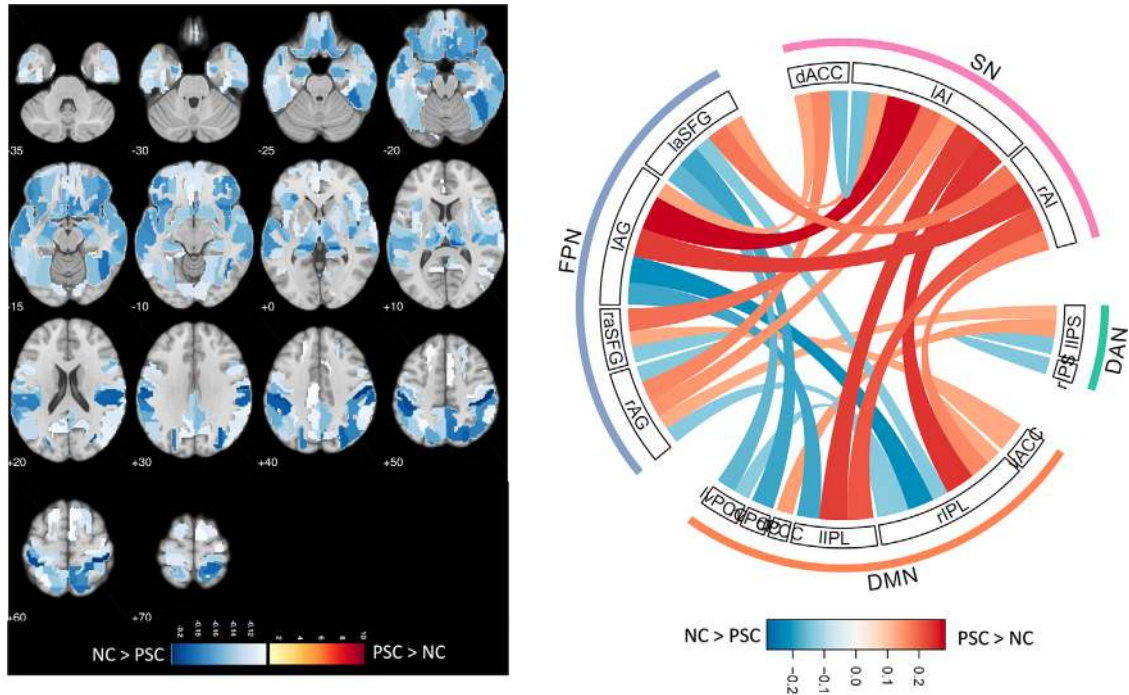


FIGURE 3 Group differences between PSC and NC in gray matter volume (left panel) and functional connectivity between nodes within four large scale networks (right panel). Hot color scheme indicates the strength of effect size of PSC showing higher GMV and FC than NC, while cold color scheme indicates the opposite effect (ie, NC > PSC)

PSC as a function of expected years to onset. To this end, we performed a second-level analysis using multiple linear regression with robust fitting algorithm as implemented in MATLAB's function "fitlm.m." Independent variables included subjects' brain scores from first level PLS (either Structure-LV or Function-LV subject scores), group information, expected years to onset and their interaction terms (eg, brain scores x group, brain scores x years to expected onset, and so on). The dependent variable was subjects' cognitive scores from the first level analysis in the corresponding PLS (Cognition-LV). Given that the interaction effects were derived from continuous variables, we tested and interpreted interactions based on simple slope analysis and slope difference tests.⁴⁰⁻⁴² Covariates of no interest included gender, handedness, head movement, and education (Figure 1). In addition, we included average GMV across all 15 nodes as a covariate in the FC-behavior analysis to ensure that the observed effects are over and above differences in the level of atrophy.

3 | RESULTS

3.1 | Group differences in neuroimaging and cognitive data

3.1.1 | Brain structure

The multiple linear regression model testing for overall group differences in GMV between PSC and NC was significant ($r = .14$, $P = .025$), reflecting expected presymptomatic differences in brain-wide atrophy. The frontal, parietal, and subcortical regions had most atrophy in PSC

(Figure 3). As expected, the group difference in GMV of these regions increased as EYO decreased (see Supplementary Materials).

