RESEARCH ARTICLE OPEN ACCESS

Frequency and Longitudinal Course of Behavioral and Neuropsychiatric Symptoms in Participants With Genetic Frontotemporal Dementia

Sonja Schönecker, MD, Francisco J. Martinez-Murcia, PhD, Jannis Denecke, MSc, Nicolai Franzmeier, PhD, Adrian Danek, MD, Olivia Wagemann, MD, Catharina Prix, MD, Elisabeth Wlasich, Mag. rer. nat, Jonathan Vöglein, MD, Sandra V. Loosli, PhD, Anna Brauer, Juan-Manuel Górriz Sáez, PhD, Arabella Bouzigues, MSc, Lucy L. Russell, PhD, Phoebe H. Foster, BSc, Eve Ferry-Bolder, John C. van Swieten, MD, PhD, Lize C. Jiskoot, PhD, DClinPsy, Harro Seelaar, MD, PhD, Raquel Sanchez-Valle, MD, PhD, Robert Laforce, Jr., MD, PhD, Caroline Graff, MD, PhD, Daniela Galimberti, PhD, Rik Vandenberghe, MD, PhD, Alexandre de Mendonça, MD, PhD, Pietro Tiraboschi, MD, Isabel Santana, MD, PhD, Alexander Gerhard, MRCP, MD, Sandro Sorbi, PhD, Markus Otto, MD, Florence Pasquier, MD, PhD, Simon Ducharme, MD, Christopher Butler, FRCP, PhD, Isabelle Le Ber, MD, PhD, Elizabeth Finger, MD, Maria Carmela Tartaglia, MD, Mario Masellis, MD, PhD, James B. Rowe, FRCP, PhD, Matthis Synofzik, MD, Fermin Moreno, MD, PhD, Barbara Borroni, MD, Jonathan D. Rohrer, FRCP, PhD, for the Genetic Frontotemporal Dementia Initiative (GENFI), Josef Priller, MD, Günter U. Höglinger, MD, and Johannes Levin, MD

Correspondence
Dr. Levin
johannes.levin@med.uni-muenchen.de

Neurology® 2024;103:e209569. doi:10.1212/WNL.0000000000209569

Abstract

Background and Objectives

Behavioral and neuropsychiatric symptoms are frequent in patients with genetic frontotemporal dementia (FTD). We aimed to describe behavioral and neuropsychiatric phenotypes in genetic FTD, quantify their temporal association, and investigate their regional association with brain atrophy.

Methods

We analyzed data of pathogenic variant carriers in the chromosome 9 open reading frame 72 (*c9orf72*), progranulin (*GRN*), or microtubule-associated protein tau (*MAPT*) gene from the Genetic Frontotemporal dementia Initiative cohort study that enrolls both symptomatic pathogenic variant carriers and first-degree relatives of known carriers. Principal component

From the Department of Neurology (S. Schönecker, A.D., O.W., C.P., E.W., J.V., S.V.L., A. Brauer, G.U.H., J.L.), LMU University Hospital, LMU Munich, Germany; Department of Signal Theory Networking and Communications (F.J.M.-M., J.-M.G.S.), Andalusian Research Institute in Data Science and Computational Intelligence (DasCI), University of Granada, Spain; Institute for Stroke and Dementia Research (J.D., N.F.), LMU University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy) (N.F., G.U.H., J.L.), Germany; Institute of Neuroscience and Physiology and Department of Psychiatry and Neurochemistry (N.F.), The Sahlgrenska Academy, University of Gothenburg, Mölndal and Gothenburg, Sweden; German Center for Neurodegenerative Diseases (DZNE) (J.V., G.U.H., J.L.), Munich, Germany; Dementia Research Centre (A. Bouzigues, L.L.R., P.H.F., E.F.-B., J.D.R.), Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom; Department of Neurology (J.C.v.S., L.C.J., H.S.), Erasmus Medical Centre, Rotterdam, the Netherlands; Alzheimer's disease and Other Cognitive Disorders Unit (R.S.-V.), Neurology Service, Hospital Clínic, Institut d'Investigacións Biomèdiques August Pi I Sunyer, University of Barcelona, Spain; Clinique Interdisciplinaire de Mémoire (R.L.), Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, Canada; Department of Neurobiology, Care Sciences and Society (C.G.), Center for Alzheimer Research, Division of Neurogeriatrics, Bioclinium, Karolinska Institutet; Unit for Hereditary Dementias (C.G.), Theme Inflammation and Aging, Karolinska University Hospital, Solna, Sweden; Fondazione Ca' Granda (D.G.), IRCCS Ospedale Policlinico, Milan; Centro Dino Ferrari (D.G.), University of Milan, Italy; Laboratory for Cognitive Neurology (R.V.), Department of Neurosciences, KU Leuven; Neurology Service (R.V.), University Hospitals Leuven; Leuven Brain Institute (R.V.), KU Leuven, Belgium; Faculty of Medicine (A.d.M.), University of Lisbon, Portugal; Fondazione IRCCS Istituto Neurologico Carlo Besta (P.T.), Milano, Italy; University Hospital of Coimbra (HUC) (I.S.), Neurology Service, Faculty of Medicine, and Center for Neuroscience and Cell Biology (I.S.), Faculty of Medicine, University of Coimbra, Portugal; Division of Psychology Communication and Human Neuroscience Wolfson Molecular Imaging Centre (A.G.), University of Manchester, United Kingdom; Department of Nuclear Medicine (A.G.), Center for Translational Neuro- and Behavioral Sciences, University Medicine Essen; Department of Geriatric Medicine (A.G.), Klinikum Hochsauerland, Arnsberg, Germany; Department of Neurofarba (S. Sorbi), University of Florence; IRCCS Fondazione Don Carlo Gnocchi (S. Sorbi), Florence, Italy; Department of Neurology (M.O.), University of Ulm, Germany; Univ Lille (F.P.); Inserm 1172 (F.P.), Lille; CHU (F.P.), CNR-MAJ, Labex Distalz, LiCEND Lille, France; Department of Psychiatry (S.D.), McGill University Health Centre, and McConnell Brain Imaging Centre (S.D.), Montreal Neurological Institute, McGill University, Montreal, Québec, Canada; Nuffield Department of Clinical Neurosciences (C.B.), Medical Sciences Division, University of Oxford; Department of Brain Sciences (C.B.), Imperial College London, United Kingdom; Sorbonne Université (I.L.B.), Paris Brain Institute, Institut du Cerveau, ICM, Inserm U1127, CNRS UMR 7225, Centre de Référence des Démences Rares ou Précoces (I.L.B.), IM2A, and Département de Neurologie (I.L.B.), AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; Department of Clinical Neurological Sciences (E.F.), University of Western Ontario, London; Tanz Centre for Research in Neurodegenerative Diseases (M.C.T.), and Sunnybrook Health Sciences Centre (M.M.), Sunnybrook Research Institute, University of Toronto, Ontario, Canada; Department of Clinical Neurosciences (J.B.R.), MRC Cognition and Brain Sciences Unit, and Cambridge University Hospitals NHS Trust, University of Cambridge, United Kingdom; Department of Neurodegenerative Diseases (M.S.), Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen; Center for Neurodegenerative Diseases (DZNE) (M.S.), Tübingen, Germany; Cognitive Disorders Unit (F.M.), Department of Neurology, Donostia Universitary Hospital; Neuroscience Area (F.M.), Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain; Neurology Unit (B.B.), Department of Clinical and Experimental Sciences, University of Brescia, Italy; and Department of Psychiatry and Psychotherapy (J.P.), Technical University Munich, Germany.

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The Article Processing Charge was funded by the authors.

Coinvestigators are listed at Neurology.org/N.

Glossary

c9orf72 = chromosome 9 open reading frame 72; **EYO** = estimated years to symptom onset; **FTD** = frontotemporal dementia; **GENFI** = Genetic Frontotemporal dementia Initiative; **GLME** = generalized linear mixed effects; **GRN** = progranulin; **LME** = linear mixed effects; ***MAPT*** = microtubule-associated protein tau; **MDS** = multidimensional scaling; **PCA** = principal component analysis.

analysis was performed to identify behavioral and neuropsychiatric clusters that were compared with respect to frequency and severity between groups. Associations between neuropsychiatric clusters and MRI-assessed atrophy were determined using voxel-based morphometry. We applied linear mixed effects and generalized linear mixed effects models to assess the longitudinal course of symptoms.

