Cognitive Composites for Genetic Frontotemporal Dementia: GENFI-Cog

Jackie M. Poos
Erasmus Medical Center: Erasmus MC https://orcid.org/0000-0001-8843-7247
Katrina M. Moore
UCL Institute of Neurology: UCL Queen Square Institute of Neurology
Jennifer Nicholas
London School of Hygiene & Tropical Medicine
Lucy L. Russell
UCL Institute of Neurology: UCL Queen Square Institute of Neurology
Georgia Peakman
UCL Institute of Neurology: UCL Queen Square Institute of Neurology
Rhian S. Convery
UCL Institute of Neurology: UCL Queen Square Institute of Neurology
Lize C. Jiskoot
Erasmus Medical Center: Erasmus MC
Emma L. van der Ende
Erasmus Medical Center: Erasmus MC
Esther van den Berg
Erasmus Medical Center: Erasmus MC
Janne M. Papma
Erasmus Medical Center: Erasmus MC
Harro Seelaar
Erasmus Medical Center: Erasmus MC
Yolande A.L. Pijnenburg
Amsterdam University Medical Centres: Amsterdam Universitair Medische Centra
Fermin Moreno
Donostia Ospitalea: Hospital Universitario de Donostia
Raquel Sanchez-Valle
University of Barcelona: Universitat de Barcelona
Barbara Borroni
University of Brescia: Universita degli Studi di Brescia
Robert Laforce
Université Laval: Universite Laval
Mario Masellis

University of Toronto

Carmela Tartaglia

University of Toronto

Caroline Graff

Karolinska University Hospital: Karolinska Universitetssjukhuset

Daniela Galimberti

University of Milan–Bicocca: Universita degli Studi di Milano-Bicocca

James Rowe

University of Cambridge

Elizabeth Finger

University of Western Ontario: Western University

Matthis Synofzik

University Hospital Tübingen Center of Neurology: Universitatsklinikum Zentrum fur Neurologie

Rik Vandenberghe

KU Leuven: Katholieke Universiteit Leuven

Alexandre Mendonça

University of Lisbon: Universidade de Lisboa

Pietro Tiraboschi

Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta: Fondazione IRCCS Istituto Neurologico Carlo Besta

Isabel Santana

University of Coimbra: Universidade de Coimbra

Simon Ducharme

McGill University

Chris Butler

University of Oxford

Alexander Gerhard

University of Manchester Institute of Brain

Johannes Levin

Ludwig-Maximilians-Universitat Munchen

Adrian Danek

Ludwig-Maximilians-Universitat Munchen

Markus Otto

University of Ulm: Universitat Ulm

Isabel Le Ber

Sorbonne Université: Sorbonne Universite

Florence Pasquier

University of Lille: Universite de Lille

John C. van Swieten

Erasmus Medical Center: Erasmus MC

Jonathan D. Rohrer (j.rohrer@ucl.ac.uk)

UCL Institute of Neurology: UCL Queen Square Institute of Neurology

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Research Article

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Abstract

Background: Clinical endpoints for upcoming therapeutic trials in frontotemporal dementia (FTD) are increasingly urgent. Cognitive composite scores are often used as endpoints but are lacking in genetic FTD. We aimed to create cognitive composite scores for genetic frontotemporal dementia (FTD) and recommend on recruitment and duration in clinical trial design.

Methods: A standardized neuropsychological test battery covering six cognitive domains was completed by 69 *C9orf72*, 41 *GRN*, and 28 *MAPT* mutation carriers with CDR® plus NACC-FTLD≥0.5 and 275 controls. Logistic regression was used to identify the combination of tests that distinguished best between each mutation carrier groups and controls. The composite scores were calculated from the weighted averages of test scores in the models based on the regression coefficients. Sample size estimates were calculated for individual cognitive tests and composites in a theoretical trial aimed at preventing progression from a prodromal stage (CDR® plus NACC-FTLD 0.5) to a fully symptomatic stage (CDR® plus NACC-FTLD ≥1). Time-to-event analysis was performed to determine how quickly mutation carriers progressed from CDR® plus NACC-FTLD=0.5 to ≥1 (and therefore how long a trial would need to be).

Results: Results from the logistic regression analyses resulted in different composite scores for each mutation carrier group. The estimated sample size to detect a treatment effect was lower for composite scores than for most individual tests. A Kaplan-Meier curve showed that after three years ~50% of individuals had converted from CDR® plus NACC-FTLD 0.5 to ≥1.