3.1.2 | Brain function

The multiple linear regression model testing for overall group differences in functional connectivity between PSC and NC was marginally significant ($r = .12$, $P = .049$). The pattern of connectivity indicated mainly increased connectivity between SN-DMN and SN-FPN in presymptomatic carriers, coupled with decreased connectivity within the networks and DMN-FPN connectivity (Figure 3).

3.1.3 | Cognitive function

We did not identify group differences in cognition and behavior ($r = .002$, $P = .807$), confirming the impression of "healthy" status among presymptomatic carriers. However, in the next section, we consider the relationships between structure, function, and cognition that underlie this maintenance of cognitive function.

3.2 | Brain-behavior relationships

3.2.1 | Structure-cognition

Partial least squares analysis of GMV and cognition identified one significant pair of latent variables ($r = .40$, $P = .019$). This volumetric latent variable expressed negative loadings in frontal (superior frontal

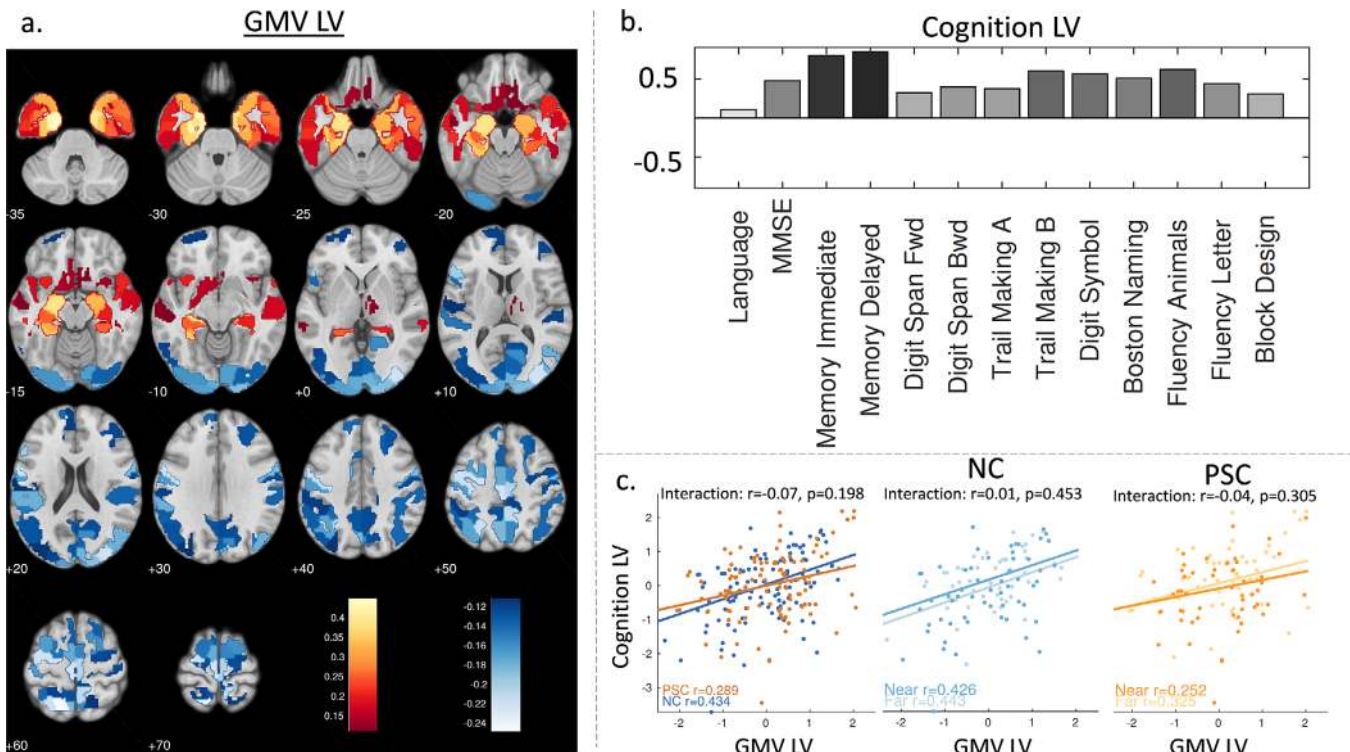


FIGURE 4 PLS analysis of gray matter volume (GMV) and cognition indicating the spatial distribution of GMV loading values (A), where hot and cold color schemes are used for the strength of positive and negative correlations with the profile of Cognition-LV (B). (C) The scatter plot on the left represents the relationship between subjects scores of GMV-LV and Cognition-LV for presymptomatic carriers (PSCs) and non-carriers (NCs). The scatter plots in the middle and right hand-side represent GMV-Cognition LV relationship as a function of expected years to onset (EYO, split in two groups, near and far, see text) in each genetic status group separately

gyrus, precentral gyrus, paracentral lobule), parietal (postcentral gyrus, precuneus, superior and inferior parietal lobule), and occipital (lateral and medial occipital cortex) regions and positive loadings in parahippocampal and hippocampal regions in addition to inferior temporal and insular cortex (Figure 4). The Cognition-LV profile expressed positively a large array of cognitive tests, with strongest values on delayed memory, Trail Making, Digit Symbol, Boston Naming, and Fluency tests. The positive correlation between volumetric and cognitive LV's confirms the expected relationship across the cohort as a whole, between cortical GMV and executive, language, and mnemonic function (Figure 4).

To understand the structure-cognition relationship in each group and in relation to the expected years of onset, we performed a second-level interaction analysis using a regression model: We entered Cognition-LV subject scores as dependent variable, and GMV LV subject scores, genetic status (ie, mutation carrier or non-carrier), expected years to onset, and their interactions as independent variables in addition to covariates of no interest. The results indicated that the relationship between GMV and cognition could not be explained by genetic status, expected years to onset, or their interactions with GMV LV subject scores. There was no evidence for genetic status- and onset-dependent differences (over and above aging and other covariates) in the associations between GMV and cognition in this analysis (Figure 4).