Results

A total of 522 participants were included: 221 *c9orf72* (138 presymptomatic), 213 *GRN* (157 presymptomatic), and 88 *MAPT* (62 presymptomatic) pathogenic variant carriers. Principal component analysis revealed 5 phenotypic clusters (67.6% of variance), labeled diverse behavioral, affective, psychotic, euphoric/hypersexual, and tactile hallucinations phenotype. In participants presenting behavioral or neuropsychiatric symptoms, affective symptoms were most frequent across groups (83.6%–88.1%), followed by diverse behavioral symptoms (68.4%–77.9%). In *c9orf72* and *GRN* pathogenic variant carriers, psychotic symptoms (32.0% and 19.4%, respectively) were more frequent than euphoric/hypersexual symptoms (28.7% and 14.2%, respectively), which was the other way around in *MAPT* pathogenic variant carriers (28.6% and 23.8%). Although diverse behavioral symptoms were associated with gray and white matter frontotemporal atrophy, only a small atrophy cluster in the right thalamus was associated with psychotic symptoms. Euphoric/hypersexual symptoms were associated with atrophy in mesial temporal lobes, basal forebrain structures, and the striatum ($p < 0.05$). Estimated time to symptom onset, genetic group, education, and sex influenced behavioral and neuropsychiatric symptoms ($p < 0.05$). Particularly, in *c9orf72* pathogenic variant carriers, psychotic symptoms may be starting decades before recognition of onset of illness.

Discussion

We identified multiple clusters of behavioral and neuropsychiatric symptoms in participants with genetic FTD that relate to distinct cerebral atrophy patterns. Their severity depends on time, affected gene, sex, and education. These clinical-genetic associations can guide diagnostic evaluations and the design of clinical trials for new disease-modifying and preventive treatments.

Introduction

Frontotemporal dementia (FTD) refers to a heterogenous group of neurodegenerative diseases. It is the second most common cause of dementia in patients below the age of 65 years[1] and is highly heritable, with approximately 30% of cases being familial and 10%–20% showing an autosomal dominant mode of inheritance.[2,3] Most genetic cases are caused by pathogenic variants in 1 of 3 genes: chromosome 9 open reading frame 72 (*c9orf72*),[4] progranulin (*GRN*),[5] and microtubule-associated protein tau (*MAPT*).[6]

The behavioral variant of FTD is the most common clinical subtype and occurs in about half of all patients with FTD. It is characterized by disinhibition, apathy, loss of empathy, compulsive behaviors, hyperorality, and a dysexecutive neuropsychological profile.[7] However, other behavioral and neuropsychiatric symptoms may be present as well.[8] Owing to these symptoms, patients with FTD are frequently misdiagnosed with depression, bipolar disorder, or schizophrenia.[9] Compared with other dementia syndromes, patients with FTD have the highest risk to be misdiagnosed as having a primary psychiatric disorder.[8,9]

Because of the clinical heterogeneity, a precise knowledge of clinical presentations correlated with genetic subgroups is essential to guide diagnostic work-up and assist in decision-making regarding genetic testing. It will also become increasingly important because disease-modifying drug trials are underway in each of the genetic FTD groups.[10-12]

We aimed to describe behavioral and neuropsychiatric phenotypes in genetic FTD, from the Genetic Frontotemporal dementia Initiative (GENFI), using a data-driven approach. GENFI is a longitudinal deep-phenotyping study of members of families affected by familial FTD, including carriers of pathogenic variants in these 3 genes.[13] We examined behavioral and neuropsychiatric symptom occurrence in the course of the disease, including the phase before clinically recognized manifestation of disease (the "presymptomatic" phase), and tested whether structural brain changes are associated with behavioral or neuropsychiatric symptoms.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was performed according to the Declaration of Helsinki (1991). Ethical approval has been obtained at the coordinating site at University College London and all participating centers. Written informed consent was obtained from every participant.

Participants

To assess behavioral and neuropsychiatric symptoms in genetic FTD, we analyzed baseline and follow-up data of pathogenic variant carriers using Data Freeze 5 from the GENFI multicenter cohort study, gathered between January 20, 2012, and May 30, 2019. GENFI includes research centers across Europe and Canada (genfi.org) and enrolls both symptomatic patients with FTD in whom a pathogenic variant in *c9orf72*, *GRN*, or *MAPT* has been detected as well as participants who are at risk of carrying a pathogenic variant because a first-degree relative was a known carrier.[13] A pathogenic *c9orf72* expansion was defined as more than 30 hexanucleotide repeats.

Participants underwent a standardized clinical assessment consisting of medical history, family history, and physical examination at baseline and during follow-up examinations. Participants not yet demonstrating clear evidence of clinically significant cognitive, behavioral, or motor symptoms were classified as presymptomatic. Age, education, Mini-Mental State Examination, and estimated years to symptoms onset (EYO) defined as the difference between the participant current age and the mean familial age at symptoms onset[13] were assessed.

Assessment of Behavioral and Neuropsychiatric Symptoms

The presence and severity of the following behavioral and neuropsychiatric symptoms was assessed through the GENFI neuropsychiatric symptom scale and the GENFI behavioral symptom scale[14] performed with the participant and carer: disinhibition, apathy, loss of sympathy/empathy, ritualistic/compulsive behavior, hyperorality and appetite changes, poor response to social/emotional cues, inappropriate trusting behavior, visual hallucinations, auditory hallucinations, tactile hallucinations, delusions, depression, anxiety, irritability, lability, agitation/aggression, euphoria/elation, aberrant motor behavior, hypersexuality, hyperreligiosity, impaired sleep, and altered sense of humor. Severity of symptoms was scored as follows: score 0 = symptoms absent, score 0.5 = questionable/very mild symptoms, score 1 = mild symptoms, score 2 = moderate symptoms, and score 3 = severe symptoms (eTable 1).

MRI Acquisition and Analysis

T1-weighted MRI scans were available in 436 of 522 participants at baseline. MRIs were acquired on 3T scanners with a 1.1 mm isotropic resolution (GE SIGNA, Philips Achieva, Siemens Trio, Siemens Prisma, Siemens Skyra). Acquisition protocols were synchronized across scanners and sites.[13]

Scans were analyzed using SPM12 (version 7219)[15] and CAT12 (version 12.8.1 r2043)[16] in MATLAB (MathWorks, Natick, MA). Native-space images were segmented into white matter, gray matter, and CSF probability maps and nonlinearly normalized to Montreal Neurological Institute space using the CAT12 preprocessing and segmentation pipeline.[16] For voxel-based morphometry analyses, Jacobian modulation was included and spatial smoothing was applied using a full width at half maximum 8 mm Gaussian Kernel to minimize intersubject anatomical differences. Study-specific gray and white matter masks were created by thresholding the average probability maps at 0.5. Statistical analyses were confined to voxels within these tissue-type–specific masks. Images were visually quality controlled based on the CAT12 report and checked for normalization by overlaying a mask outline of the template. Images with failed registration, aberrant movement, strong Gibbs ringing, prior stroke lesions, or cysts were excluded.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows (version 28.0; IBM Corp., Armonk, NY). Nondichotomized mean scores of demographic data were compared through Kruskal-Wallis and post hoc Bonferroni corrected Mann-Whitney *U* tests. χ^2 tests were used to check for significant differences in dichotomized variables. The standard statistical significance level was set at $p < 0.05$.

To identify symptom clusters, we applied principal component analysis (PCA) with varimax rotation. Variables with factor loadings above 0.4 were considered as part of a cluster. Components were labeled *post hoc* according to the pattern of symptoms. No a priori assumptions regarding the clustering of symptoms were applied. To visualize the similarity of variables assigned to a specific component, multidimensional scaling (MDS) using Euclidian distance was performed. To visualize possible gene-clustering between the phenotype clusters, a between-cases MDS was performed. The variance in each dimension was calculated, and a Levene's test was performed to assess possible inequality of variances.

We calculated sum scores from the variables of each component to test for gene-specific differences of symptoms. Sum scores at baseline were compared through Kruskal-Wallis and *post hoc* Bonferroni-corrected Mann-Whitney tests.

As tactile hallucinations have been described to be more frequent with increasing severity of parkinsonian features, we assessed for each phenotype the correlation with progressive supranuclear palsy-like, Parkinson disease-like, and corticobasal syndrome-like signs[17] by applying Spearman's tests.

To assess the proportion of the predominant phenotype of participants with behavioral or neuropsychiatric symptoms depending on the underlying pathogenic variant, cases were assigned to the component with the highest PCA-based sum score.