DISCUSSION: We created gene-specific cognitive composite scores for *C9orf72, GRN* and *MAPT* mutation carriers, which resulted in substantially lower estimated sample sizes to detect a treatment effect than the individual cognitive tests. The GENFI-Cog composites have potential as cognitive endpoints for upcoming clinical trials. The results from this study provide recommendations for estimating sample size and trial duration.

Background

Frontotemporal dementia (FTD) encompasses a heterogeneous group of early onset neurodegenerative disorders caused by prominent frontal and/or temporal lobe degeneration with a wide range of overlapping clinical features (1). The two main phenotypes are behavioural variant FTD (bvFTD), with prominent behavioural changes and executive dysfunction (2), and primary progressive aphasia (PPA), with impairment in language comprehension and/or production (3). FTD is a highly heritable disease, with 20–30% of cases having an autosomal dominant pattern of inheritance(4). The most common causes of genetic FTD are mutations in *MAPT*, *GRN*, and *C9orf72* genes (4).

Clinical trials testing disease-modifying treatments for FTD are now underway and clinical endpoints to monitor treatment response are therefore urgently needed. It is believed that interventions may have the most profound effect if initiated in the earliest stages of the disease, however, a major challenge facing

these clinical trials is the lack of outcome measures that are sensitive enough to track the effect of treatment in the early stages of the disease (5–7).

Traditional clinical outcomes such as progression to clinical diagnosis or cognitive outcome measures developed for Alzheimer's disease (AD) trials might not be well-suited to serve as endpoints for early-stage FTD treatment trials because of the large sample size and long trial duration that would be required to measure possible treatment effects or due to the psychometric properties of the tests themselves (8–10). Sensitive outcome measures in AD, such as the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), might not be sensitive to decline in FTD (10, 11). Multiple genetic FTD cohort studies have investigated a wide range of cognitive instruments and found gene-specific cognitive impairment and/or decline in language, executive function, social cognition, attention/mental processing speed and memory, in symptomatic and presymptomatic stages (12–27). However, due to the subtlety of cognitive decline in the early stages of the disease, using individual cognitive tests as outcome measure might not be sensitive enough to detect a treatment effect. Furthermore, an individual cognitive test is limited to measuring only one specific symptom and due to the heterogeneity of symptoms between FTD patients, tests from multiple cognitive domains would need to be included. A selection of the most sensitive tests for each genetic group would enable shortening of the neuropsychological test battery thereby significantly minimizing time and other resource costs compared to using a broad range of individual neuropsychological tests (28).

Composite scores are often used in clinical trials to reduce the number of variables used as outcome measures (8). A composite score is any measure which combines the results of multiple cognitive and clinical assessments into a single summary score (29). As a result, it provides a measure of multiple domains but can serve as a single primary endpoint in clinical trials (8). Such composites have been developed in several neurodegenerative disorders, such as AD (e.g. the ADAS-Cog (11)), Parkinson's disease (PD) (e.g. the Unified Parkinson's Disease Rating Scale (UPDRS (30))), and Huntington's disease (HD) (e.g. the Unified Huntington's Disease Rating Scale (UHDRS (29))), but are, as of yet, lacking in (genetic) FTD.

Therefore, the aim of this study was to create gene-specific cognitive composite scores for *MAPT*, *GRN* and *C9orf72* mutation carriers in the early symptomatic stage by empirically determining the combination of neuropsychological tests most sensitive to differentiate mutation carriers from non-carriers. Data was collected within the Genetic FTD Initiative (GENFI), an international genetic FTD cohort study aimed at developing novel markers of disease onset and progression (14). To evaluate their performance we compared sample size requirements between each of the proposed composites and individual cognitive tests for a theoretical trial aimed at preventing progression from a prodromal stage (CDR® plus NACC-FTLD (31) = 0.5) to a fully symptomatic stage (CDR® plus NACC-FTLD $\geq$ 1). Lastly, we performed time-to-event analyses to determine how many people progressed from a CDR® plus NACC FTLD 0.5 to $\geq$ 1, to provide recommendations on the duration of such clinical trials.