3.2.2 | Connectivity-cognition

PLS analysis of functional connectivity and cognition also identified one significant pair of LVs (Function-LV and Cognition-LV, $r = .32$, $P = .020$; see Figure 5). This Function-LV reflected weak between-network connectivity, coupled with strong within-network connectivity. This pattern indicates the segregation or modularity of large-scale brain networks. The Cognition-LV expressed all tests, with positive loading values indicating that higher performance on a wide range of cognitive tests is associated with stronger functional network segregation. Cognitive deficits were associated with loss of segregation, with increased between-network connectivity and decreased within-network connectivity.

To further test whether the observed behaviorally relevant pattern of connectivity is differentially expressed between genetic status groups and expected years of onset, we constructed a second-level regression model with robust error estimates by including Function-LV subject scores, genetic status, expected years of onset, and their interaction terms as independent variables and Cognition-LV as dependent variable in addition to covariates of no interest (Figure 5).

We found evidence for significant interaction between expected years of onset and Function-LV ($r = .21$, $P < .001$) and between group and Function-LV ($r = .16$, $P = .002$) explaining unique vari-

feature of healthy aging, but we have shown that it also characterizes presymptomatic FTD, over and above the age effects in their other family members, despite widespread progressive atrophy. The multivariate approach reveals two key findings: (1) stronger within-network and weaker between-network functional connectivity is associated with better cognition, more strongly in presymptomatic carriers than in age-matched non-carriers, and (2) as carriers approach their estimated age of symptom onset, and atrophy becomes evident, the maintenance of good cognition is increasingly associated with sustaining balance of within- and between-network integration.

This balance of within- and between-network connectivity is characteristic of segregated and specialized network organization of brain systems. Such functional segregation varies with physiological aging,^{17,18,43} with cognitive function,¹⁸ and in individuals at risk for AD.⁴⁴ Graph-theoretic quantification of network organization confirms the relevance of modularity and efficiency to function in FTD.¹⁶ Conversely, the loss of neural systems' modularity mirrors the loss of functional specialization with age⁴⁵ and dementia.⁴⁴ Here, we show the significance of the maintenance of this functional network organization, with a progressively stronger correlation with cognitive performance as seemingly healthy adults approach the age of expected onset of FTD.