We assessed for each component the association between sum scores and patterns of gray and white matter atrophy using voxelwise linear regression, controlling for age, sex, education, handedness, and study site. T-maps were thresholded at a family-wise error-corrected α of 0.05.

We applied hierarchical modeling, namely, linear mixed effects (LME) and generalized linear mixed-effects (GLME) models,[18] to describe the evolution of sum scores of pathogenic variant carrier groups. We used 2-part models that were composed of a GLME binomial model for the presence/absence of symptomatology for each sum score and an LME for the evolution of participants presenting positive sum scores. In each case, we tested several models including random intercepts per participant to account for the longitudinal evolution of the participants.[13] Random intercepts per family and site were tested. Fixed effect variables included EYO, pathogenic variant carrier group, education, sex, and the interaction of EYO with pathogenic variant carrier group and sex, respectively. Given the exponential nature of the sum score aggregation of symptoms, a logarithmic transformation of the sum score response was applied, leading to nonlinear time dependence. Higher order contributions and other quadratic or exponential transformations of this and other variables showed no improvement of the model in terms of the Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

We applied a Wald χ^2 test to the model to assess whether the estimated coefficients for the fixed variables were statistically significant for each of the 5 sum scores. A 3-way empirical significance was estimated from a Monte Carlo sampling of the models for each sum score[19] every 5 years to identify each sign's degree of differentiation and controlling all other variables. As an indicator of the point in time at which symptoms start to increase, the time at which the lower 95% CI crosses 0 on the x-axis was used. We also reported the evolution of showing symptoms for a given phenotype over EYO through statistical testing of the GLME model, reporting Šidák-Holm–adjusted *p*-values. These analyses were performed using R 3.6.3.

Data Availability

Data will be shared according to the GENFI data-sharing agreement, after review by the GENFI data access committee with final approval granted by the GENFI steering committee.

Results

Demographics

A total of 522 participants, including 221 *c9orf72*, 213 *GRN*, and 88 *MAPT* pathogenic variant carriers, were included in the analysis (Table 1). *MAPT* pathogenic variant carriers were significantly younger compared with *c9orf72* and *GRN* pathogenic variant carriers at baseline. The proportion of presymptomatic participants was lower in *c9orf72* compared with *GRN* pathogenic variant carriers. Follow-up duration was significantly longer in *MAPT* compared with *c9orf72* pathogenic variant carriers. Groups did not differ in education, sex, MMSE, and EYO.[13,20]

Principal Component Analysis and Multidimensional Scaling

PCA with varimax rotation revealed the presence of 5 components with eigenvalues above 1 explaining 67.6% of

Table 1 Demographics of the Study Sample

	C9orf72 (n = 221)	*GRN* (n = 213)	*MAPT* (n = 88)	*p* Value
Follow-up 1	122/221[c]	118/213[c]	62/88[a,b]	0.032
Follow-up 2	44/221[b,c]	75/213[a]	40/88[a]	<0.001
Follow-up 3	19/221	31/213	11/88	0.150
Follow-up 4	0/221	3/213	1/88	0.221
Follow-up duration, mo	12.0 (13.3)[c]	14.3 (15.0)	17.7 (14.0)[a]	0.006
Baseline				
Age, y	51.2 (13.6)[c]	51.0 (13.6)[c]	45.3 (13.1)[a,b]	0.001
Education, y	13.9 (3.2)	13.9 (3.7)	14.1 (3.3)	0.765
Sex, female/male	113/108	129/84	48/40	0.139
EYO, y	−7.3 (13.3)	−9.7 (13.5)	−7.5 (13.1)	0.116
Symptoms, presymptomatic/symptomatic	138/83[b]	157/56[a]	62/26	0.037
MMSE	27.2 (4.7)	26.9 (6.0)	27.4 (5.1)	0.201

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; EYO = estimated years to symptom onset; *MAPT* = microtubule-associated protein tau; MMSE = Mini-Mental State Examination.
Significantly different compared with [a]*c9orf72*, [b]*GRN*, [c]*MAPT*.

Table 2 Rotated Component Matrix

	Component				
	Diverse behavioral phenotype	Affective phenotype	Psychotic phenotype	Euphoric/hypersexual phenotype	Tactile hallucinations phenotype
Poor response to social/emotional cues	0.882	0.138	0.158	0.118	−0.003
Loss of sympathy/empathy	0.858	0.170	0.253	0.091	−0.005
Apathy	0.818	0.245	0.207	0.044	−0.012
Ritualistic/compulsive behavior	0.804	0.173	0.103	0.142	0.108
Hyperorality and appetite changes	0.771	0.196	0.148	0.326	−0.089
Inappropriate trusting behavior	0.725	0.012	0.115	0.368	0.022
Disinhibition	0.714	0.139	0.157	0.408	0.096
Aberrant motor behavior	0.671	0.156	0.202	0.035	0.240
Altered sense of humor	0.601	0.063	0.125	0.507	−0.208
Agitation/aggression	0.502	0.377	−0.099	0.297	0.207
Depression	0.032	0.818	0.140	−0.032	−0.090
Anxiety	0.176	0.754	0.151	0.057	0.067
Impaired sleep	0.220	0.697	0.103	0.154	0.075
Irritability/lability	0.403	0.590	−0.055	0.243	0.173
Auditory hallucinations	0.162	0.080	0.832	−0.053	0.024
Visual hallucinations	0.194	0.075	0.787	0.040	0.044
Delusions	0.242	0.149	0.681	0.314	0.156
Hyperreligiosity	0.114	0.139	0.445	0.357	−0.195
Euphoria/elation	0.344	0.111	0.085	0.768	0.059
Hypersexuality	0.151	0.095	0.093	0.702	0.139
Tactile hallucinations	0.077	0.096	0.075	0.105	0.892

variance. The variables group in the components as follows (Table 2):

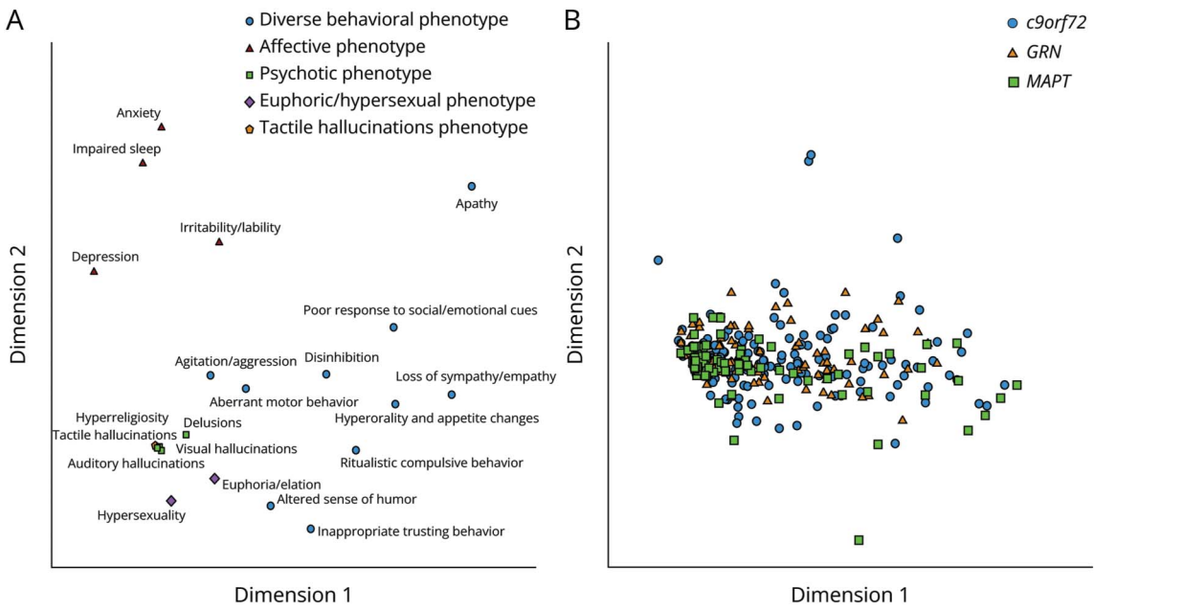
1. Poor response to social/emotional cues, loss of sympathy/empathy, apathy, ritualistic/compulsive behavior, hyperorality and appetite changes, inappropriate trusting behavior, disinhibition, aberrant motor behavior, altered sense of humor, and agitation/aggression, we call this the diverse behavioral phenotype.
2. Depression, anxiety, impaired sleep, and irritability/lability, we call this the affective phenotype.
3. Auditory hallucinations, visual hallucinations, delusions, and hyperreligiosity, we call this the psychotic phenotype.
4. Euphoria/elation and hypersexuality, we call this the euphoric/hypersexual phenotype.
5. Tactile hallucinations, we call this the tactile hallucinations phenotype.