Methods

Participants

Data was included from the fifth GENFI data freeze in which participants from confirmed genetic FTD families were recruited between 30th January 2012 and 31th May 2019 in 24 centres across Europe and Canada. A total of 69 *C9orf72*, 41 *GRN* and 28 *MAPT* mutation carriers with a CDR® plus NACC FTLD ≥ 0.5 and 275 mutation negative controls (i.e. family members who tested negative for the mutation) were included in this study. Of the mutation carrier group, 41 *C9orf72*, 17 *GRN* and 16 *MAPT* mutation carriers fulfilled diagnostic criteria for bvFTD (2) (*C9orf72* = 36, *GRN* = 11, *MAPT* = 16), PPA (3) (*GRN* = 6) or FTD with amyotrophic lateral sclerosis (FTD-ALS) (32) (*C9orf72* = 5). Participant characteristics are summarized in Table 1.

Procedure

All participants completed a comprehensive neuropsychological test battery covering six cognitive domains: language (modified Camel and Cactus Test (33); Boston Naming Test (BNT, short 30 item version) (34); category fluency (animals) (35)), attention/processing speed and executive function (WMS-R Digit span (34); Trail Making Test (TMT)(36); WAIS-R Digit Symbol test (34); D-KEFS Color-Word Interference Test (CWIT) (37); phonemic fluency (35)); verbal and visuospatial memory (Free and Cued Selective Reminding Test (FCSRT) (20); Benson Figure recall), social cognition (Facial Emotion Recognition test (38)), and visuoconstruction (Benson Figure copy). The Mini-Mental State Examination (MMSE (39)) was administered to measure global cognitive functioning and clinical status was determined by means of a structured clinical interview, including the CDR® plus NACC FTLD (31).

Statistical methods

Statistical analyses were performed using Stata version 14 and R version 3.6.2. We compared continuous demographic data between mutation carrier groups with Kruskal-Wallis and post-hoc Mann-Whitney tests. A chi-square test was used to compare sex between groups.

All neuropsychological data were converted to Z-scores corrected for age, education and sex compared to controls. The FCSRT test scores were also corrected for language as the test was administered in different languages across the different GENFI sites. Z-scores for tests with reaction times (i.e. TMT and D-KEFS Color-Word Interference Test) were inversed so that lower Z scores indicated worse performance on all tests. A detailed description of how the corrected Z-scores were calculated can be found in Additional file 1.

Creating the composite scores

Least absolute shrinkage and selection operator (LASSO) (40) logistic regression models with 10-fold cross validation were used to identify the combination of neuropsychological tests that discriminated best between each mutation carrier group and controls. A separate model was fitted for each genetic group with carrier status as the outcome and the neuropsychological tests as the predictors. A detailed

description of the statistical methods can be found in the Appendix. The glmnet package in R was used to fit the LASSO models and carry out the cross-validation.

From the resulting model two different cognitive composite scores were calculated: (1) an average of the scores for all cognitive tests that were selected in the model; and (2) a weighted average of the scores for all cognitive tests that were selected in the model, using the regression coefficients to determine the weights.

Sample size calculation

For each outcome the sample size was calculated for a hypothetical two arm study with 1:1 randomization to placebo versus active drug with 80% power to detect a treatment effect at a 5% significance level. The focus of future studies is likely to be on treating people with very early symptomatic disease and so we focused on calculating sample sizes for a trial of prodromal mutation carriers (i.e. CDR® plus NACC FTLD = 0.5) where the therapeutic drug had an effect on the progression to being fully symptomatic (i.e. CDR® plus NACC FTLD = 1). We therefore calculated sample sizes for a 10%, 20% and 40% effect size where a 100% treatment effect would be the difference in mean between the CDR® plus NACC FTLD 0.5 and 1 groups. Choosing the effect size in this way assumes that the hypothetical treatment will prevent a given proportion of the decline in cognitive scores seen between these two groups. For example, a 20% treatment effect assumes that the untreated group will experience the change seen between CDR® plus NACC FTLD 0.5 and 1 groups but the treated group will only experience 80% of this change (i.e. 20% less). See Additional file 1 for more details on the sample size calculations.

Time-to-event analysis

To provide recommendations on the timeline for the hypothesized trial we present Kaplan-Meier curves showing the cumulative proportion of participants who progressed from a CDR® plus NACC FTLD 0.5 to ≥ 1 within the GENFI cohort over time. In this analysis the censoring date was the date of conversion or the date of last follow-up. There were 64 mutation carriers (21 *C9orf72*, 27 *GRN* and 16 *MAPT*) that had a CDR® plus NACC FTLD of 0.5 and one or multiple follow-up visits and were included in the time to event analysis (Fig. 1). A log rank test was performed to compare the rate of progression between genetic groups.