The uncoupling of brain function from brain structure indicates that there may be independent and synergistic effects of multiple factors leading to cognitive preservation. This is consistent with a previous work in healthy aging where brain activity and connectivity provide independent and synergistic predictions of performance across the lifespan.¹⁹ Therefore, future studies need to consider the independent and synergistic effects of many possible biomarkers, based on MRI, computed tomography, positron emission tomography, CSF, blood, and brain histopathology. For example, functional network impairment may be related to tau expression and tau pathology, amyloid load, or neurotransmitter deficits in neurodegenerative diseases, independent of atrophy.^{30,46–48} It is important to note that studies need to recognize the rich multivariate nature of cognition and of neuroimaging in order to improve stratification procedures, for example, based on integrative approaches that explain individual differences in cognitive impairment.^{30,49} On a clinical level, this may facilitate future studies to establish whether presymptomatic carriers who maintain such connectivity profiles and thereby neuropsychological function in the presence of atrophy may have a lower risk of progression and better prognosis—information that will be important for future trialists, patients, and carers.

We also recognize the difficulty in determining a unique contribution of each factor (eg, brain structure and brain function), given the increasing interaction between factors in advanced stages of disease.⁵⁰ This is further complicated by these alterations becoming irreversible with progression of neurodegeneration.⁵¹ This suggests that the critical interplay between multiple factors (including brain structure and function) may be better studied in the asymptomatic and preclinical stages as well as across the healthy lifespan, which could still be modifiable and their influences are likely to be more separable.

Our findings agree with the model of compensation in the presymptomatic and early phases of Huntington disease, where network coupling predicted better cognitive performance.⁵² In a recent longitudinal study, a non-linear concave-down pattern of both brain activity and behavior was present, despite a linear decline in brain volume over time.⁵³ Similar effects have been observed also in healthy aging and amnesic mild cognitive impairment, where greater connectivity with the default-mode network and weaker connectivity between default-mode network and dorsal-attention network was associated with higher cognitive status in both groups.⁵⁴ Network integrity may also play a role in compensatory mechanisms in non-cognitive symptoms, such as motor impairment in Parkinson disease.⁵⁵ Accordingly, increased network efficiency and connectivity have been shown in prodromal phases, followed by decreased local connectivity in symptomatic phases, suggesting the emergence and dissipation of neural compensation.⁵⁶

The current study has several limitations. First, despite the large size of the overall GENFI cohort, we did not analyze each genetic group separately. The subdivision of each clinical group (PSC, NC) by three genes would have led to small and unbalanced subgroups, lowering statistical power and robustness. Moreover, genetic FTD is also characterized by multiple mutations within *MAPT* and *GRN*, and pleiotropy of clinical phenotypes from the same mutation.¹⁰ Pleiotropy of clinical phenotype is avoided by the study of presymptomatic carriers, but we cannot rule out pleiotropy of intermediate phenotypes expressed as say neural network diversity. In FTD as in other dementias, clinical heterogeneity is modified by environmental factors such as education (which may be a surrogate of cognitive reserve^{12,57}). In addition, our analysis included the estimated age at onset in some models, but we recognize that the precision of the estimated years at onset (based on family history of onset) varies across mutations and families,^{7,58} being highest for *MAPT* and low for *C9orf72* expansion. Genetic modifiers such as *TMEM106B*⁵⁹ and *APOE*⁶⁰ have also been identified. Further work with larger cohorts is required to test for gene-specific effects, and the role of environmental and genetic moderators on the relationships between brain structure, functional networks, and cognition. The harmonization of sequences and data acquisition protocols in this multi-site neuroimaging study aimed to reduce the susceptibility to systematic differences across scanning platforms, but residual site variance cannot be ruled out.^{38,61} The inclusion of study site as a covariate of no interest⁶¹ and the nature of our multivariate approach to identify shared signals between brain and behavioral data reduce residual effects of scanner variance.^{38,62} Future studies may use alternative brain measures that reflect differences in cortical surface and thickness estimates,^{63,64} or which infer neural connectivity directly from neurophysiology or from the separation of neurovascular from neuronal contributors to blood oxygen level-dependent (BOLD) fMRI variance,^{18,65} given the confounding effects of age, drug, or disease on neurovascular signals.^{66,67}

The current study is cross-sectional. Therefore, we cannot infer longitudinal progression within subjects as the unambiguous cause of the effects we observe in relation to expected years of onset. Accumulating evidence suggests that network integrity serves to maintain performance with either physiological ageing or pathological conditions.