MDS confirmed the grouping of variables as reasonable (normalized raw stress 0.008) (Figure 1A). A between cases MDS (normalized raw stress 0.008) was performed (Figure 1B). The Levene's test detected significant inequality of variances in both dimensions ($p < 0.001$) with highest variances in dimension 1 in *MAPT* and highest variances in dimension 2 in *c9orf72* pathogenic variant carriers.

Severity and Frequency of Behavioral and Neuropsychiatric Symptoms

The Kruskal-Wallis test detected significant group differences of sum scores of the diverse behavioral, psychotic, euphoric/hypersexual, and tactile hallucinations phenotype with *c9orf72* pathogenic variant carriers showing significantly higher sum scores compared with *GRN* pathogenic variant carriers at baseline (Figure 2A). No significant group differences could be detected regarding the severity of affective symptoms. However, sum scores were highest in *c9orf72* and lowest in *GRN* pathogenic variant carriers.

Figure 1 Multidimensional Scaling of Behavioral and Neuropsychiatric Symptoms and Genetic Cases, Respectively



(A) Two-dimensional spatial representation based on the similarity of variables as revealed by MDS. Variables that have been assigned to a specific phenotype by PCA are color-coded. (B) Two-dimensional spatial representation based on the similarity of cases as revealed by MDS. Cases are color-coded according to the affected gene. *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; MDS = multidimensional scaling; PCA = principal component analysis.

When looking at the group of participants showing behavioral or neuropsychiatric symptoms at baseline, significant differences regarding the frequency of symptoms could be detected for the euphoric/hypersexual and tactile hallucinations phenotype (Figure 2B), with *c9orf72* pathogenic variant carriers showing a higher frequency of symptoms compared with *GRN* pathogenic variant carriers. When looking at the whole cohort (eFigure 1), chi-square analysis detected additional significant group differences regarding the frequency of symptoms of the diverse behavioral and psychotic phenotype with a significantly higher frequency of symptoms in *c9orf72* compared with *GRN* pathogenic variant carriers.

In participants showing behavioral or neuropsychiatric symptoms, affective symptoms were most frequent across groups (83.6%–88.1%), followed by diverse behavioral symptoms (68.4%–77.9%). In *c9orf72* and *GRN* pathogenic variant carriers, psychotic symptoms (32.0% and 19.4%, respectively) were more frequent compared with euphoric/hypersexual symptoms (28.7% and 14.2%, respectively). In *MAPT* pathogenic variant carriers, euphoric/hypersexual symptoms (28.6%) occurred more frequently than psychotic symptoms (23.8%). Tactile hallucinations were least common (0%–8.2%). This was the case in all genetic groups.

No significant correlations between behavioral and neuropsychiatric phenotypes and parkinsonian signs could be detected.

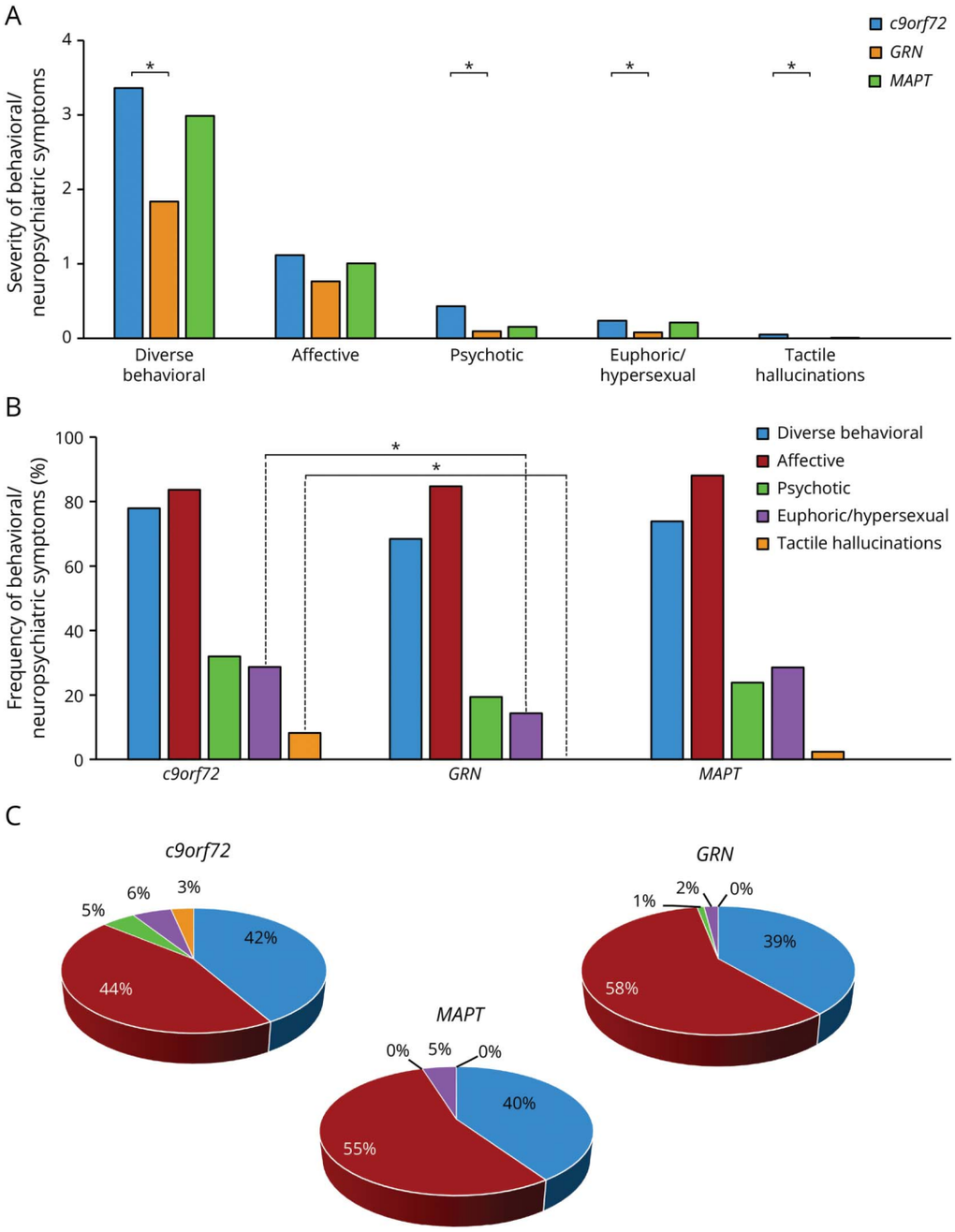
Predominance Phenotype

The frequency of the predominating phenotype did not differ significantly between groups (Figure 2C). A predominant affective phenotype was most common (44%–58%), followed by a diverse behavioral (39%–42%) and then a euphoric/hypersexual phenotype (2%–6%). Although a predominant psychotic phenotype was present in 5% of *c9orf72* and 1% of *GRN* pathogenic variant carriers, no *MAPT* pathogenic variant carrier showed predominant psychotic symptoms. Only in *c9orf72* pathogenic variant carriers, a predominant tactile hallucinations phenotype could be detected (3%), with 50% of these participants also exhibiting delusions, but none accompanying visual or auditory hallucinations.

Atrophy Patterns

Voxelwise regression revealed sum scores of the diverse behavioral phenotype to be associated with frontotemporal gray and white matter atrophy (Figure 3, eFigure 2). Only a small atrophy cluster correlating with sum scores of the psychotic phenotype in the right thalamus could be detected. Sum scores of the euphoric/hypersexual phenotype were associated with right greater than left atrophy in basal forebrain structures, the striatum, mesial temporal lobes and to a lesser extent with atrophy in the orbitofrontal cortex, the inferior, superior, and middle temporal lobe, the anterior cingulate cortex, and the inferior frontal gyrus. No atrophy cluster correlating with the affective or tactile hallucinations phenotype could be detected.