Results

Demographics

Participant characteristics for all mutation carriers are summarized in Table 1. Overall, the number of males to females differed between groups ($p = 0.020$). *C9orf72*, *GRN* and *MAPT* mutation carriers were older, had lower MMSE and higher CDR® plus NACC FTLD sum of boxes scores than controls (all $p < 0.010$). In addition, *C9orf72* mutation carriers had higher CDR® plus NACC FTLD sum of boxes scores than *GRN* mutation carriers ($p = 0.007$). There were no differences between groups in years of education

(p = 0.290). The characteristics of participants when individually stratified by CDR® plus NACC FTLD global score (i.e. in 0.5, 1, 2 and 3 groups) can be found in Additional file 1.

Table 1
Participant characteristics and neuropsychological test results.

	C9orf72	*GRN*	*MAPT*	Controls
Number of participants	69	41	28	275
Sex f:m	30:39	20:21	14:14	160:115
Age	55 (12.0)	53.0 (11.4)	51.1 (12.6)	45.8 (12.7)
Education	13.7 (3.1)	14.0 (3.5)	14.3 (3.4)	14.6 (3.4)
MMSE	27.1 (3.2)	26.6 (7.0)	27.5 (3.0)	29.3 (2.1)
CDR® plus NACC FTLD sob	5.9 (5.5)	3.4 (4.8)	4.8 (5.0)	0.2 (0.6)
Language				
Camel and Cactus Test	-1.81 (2.81)	-0.57 (1.36)	-2.10 (3.08)	-
Boston Naming Test	-1.77 (3.32)	-0.68 (1.62)	-2.63 (3.16)	-
Category fluency	-1.20 (1.05)	-0.54 (1.04)	-0.84 (1.14)	-
Attention and mental processing speed				
Digit span forward	-0.39 (1.19)	-0.08 (1.26)	0.13 (1.23)	-
Trail Making Test - part A	-1.37 (2.17)	-0.69 (1.63)	-0.72 (1.54)	-
Digit Symbol	-1.18 (1.30)	-0.62 (1.23)	-0.67 (1.31)	-
D-KEFS CWIT - color naming	-2.85 (3.58)	-0.52 (1.85)	-1.30 (2.17)	-
D-KEFS CWIT - word naming	-1.86 (3.11)	-0.02 (1.46)	-0.54 (1.47)	-
Executive function				
Digit span backward	-0.53 (1.23)	-0.49 (1.23)	-0.19 (0.98)	-
Trail Making Test - part B	-2.44 (2.95)	-1.81 (3.06)	-1.37 (2.58)	-
D-KEFS CWIT - ink naming	-3.46 (3.91)	-1.13 (2.21)	-1.16 (2.54)	-
Phonemic fluency	-1.18 (1.18)	-0.08 (1.33)	-0.64 (1.28)	-
Visuoconstruction				
Benson Figure copy	-0.90 (1.90)	-0.06 (1.16)	-0.46 (1.39)	-

Values are: mean Z-scores corrected for age, years of education and sex (standard deviation) unless otherwise specified. For the FCSRT an additional correction was made for language in which the test was administered. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; MMSE = Mini-Mental State Examination; CDR® plus NACC FTLD sob = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration sum of boxes; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

	C9orf72	*GRN*	*MAPT*	Controls
Memory				
Benson Figure recall	-0.72 (1.57)	-0.75 (1.46)	-1.27 (1.91)	-
FCSRT free recall	-1.68 (1.36)	-0.72 (1.49)	-1.71 (1.80)	-
FCSRT total recall	-2.20 (3.56)	-1.42 (3.05)	-2.86 (3.62)	-
FCSRT delayed free recall	-1.59 (1.59)	-0.97 (1.58)	-1.72 (2.04)	-
FCSRT delayed total recall	-2.10 (3.81)	-1.13 (3.09)	-2.82 (4.02)	-
Social cognition				
Facial Emotion Recognition Test	-1.67 (1.87)	-1.00 (1.47)	-1.04 (1.59)	-

Values are: mean Z-scores corrected for age, years of education and sex (standard deviation) unless otherwise specified. For the FCSRT an additional correction was made for language in which the test was administered. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; MMSE = Mini-Mental State Examination; CDR® plus NACC FTLD sob = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration sum of boxes; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