However, longitudinal mediation studies and pharmacological or electroceutical interventions would be needed to prove its causal role in cognitive preservation. Finally, our findings are limited to autosomal dominant FTD, which represents a minority of FTD: Generalization to sporadic forms of disease would be speculative.

In conclusion, we used a multivariate data-driven approach to demonstrate that brain functional integrity may facilitate presymptomatic carriers to maintain cognitive performance in the presence of progressive brain atrophy for years before the onset of symptoms. The multivariate approach to cognition and brain function is well-suited to address the effects of multiple interacting risk factors on biomarkers of the progression of neurodegeneration, ahead of clinical conversion to dementia. The approach and our findings have implications for the design of presymptomatic disease-modifying therapy trials, which are likely to rely initially on surrogate markers of brain health rather than clinical end points.

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CONFLICT OF INTEREST

There were no financial or other conflicts of interest requiring declaration.

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APPENDIX

List of other GENFI consortium members

Sónia Afonso - Instituto Ciencias Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal

Maria Rosario Almeida - Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal

Sarah Anderl-Straub - Department of Neurology, Ulm University, Ulm, Germany

Christin Andersson - Medical Psychology, Karolinska University hospital-Solna, Stockholm Sweden

Anna Antonell - Alzheimer's disease and other cognitive disorders unit, Neurology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques, Barcelona, Spain

Silvana Archetti - Biotechnology Laboratory, Department of Diagnostics, Spedali Civili Hospital, Brescia, Italy

Andrea Arighi - Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy

Mircea Balasa - Alzheimer's disease and other cognitive disorders unit, Neurology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques, Barcelona, Spain

Myriam Barandiaran - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain

Nuria Bargalló - Radiology Department, Image Diagnosis Center, Hospital Clínic and Magnetic Resonance Image core facility, IDIBAPS, Barcelona, Spain

Robert Bartha - Department of Medical Biophysics, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada

Benjamin Bender - Department of Diagnostic and Interventional Neuroradiology, University of Tuebingen, Tuebingen, Germany

Luisa Benussi - Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Valentina Bessi - Department of Neuroscience, Psychology, Drug Research, and Child Health, University of Florence, Florence, Italy

Giuliano Binetti - Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Sandra Black - LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, Toronto, Canada

Martina Bocchetta - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square London, UK

Sergi Borrego-Ecija - Alzheimer's disease and other cognitive disorders unit, Neurology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques, Barcelona, Spain

Jose Bras - Dementia Research Institute, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Rose Bruffaerts - Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium

Paola Caroppo - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

David Cash - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Miguel Castelo-Branco - Neurology Department, Centro Hospitalar e Universitário de Coimbra, Instituto de Ciências Nucleares Aplicadas à Saúde (ICNAS), Coimbra, Portugal

Rhian Convery - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Thomas Cope - Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK

Maura Cosseddu - Centre for Neurodegenerative Disorders, Neurology Unit, Spedali Civili Hospital, Brescia, Italy

María de Arriba - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain

Giuseppe Di Fede - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

Zigor Díaz - CITA Alzheimer, San Sebastian, Spain

Katrina M Moore - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Diana Duro - Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal

Chiara Fenoglio - University of Milan, Centro Dino Ferrari, Milan, Italy

Camilla Ferrari - Department of Neuroscience, Psychology, Drug Research, and Child Health, University of Florence, Florence, Italy

Carlos Ferreira - Instituto Ciências Nucleares Aplicadas à Saúde, Universidade de Coimbra, Coimbra, Portugal

Catarina B. Ferreira - Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Toby Flanagan - Faculty of Biology, Medicine and Health, Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK

Nick Fox - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Morris Freedman - Division of Neurology, Baycrest Centre for Geriatric Care, University of Toronto, Toronto, Canada