Figure 2 Severity and Frequency of Behavioral and Neuropsychiatric Symptoms and Proportion of the Dominant Clinical Phenotype Depending on the Affected Gene

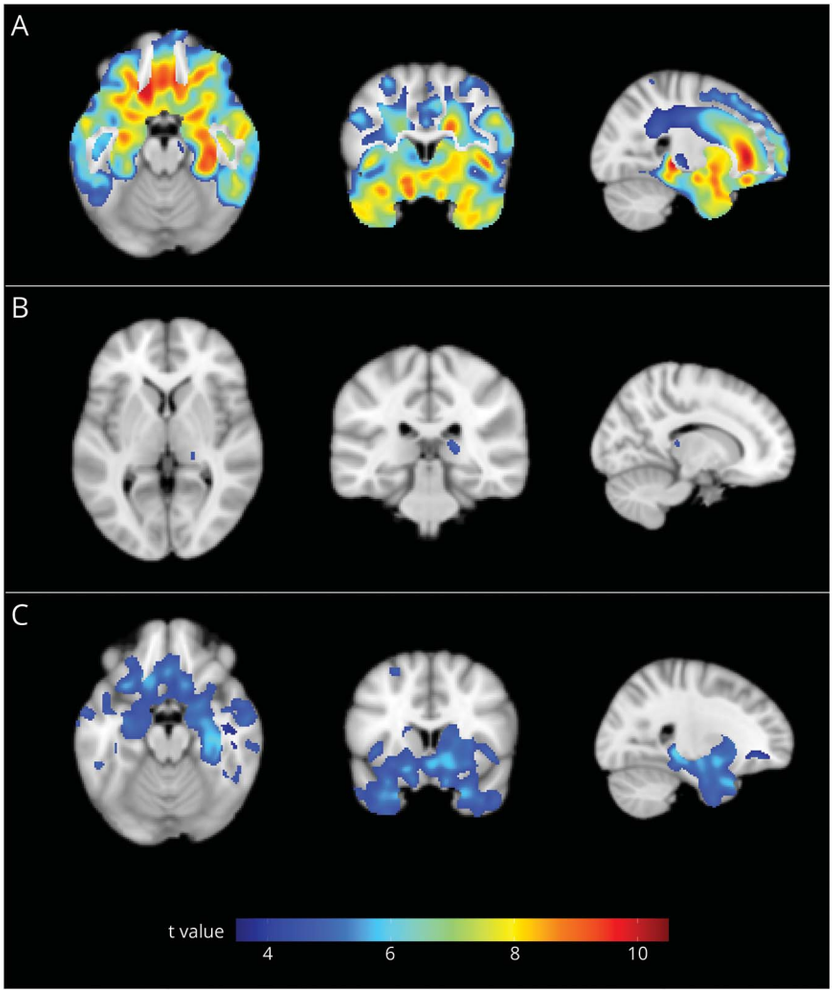


(A) Comparison of the severity of behavioral and neuropsychiatric symptoms as defined by the sum scores of the individual phenotypes according to the underlying pathogenic variant. (B) Comparison of the frequency of symptom occurrence between pathogenic variant carriers showing behavioral or neuropsychiatric symptoms. Patients may present symptoms of different behavioral or neuropsychiatric phenotypes. Therefore, the sum of frequencies does not add up to 100%. * indicates significant differences. (C) Cases were assigned to the component with the highest PCA-based sum score. As patients may present behavioral and neuropsychiatric symptoms of other phenotypes in addition to the symptoms of the predominating phenotype, Figure 2C is not congruent with Figure 2B.

Binomial Generalized Linear Mixed Model

The predicted probability of developing symptoms over EYO is depicted in Figure 4 (eTable 2). We noted a significant effect of EYO on the probability of developing symptoms of each phenotype and a significant effect of sex on the probability of developing diverse behavioral ($p < 0.05$) and euphoric/hypersexual ($p < 0.01$) symptoms. The pathogenic variant carrier group had a significant effect on the probability of developing psychotic, euphoric/hypersexual symptoms, and tactile hallucinations ($p < 0.05$). The interaction of EYO

Figure 3 Correlation of Sum Scores of Behavioral and Neuropsychiatric Phenotypes With Cerebral Atrophy Using Linear Regression Models



T-maps from the analysis of gray and white matter were merged for visualization purposes. (A) Diverse behavioral phenotype, (B) psychotic phenotype, and (C) euphoric/hypersexual phenotype.

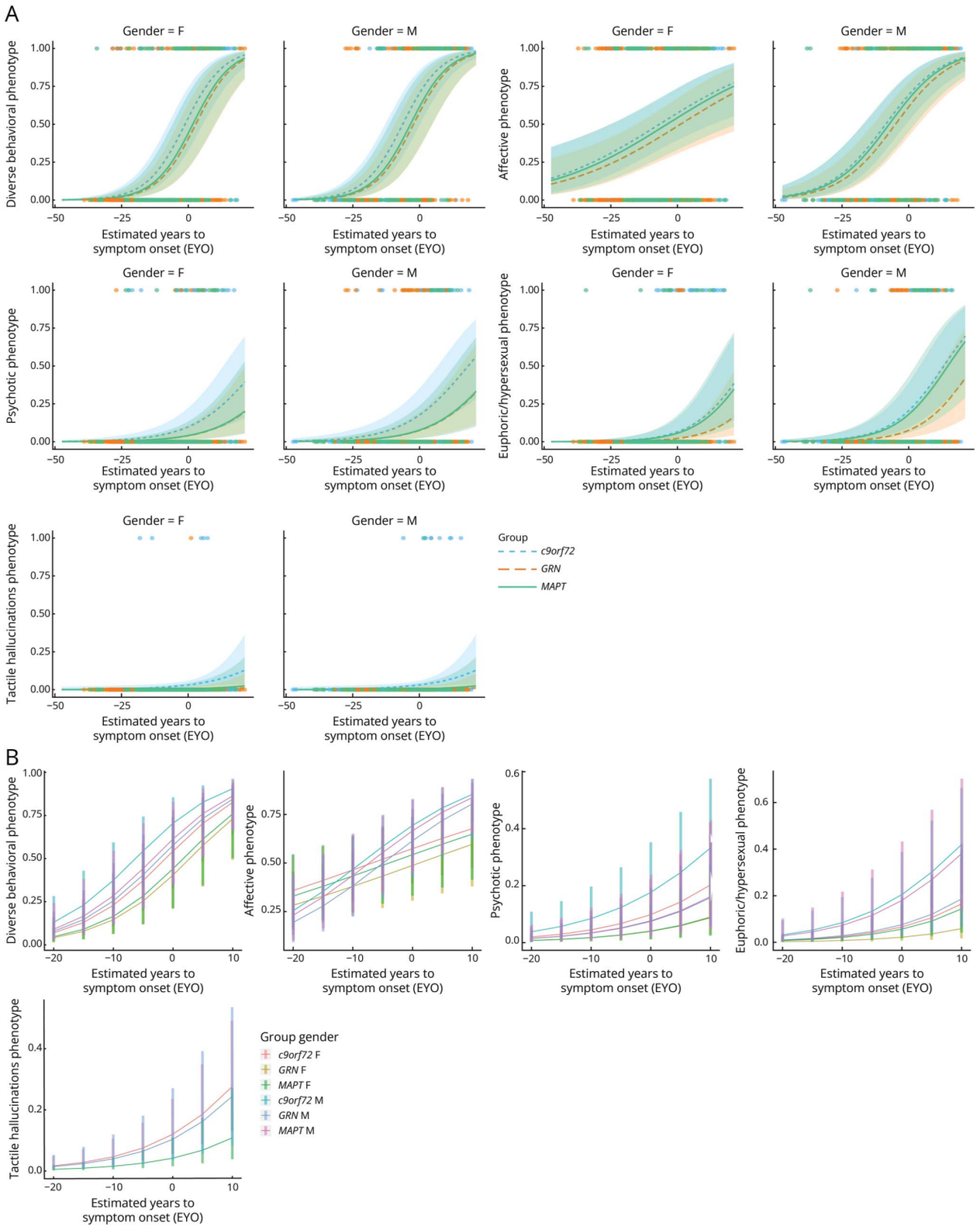
and sex significantly affected the probability of developing affective symptoms ($p < 0.05$).

LME Models

The distribution of log-transformed sum scores of participants developing symptoms over EYO is depicted in Figure 5 (eTable 3). Wald tests revealed a significant effect of EYO on the sum scores of the diverse behavioral ($p < 0.001$) and affective ($p = 0.001$) and a significant effect of education on the sum scores of the diverse behavioral ($p = 0.004$) and psychotic phenotype ($p < 0.05$). Sex had a significant effect on the diverse behavioral ($p = 0.007$) and pathogenic variant carrier group on the psychotic phenotype ($p < 0.05$). For the sum scores of the euphoric/hypersexual and the tactile hallucinations phenotype, no variable reached statistical significance.