Logistic regression analyses

Results from the logistic regression model can be seen in Table 2. A combination of category fluency, D-KEFS CWIT – color, word and ink naming, TMT – part B, the Benson Figure copy, FCSRT free recall and the Facial Emotion Recognition Test was most sensitive to discriminate *C9orf72* repeat expansion carriers from controls. For *GRN* mutation carriers a combination of the Camel and Cactus Test, TMT – part B, D-KEFS CWIT – ink naming, Benson Figure recall, FCSRT total and delayed free recall and the Facial Emotion Recognition Test was most sensitive. In *MAPT* mutation carriers, a combination of the Camel and Cactus Test, BNT, D-KEFS CWIT – color naming, Benson Figure recall, FCSRT free, total and delayed free recall, and the Facial Emotion Recognition Test was most sensitive to differentiate from controls. For each mutation carrier group, the average and weighted composite scores were calculated, including the tests with a negative coefficient in Table 2. A summary of the included tests that were included in GENFI-Cog per gene group can be seen in Fig. 2.

Table 2
Regression coefficients and corresponding weights.

	C9orf72		*GRN*		*MAPT*	
Language						
	Coef.	**Weight**	**Coef.**	**Weight**	**Coef.**	**Weight**
Camel and Cactus Test			-0.004	0.003	-0.04	0.04
Boston Naming Test					-0.39	0.40
Category fluency	-0.13	0.09				
Attention and mental processing speed						
Digit span forward						
Trail Making Test - part A						
Digit Symbol						
D-KEFS CWIT - color naming	-0.06	0.04			-0.09	0.09
D-KEFS CWIT - word naming	-0.04	0.03	0.09*			
Executive function						
Digit span backward						
Trail Making Test - part B	-0.07	0.05	-0.28	0.23		
D-KEFS CWIT - ink naming	-0.29	0.20	-0.24	0.20		
Phonemic fluency			0.24*			
Visuoconstruction						
Benson Figure copy	-0.09	0.06				
Memory						
Benson Figure recall			-0.06	0.05	-0.01	0.01
FCSRT free recall	-0.50	0.35			-0.06	0.06
FCSRT total recall			-0.05	0.04	-0.30	0.31
FCSRT delayed free recall			-0.16	0.13	-0.005	0.005

Data are presented as coefficients and weights. Coefficient gives the change in log odds of being a mutation carrier for each Z score increase in the score on the cognitive test. Weight gives the weighting used when calculating the weighted cognitive composite score. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. *Positive coefficients indicate better performance in mutation carriers compared to controls and were not included in the composite score.

	C9orf72		*GRN*		*MAPT*	
FCSRT delayed total recall						
Social cognition						
Facial Emotion Recognition Test	-0.26	0.18	-0.42	0.35	-0.08	0.08

Data are presented as coefficients and weights. Coefficient gives the change in log odds of being a mutation carrier for each Z score increase in the score on the cognitive test. Weight gives the weighting used when calculating the weighted cognitive composite score. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. *Positive coefficients indicate better performance in mutation carriers compared to controls and were not included in the composite score.

Sample size calculation

Sample size estimates can be observed in Table 3. In *C9orf72* repeat expansion carriers, both the average and weighted composite score resulted in lower sample sizes than most individual cognitive tests. The only test that resulted in a lower sample size than the composite score was the D-KEFS CWIT – ink naming, with the Digit Symbol test also resulting in a lower sample size than the average but not the weighted composite score. In *GRN* mutation carriers, again both composite scores resulted in lower sample sizes than for most individual cognitive tests except the TMT – part B. The TMT – part A also resulted in a lower sample size than the weighted composite, but not the average composite. In addition, the D-KEFS CWIT – ink naming resulted in a sample size of less than 100, albeit not lower than the composites. In *MAPT* mutation carriers, both composites resulted in estimated samples sizes smaller than 130 with an effect size of 0.1, but the TMT – part A, Digit Symbol test, D-KEFS CWIT – color and ink naming resulted in even lower sample sizes ($n < 100$). In *C9orf72* and *MAPT* mutation carriers, the weighted composite score resulted in a lower estimated sample size than the average composite, whereas in *GRN* mutation carriers the average composite resulted in a lower sample size. For *GRN* (all $n < 60$) and *MAPT* (all $n < 125$) mutation carriers lower sample sizes would be necessary to detect a treatment effect than for *C9orf72* repeat expansion carriers (all $n \leq 306$).

Table 3
Sample size per arm for a hypothetical clinical trial using different cognitive outcome measures.