Giorgio Fumagalli - Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

Alazne Gabilondo - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain

Roberto Gasparotti - Neuroradiology Unit, University of Brescia, Brescia, Italy

Serge Gauthier - Department of Neurology and Neurosurgery, McGill University, Montreal, Québec, Canada

Stefano Gazzina - Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Giorgio Giaccone - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

Ana Gorostidi - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain

Caroline Greaves - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square London, UK

Rita Guerreiro - Dementia Research Institute, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

Carolin Heller - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Tobias Hoegen - Department of Neurology, Ludwig-Maximilians-University of Munich, Munich, Germany

Begoña Indakoetxea - Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain

Vesna Jelic - Division of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden, Theme Aging, Karolinska University Hospital-Huddinge, Sweden

Lize Jiskoot - Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands

Hans-Otto Karnath - Section of Neuropsychology, Department of Cognitive Neurology, Center for Neurology & Hertie-Institute for Clinical Brain Research, Tübingen, Germany

Karolinska Institutet - Department NVS, Center for Alzheimer Research, Division of Neurogenetics, Stockholm, Sweden and Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital-Solna, Stockholm, Sweden

Ron Keren - University Health Network Memory Clinic, Toronto Western Hospital, Toronto, Canada

Tobias Langheinrich - Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK

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 Department, Hospital Clinic, Institut d'Investigacions Biomèdiques, Barcelona, Spain

Gemma Lombardi - Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

Sandra Loosli - Department of Neurology, Ludwig-Maximilians-University of Munich, Munich, Germany

Carolina Maruta - Lisbon Faculty of Medicine, Language Research Laboratory, 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, The Netherlands

Sara Mitchell - LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, Toronto, Canada

Benedetta Nacmias - Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

Mollie Neason - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Jennifer Nicholas - Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

Jaume Olives - Alzheimer's disease and other cognitive disorders unit, Neurology Department, Hospital Clinic, Institut d'Investigacions Biomèdiques, Barcelona, Spain

Alessandro Padovani - Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Jessica Panman - Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands

Janne Pappa - Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands

Irene Piaceri - Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence

Michela Pievani - Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Yolande Pijnenburg - VUMC, Amsterdam, The Netherlands

Cristina Polito - Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Florence, Italy

Enrico Premi - Stroke Unit, Neurology Unit, Spedali Civili Hospital, Brescia, Italy

Sara Prioni - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

Catharina Prix - Department of Neurology, Ludwig-Maximilians-University Munich, Germany

Rosa Rademakers - Department of Neurosciences, Mayo Clinic, Jacksonville, Florida, USA

Veronica Redaelli - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, Italy

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

Pedro Rosa-Neto - Translational Neuroimaging Laboratory, McGill University Montreal, Québec, Canada

Giacomina Rossi - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milan, 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 Universitário de Coimbra, Coimbra, Portugal

Elio Scarpini - University of Milan, Centro Dino Ferrari, Milan, Italy; Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy

Sonja Schönecker - Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany

Elisa Semler - Department of Neurology, Ulm University, Ulm, Germany

Rachelle Shafei - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK

Christen Shoosmith - Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

Miguel Tábuas-Pereira - Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal

Mikel Tainta - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, 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 - University Health Network Memory Clinic, Toronto Western Hospital, Toronto, Canada

David L Thomas - Neuroradiological Academic Unit, UCL Institute of Neurology, 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 - University of Cambridge, Cambridge, UK

Pietro Tiraboschi - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milano, Italy

Philip Vandamme - 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 - University of Oxford, UK

Ana Verdelho - Department of Neurosciences, Santa Maria Hospital, University of Lisbon, Portugal

Jorge Villanua - OSATEK Unidad de Donostia, San Sebastian, Gipuzkoa, Spain

Jason Warren - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK.

Carlo Wilke - Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany.

Ione Woollacott - Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK.

Elisabeth Wlasich - Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany.

Henrik Zetterberg - Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK.

Miren Zulaica - Neuroscience Area, Biodonostia Health Research Institute, Paseo Dr Begiristain sn, CP 20014, San Sebastian, Gipuzkoa, Spain.