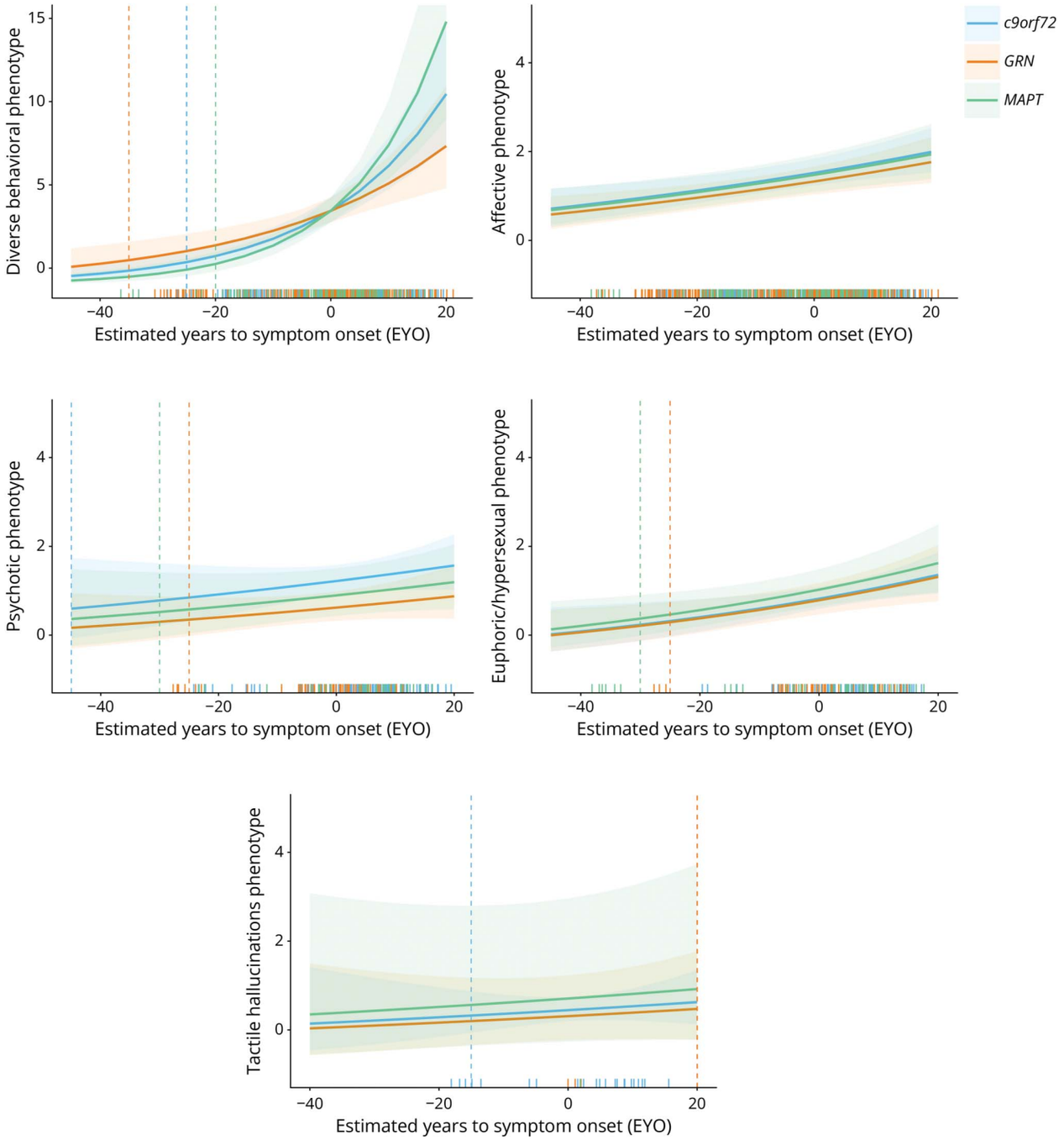
As a possible indicator of an increase of symptoms in participants developing the respective symptoms, we determined the point in time at which the lower 95% CI of the model crosses the x-axis. While the amount of affective symptoms was above 0 from the beginning, diverse behavioral symptoms started to increase up to 30 years before the estimated onset in male pathogenic variant carriers. Symptoms increased earliest in *GRN* followed by *c9orf72* and then *MAPT* pathogenic variant carriers. Psychotic symptoms increased earliest in male *c9orf72* (up to 40 years before the estimated onset) followed by *MAPT* and then *GRN* pathogenic variant carriers. By contrast, euphoric/hypersexual symptoms started earliest in male *MAPT* (35 years before the estimated onset) followed by *c9orf72* and *GRN* pathogenic variant carriers (30 years before the estimated onset). Diverse behavioral, psychotic, and euphoric/hypersexual symptoms started to increase about 10 years later in female compared with male pathogenic variant carriers. Although no clear onset of tactile hallucinations could be detected in *GRN* and *MAPT*, in *c9orf72* pathogenic variant carriers, an increase of symptoms could be detected up to 10 years before the estimated onset.

Figure 4 Predicted Probability of Developing Symptoms (With 95% CI) vs Estimated Years to Symptom Onset



(A) Predicted probability of developing symptoms of male and female participants separately. Individual data points are not plotted to prevent disclosure of genetic status. However, the time of the examination is marked on the x-axis by a colored dash. (B) Overlay of the probability of the 3 genetic variant career groups and of male and female participants in each group of developing symptoms.

Figure 5 Calculated Sum Scores (With 95% CI) vs Estimated Years to Symptom Onset



Given the exponential nature of the sum score aggregation of symptoms, a logarithmic transformation of the sum score response was applied. The point in time at which the lower 95% CI crosses the x-axis is marked by a vertical bar in the respective color for each group. Individual data points are not plotted to prevent disclosure of genetic status. However, the time of the examination is marked on the x-axis by a colored dash.

While the sum scores of the diverse behavioral phenotype were initially highest in *GRN* followed by *c9orf72* pathogenic variant carriers, the amount of symptoms increased mostly in *MAPT* pathogenic variant carriers over time. At an EYO of 0, sum scores were almost the same across groups. Fifteen years later sum scores were significantly higher in *MAPT* compared with *GRN* pathogenic variant carriers. As LME was performed on longitudinal data of participants developing the respective behavioral or neuropsychiatric symptom, the results are not in contradiction with the results regarding the severity of symptoms at baseline. According to the model, sum scores of the affective phenotype were significantly higher in *c9orf72*

and *MAPT* compared with *GRN* pathogenic variant carriers already 45, respectively, 30 years before the estimated onset and remained lowest in *GRN* pathogenic variant carriers. Forty-five years before the estimated onset, we noted significantly higher sum scores of the psychotic phenotype in *c9orf72* compared with *GRN* pathogenic variant carriers and significantly higher sum scores of the euphoric/hypersexual phenotype in *MAPT* compared with *c9orf72* and *GRN* pathogenic variant carriers. We noted no significant group differences of tactile hallucinations.

Discussion

We present a data-driven approach to demonstrate the phenotypic range of behavioral and neuropsychiatric symptoms and their association with time and cerebral atrophy in participants with genetic FTD. PCA confirmed the presence of 5 clusters of behavioral and neuropsychiatric symptoms, namely, a diverse behavioral, affective, psychotic, euphoric/hypersexual, and tactile hallucinations phenotype.

Except for affective symptoms which were most frequent in *MAPT* pathogenic variant carriers, the prevalence and severity of symptoms was highest in *c9orf72* followed by *MAPT* pathogenic variant carriers. Affective symptoms were frequent across all groups and represented the most common predominating phenotype. This agrees with previous studies showing a high frequency of depression and anxiety in patients with genetic FTD[14,21] and corresponds to the fact that the most common misdiagnosis in patients with FTD is major depressive disorder.[9] Diverse behavioral symptoms were frequent across groups and were slightly more frequent at baseline in *c9orf72* pathogenic variant carriers. However, the frequency of a predominating diverse behavioral phenotype was similar between groups. As expected,[22,23] psychotic symptoms were most frequent in *c9orf72* pathogenic variant carriers. Previous studies reported a high prevalence of psychotic symptoms reaching up to 60% in late presentations of FTD in *c9orf72* pathogenic variant carriers,[24] presenting with bizarre somatic and persecutory delusions and multimodal hallucinations. We were able to add to these data an early occurrence of psychotic symptoms in *c9orf72* pathogenic variant carriers, already in the presymptomatic phase. Unfortunately, however, we have no information regarding the exact nature of delusions presented in our cohort. The high prevalence of psychotic symptoms in *c9orf72* pathogenic variant carriers aligns with studies indicating a higher risk of psychiatric disorders, including schizophrenia, late-onset psychosis unrelated to schizophrenia and autism spectrum disorders, among kindreds of *c9orf72* pathogenic variant carriers,[25] and has recently led to the proposal of including psychotic symptoms into a clinical rating scale, expanding on the CDR framework as the CDR-plus-NACC FTLD-N[14] (Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behaviour and Language Domains) to improve accuracy of rating disease stage. In our study, the symptoms euphoria/elation and hypersexuality grouped in one component. Data on sexual function in FTD are limited. Previous reports have described heightened sexual activity in 13%[26] to 17%[27] of patients with FTD which is comparable with our results (11.7% in the whole cohort). Besides hypersexuality, hyposexual behavior seems to be frequent in patients with FTD.[28] Clinicians may not routinely enquire about sexual function; therefore, the number of patients with FTD showing changes in sexual function may be higher. Tactile hallucinations were rare across all groups.[29,30] Of interest, they did not group with the other psychotic symptoms. This may be due to differing neuroanatomical correlates.

Psychotic symptoms and tactile hallucinations were most frequent in *c9orf72* pathogenic variant carriers and rare in *GRN* and *MAPT* pathogenic variant carriers. Only 1% of *GRN* and none of the *MAPT* pathogenic variant carriers exhibited predominating psychotic symptoms, and in neither group, predominating tactile hallucinations could be detected. The presence of predominant psychotic symptoms or tactile hallucinations therefore almost excludes the presence of these pathogenic variants.

Although an extensive phenotypic variability is known across the investigated pathogenic variants,[17,31] the between cases MDS demonstrates tightly overlapping phenotype clusters, albeit with higher variance in *MAPT* and *c9orf72* pathogenic variant carriers and a more consistent syndrome for *GRN* pathogenic variant carriers. This is reflected by the higher severity of symptoms in *c9orf72* and *MAPT* pathogenic variant carriers.

In agreement with the concept that the anatomical distribution of pathologic brain changes determines the clinical phenotype,[32] we demonstrated robust clinical-anatomic correlations. Although diverse behavioral symptoms were associated with widespread frontotemporal atrophy,[3,33] only a small atrophy cluster associated with sum scores of the psychotic phenotype located in the right thalamus could be detected. Previous studies demonstrated a correlation of psychotic symptoms with thalamic atrophy in patients with FTD.[21,23] The thalamus seems to be preferentially affected in *c9orf72* pathogenic variant carriers,[34,35] possibly explaining the higher prevalence of psychotic symptoms. A previous study from the GENFI cohort demonstrated associations of visual hallucinations, auditory hallucinations, and delusions with specific atrophy patterns, but mainly in *GRN* pathogenic variant carriers.[21] The differing association of psychotic symptoms with regional brain atrophy in our cohort may be due to the joint analysis of psychotic symptoms and the pooled analysis of pathogenic variant carrier groups.

Euphoric/hypersexual symptoms were associated with right-sided atrophy in basal forebrain structures, the striatum and mesial temporal lobes. This is consistent with a previous case series showing right-sided greater than left-sided frontotemporal atrophy with prominent right temporolimbic

involvement in patients with FTD demonstrating hypersexual behavior.[26] Neuroimaging studies in healthy controls suggest an involvement of brain areas related to reward processing, including the striatum, mesial temporal lobe, and anterior cingulate cortex in sexual arousal.[36] Euphoric/hypersexual symptoms were comparatively common in *MAPT* pathogenic variant carriers. The observed association of euphoric/hypersexual symptoms and atrophy in basal forebrain structures may therefore stem from the higher prevalence of basal forebrain atrophy in *MAPT* pathogenic variant carriers described in previous studies.[37] Regarding the affective and tactile hallucinations phenotype, no significant associations with cerebral atrophy could be detected. Previous studies suggested major depressive and anxiety disorders to be caused by the interaction of multiple brain regions[38] and described gray matter volume reductions in frontolimbic and cerebellar regions in major depressive disorder and of frontotemporal regions in anxiety disorders.[39] However, a study on genetic FTD demonstrated distinct anatomical correlates of mood disorders.[21] Although in *c9orf72* pathogenic variant carriers, frontal, parietal, and cerebellar atrophy correlated with mood disorders, in *GRN* pathogenic variant carriers, mood disorders were associated with atrophy in the frontoinsular cortex, precuneus and posterior cingulate cortex, and in *MAPT* pathogenic variant carriers, depression and anxiety were associated with atrophy in the temporoparietal cortex. This differing distribution of neurodegeneration could have obscured groupwise atrophy patterns in our cohort. The lack of atrophy patterns correlating with tactile hallucinations may be due to the small number of participants reporting them (n = 11).

Previous studies in genetic FTD described changes in neuropsychological measures and structural imaging 5–10[13] and of motor signs up to 25 years before the expected onset.[17] We added to these data an early occurrence of behavioral and neuropsychiatric, especially psychotic symptoms in *c9orf72* pathogenic variant carriers which may be starting decades before the expected onset. Previous studies have shown that especially young patients with FTD showing psychotic symptoms are frequently misdiagnosed as having a primary psychiatric disorder.[9,29] Owing to the possible early onset of psychotic symptoms, a diagnosis of FTD and further genetic testing should also be considered in young patients demonstrating psychotic symptoms.

No clear onset could be detected regarding affective symptoms. This is probably due to the high frequency of affective symptoms in the general population. The lifetime prevalence of major depressive and anxiety disorders is reported to range between 10% and 34%.[40,41] Previous studies have shown a higher rate of mood and anxiety disorders in women, which is consistent with the higher probability of showing affective symptoms in women in our cohort 50 to 10 years before EYO. In contrast to the general population, the prevalence of affective symptoms increased over time. In our cohort, the probability of showing affective symptoms shows a sigmoid curve in men with a steep increase approximately 10 years before EYO, which suggests a disease-related increase of symptomatology.

We identified an effect of sex on the probability and severity of diverse behavioral and euphoric/hypersexual symptoms with symptoms occurring later in women. This is in line with a previous study showing a higher behavioral and executive reserve in female patients with FTD[42] and the higher prevalence of the behavioral variant of FTD in men.[43-46] Female patients are more frequently diagnosed with primary progressive aphasia. Considering the opposite prevalence of behavioral variant FTD and primary progressive aphasia, a sex-specific vulnerability to neurodegeneration for women in left frontotemporal regions and men in right frontal and/or bilateral temporal regions has been proposed.[45,46]

Previous studies indicated higher education to be associated with higher resilience of cognitive performance relative to a given level of neurodegeneration.[47,48] Most studies investigated the association with global cognitive function. In our study, a significant effect of education on the course of behavioral and psychotic symptoms in participants with genetic FTD could be detected, suggesting education to represent a potentially modifiable risk factor.

Besides the high number of participants with genetic FTD included in the analysis, the identification of natural clusters of symptoms by PCA represents a key strength of our study. Applying a data-driven approach allows for an objective analysis that does not follow classical clinical concepts and is not influenced by a priori assumptions.

A limitation of the study is the lack of comparison with healthy controls. However, the primary aim was to compare behavioral and neuropsychiatric symptoms and their development over time between the different pathogenic variant carrier groups. Another limitation is the method used for estimation of EYO. There is a significant correlation between an individual's age and mean familial age at onset for *MAPT* pathogenic variants, this correlation is weak for *c9orf72* and *GRN* such that EYO becomes a surrogate of age.[20] Furthermore, we acknowledge the lack of comparison with biofluid biomarkers. Serum and CSF TDP-43 levels have been shown to be decreased in *c9orf72* pathogenic variant carriers and to correlate with behavioral signs and signs of motor neuron disease. Given the high prevalence of psychotic symptoms among *c9orf72* pathogenic variant carriers, these might also be associated with reduced TDP-43 levels.[49] Furthermore, as plasma p-tau 181 is known to be elevated in *MAPT* pathogenic variant carriers,[50] an association with affective symptoms which were most frequent in this pathogenic variant carrier group seems conceivable. Other nonspecific biomarkers such as neurofilament light chain or t-tau that correlates with disease severity in FTD may show an association with neuropsychiatric symptoms and might furthermore aid in discriminating FTD and primary psychiatric disorders. Future studies will be needed to investigate associations of neuropsychiatric symptoms with biofluid biomarkers

according to each underlying proteinopathy. In addition, research regarding the association of psychotic symptoms with psychiatric diseases within the family and a more detailed analysis of psychotic modalities is of interest.

Keeping these limitations in mind, our data reveal the presence of 5 natural clusters of behavioral and neuropsychiatric symptoms in participants with genetic FTD, correlating with cerebral atrophy. Their severity increases over time and depends on the affected gene, sex, and education. The emergence of behavioral and neuropsychiatric symptoms occurs in what is otherwise regarded as the presymptomatic phase, before clinical manifestation of illness onset is recognized. Given the heterogeneity of signs and symptoms and phenotypic overlap, these clinical-genetic associations will help clinicians in their diagnostic work-up, assist in decision-making regarding genetic testing, and the design of preventive and disease-modifying treatments.

Acknowledgment

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

Study Funding

This work is co-funded by the UK Medical Research Council (MR/M023664/1), Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy ID 390857198), the Italian Ministry of Health, 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 and the Bluefield Project, as well as a JPND grant "GENFIprox." Nonfinancial support was also provided through the European Reference Network for Rare Neurological Diseases (ERN-RND), one of 24 ERNs funded by the European Commission (ERNRND: 3HP 767231). JGS was supported by the Ministerio de Ciencia e Innovación (España)/FEDER under the RTI2018-098913-B100 project and the Consejería de Economía, Innovación, Ciencia y Empleo (Junta de Andalucía) and FEDER under the CV20-45250 and A-TIC-080-UGR18 projects. MM was also funded by a Canadian Institutes of Health Research operating grant (MOP 327387) and funding from the Weston Brain Institute. J.B. Rowe was funded from the Welcome Trust (103838; 220258), the Medical Research Council (MC_UU_00030/14; SUAG/051 G101400), and the National Institute for Health Research Cambridge Biomedical Research Centre (NIHR203312: BRC-1215-20014). F.J. Martinez-Murcia received grant RYC2021-030875-I funded by MCIN/AEI/10.13039/501100011033 and the European Union Nex GenerationEU/PRTR.

Disclosure

S. Schönecker, F.J. Martinez-Murcia, J. Denecke, N. Franzmeier, A. Danek, O. Wagemann, C. Prix, E. Wlasich, J. Vöglein, S.V. Loosli, A. Brauer, J.-M. Górriz Sáez, A. Bouzigues, L.L. Russell, P.H. Foster, E. Ferry-Bolder, J.C. van Swieten, L.C. Jiskoot, H. Seelaar, R. Laforce, C. Graff, D. Galimberti, R. Vandenberghe, A. de Mendonça, P. Tiraboschi, I. Santana, A. Gerhard, S. Sorbi, M. Otto, F. Pasquier, C.R. Butler, I. Le Ber, E. Finger, M.C. Tartaglia, M. Masellis, J.B. Rowe, F. Moreno, J.D. Rohrer, J. Priller, and G.U. Höglinger report no disclosures relevant to the manuscript. S. Ducharme receives salary funding from the Fonds de Recherche du Québec-Santé, is involved with sponsored research (Biogen, Ionis Pharmaceuticals, Wave Life Sciences, Janssen), advisory boards (Biogen, Eisai, QuRALIS), has received speaking honorarium (Eisai), and is the co-founder of AFX Medical Inc. R. Sanchez-Valle has served in Advisory board meetings for Wave Life Sciences, Ionis, and Novo Nordisk and received personal fees for participating in educational activities from Janssen, Roche Diagnostics, and Neuroxpharma and funding to her institution for research projects from Biogen and Sage Pharmaceuticals. B. Borroni has served at scientific boards for Denali, Wave, Alector, and Aviadobio. M. Synofzik has received consultancy honoraria from Janssen Pharmaceuticals, Ionis Pharmaceuticals, and Orphazyme Pharmaceuticals, all unrelated to the present manuscript. J. Levin reports speaker fees from Bayer Vital, Biogen, and Roche, consulting fees from Axon Neuroscience and Biogen, author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers. In addition, he reports compensation for serving as a chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH, and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 21, 2023. Accepted in final form June 3, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix 1 Authors

Name	Location	Contribution
Sonja Schönecker, MD	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Francisco J. Martinez-Murcia, PhD	Department of Signal Theory Networking and Communications, Andalusian Research Institute in Data Science and Computational Intelligence (DasCI), University of Granada, Spain	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Jannis Denecke, MSc	Institute for Stroke and Dementia Research, LMU University Hospital, LMU Munich, Germany	Analysis or interpretation of data

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Nicolai Franzmeier, PhD	Institute for Stroke and Dementia Research, LMU University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy), Germany; Institute of Neuroscience and Physiology and Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy, University of Gothenburg, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Adrian Danek, MD	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Olivia Wagemann, MD	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Catharina Prix, MD	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Elisabeth Wlasich, Mag. rer. nat	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Jonathan Vöglein, MD	Department of Neurology, LMU University Hospital, LMU Munich; German Center for Neurodegenerative Diseases (DZNE), Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Sandra V. Loosli, PhD	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Anna Brauer	Department of Neurology, LMU University Hospital, LMU Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Juan-Manuel Górriz Sáez, PhD	Department of Signal Theory Networking and Communications, Andalusian Research Institute in Data Science and Computational Intelligence (DasCI), University of Granada, Spain	Drafting/revision of the manuscript for content, including medical writing for content
Arabella Bouzigues, MSc	Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lucy L. Russell, PhD	Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Phoebe H. Foster, BSc	Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Eve Ferry-Bolder	Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
John C. van Swieten, MD, PhD	Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lize C. Jiskoot, PhD, DClinPsy	Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Harro Seelaar, MD, PhD	Department of Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Raquel Sanchez-Valle, MD, PhD	Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacións Biomèdiques August Pi I Sunyer, University of Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Robert Laforce, Jr., MD, PhD	Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Caroline Graff, MD, PhD	Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Bioclinium, Karolinska Institutet; Unit for Hereditary Dementias, Theme Inflammation and Aging, Karolinska University Hospital, Solna, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Daniela Galimberti, PhD	Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milan; Centro Dino Ferrari, University of Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Rik Vandenberghe, MD, PhD	Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven; Neurology Service, University Hospitals Leuven; Leuven Brain Institute, KU Leuven, Belgium	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Appendix 1 *(continued)*

Name	Location	Contribution
Alexandre de Mendonça, MD, PhD	Faculty of Medicine, University of Lisbon, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Pietro Tiraboschi, MD	Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Isabel Santana, MD, PhD	University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra; Center for Neuroscience and Cell Biology, Faculty of Medicine, University of Coimbra, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexander Gerhard, MRCP, MD	Division of Psychology Communication and Human Neuroscience Wolfson Molecular Imaging Centre, University of Manchester, United Kingdom; Department of Nuclear Medicine, Center for Translational Neuro- and Behavioral Sciences, University Medicine Essen; Department of Geriatric Medicine, Klinikum Hochsauerland, Arnsberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sandro Sorbi, PhD	Department of Neurofarba, University of Florence; IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Markus Otto, MD	Department of Neurology, University of Ulm, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Florence Pasquier, MD, PhD	Univ Lille; Inserm 1172, Lille; CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Simon Ducharme, MD	Department of Psychiatry, McGill University Health Centre, and McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Québec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christopher Butler, FRCP, PhD	Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford; Department of Brain Sciences, Imperial College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Isabelle Le Ber, MD, PhD	Sorbonne Université, Paris Brain Institute, Institut du Cerveau, ICM, Inserm U1127, CNRS UMR 7225, Centre de Référence des Démences Rares ou Précoces, IM2A, and Département de Neurologie, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Elizabeth Finger, MD	Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Maria Carmela Tartaglia, MD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mario Masellis, MD, PhD	Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
James B. Rowe, FRCP, PhD	Department of Clinical Neurosciences, MRC Cognition and Brain Sciences Unit, and Cambridge University Hospitals NHS Trust, University of Cambridge, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Matthis Synofzik, MD	Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen; Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Fermin Moreno, MD, PhD	Cognitive Disorders Unit, Department of Neurology, Donostia Universitary Hospital; Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Barbara Borroni, MD	Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jonathan D. Rohrer, FRCP, PhD	Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Josef Priller, MD	Department of Psychiatry and Psychotherapy, Technical University Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Günter U. Höglinger, MD	Department of Neurology, LMU University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Johannes Levin, MD	Department of Neurology, LMU University Hospital, LMU Munich; Munich Cluster for Systems Neurology (SyNergy); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at Neurology.org/N.

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