Outcome measures	*C9orf72*			*GRN*			*MAPT*		
	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%
Cognitive composite scores									
Average composite	306	76	19	27	7	2	124	31	8
Weighted composite	214	53	13	53	13	3	90	23	6
Language									
Camel and Cactus Test	4946	1237	309	292	73	18	357	89	22
Boston Naming Test	1109	277	69	213	53	13	223	56	14
Category fluency	1584	396	99	781	195	49	400	100	25
Attention and mental processing speed									
Digit span forward	130210	32553	8138	2677	669	167	17773	4443	1111
Trail Making Test - part A	2272	568	142	45	11	3	69	17	4
Digit Symbol	254	64	16	925	231	58	80	20	5
D-KEFS CWIT - color naming	866	216	54	502	126	31	66	17	4
D-KEFS CWIT - word naming	19224	4806	1202	3310	828	207	150	37	9

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; ES = effect size as a proportion of the difference between the outcome in the CDR® plus NACC-FTLD 0.5 group and the outcome in the CDR® plus NACC-FTLD 1 group; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. The sample size per arm was estimated as: $n=(1-\rho^2)(2\sigma^2)/\delta^2 f(\alpha,\beta)$. Where, ρ is the correlation between baseline and follow-up measures of the outcome, σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group, δ is the treatment effect (effect size multiplied by difference in mean between CDR® plus NACC-FTLD 0.5 and 1 group), α is the significance level (0.05), 1- β is the power to detect a treatment effect (80%).

Outcome measures	*C9orf72*			*GRN*			*MAPT*		
	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%
Executive functioning									
Digit span backward	1724	431	108	840	210	52	26218	6555	1639
Trail Making Test - part B	1275	319	80	25	6	2	81	20	5
D-KEFS CWIT - ink naming	61	15	4	70	17	4	26	7	2
Phonemic fluency	558	139	35	2229	557	139	161	40	10
Visuoconstruction									
Benson Figure copy	5911	1478	369	2119	530	132	6282036	1570509	392627
Memory									
Benson Figure recall	1044	261	65	657	164	41	7611	1903	476
FCSRT free recall	1302	326	81	294	74	18	521	130	33
FCSRT total recall	1020	255	64	477	119	30	524	131	33
FCSRT delayed free recall	606	152	38	767	192	48	261	65	16
FCSRT delayed total recall	358	89	22	193	48	12	681	170	43
Social cognition									

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; ES = effect size as a proportion of the difference between the outcome in the CDR® plus NACC-FTLD 0.5 group and the outcome in the CDR® plus NACC-FTLD 1 group; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. The sample size per arm was estimated as: $n=(1-\rho^2)(2\sigma^2)/\delta^2 f(\alpha,\beta)$. Where, ρ is the correlation between baseline and follow-up measures of the outcome, σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group, δ is the treatment effect (effect size multiplied by difference in mean between CDR® plus NACC-FTLD 0.5 and 1 group), α is the significance level (0.05), 1- β is the power to detect a treatment effect (80%).

Outcome measures	*C9orf72*			*GRN*			*MAPT*		
	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%
Facial Emotion Recognition Test	7570	1892	473	7805	1951	488	147	37	9

Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; ES = effect size as a proportion of the difference between the outcome in the CDR® plus NACC-FTLD 0.5 group and the outcome in the CDR® plus NACC-FTLD 1 group; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. The sample size per arm was estimated as: n=(1-ρ^2)(2σ^2)/δ^2 f(α,β). Where, ρ is the correlation between baseline and follow-up measures of the outcome, σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group, δ is the treatment effect (effect size multiplied by difference in mean between CDR® plus NACC-FTLD 0.5 and 1 group), α is the significance level (0.05), 1- β is the power to detect a treatment effect (80%).

Time-to-event analysis

Kaplan-Meier curves can be seen in Fig. 1. For *C9orf72* repeat expansion carriers, the probability of converting to a CDR® plus NACC FTLD of ≥ 1 increases from 6% after one year (SE = 0.06, 95% CI 0.01–0.35) to 27% after two years (SE = 0.14, 95% CI 0.1–0.64) and 63% after three years (SE = 0.27, 95% CI 0.21–0.98). In *GRN* mutation carriers, the probability of converting to a CDR® plus NACC FTLD of ≥ 1 increased from 4% after one year (SE = 0.04, 95% CI 0.01–0.24) to 43% after three years (SE = 0.14, 95% CI 0.22–0.72). In *MAPT* mutation carriers, the probability of converting to a global score of ≥ 1 increased from 10% after one year (SE = 0.10, 95% CI 0.01–0.49) to 42% during the second year (SE = 0.20, 95% CI 0.14–0.85). The Kaplan-Meier curve for *MAPT* mutation increased to 100% after three years in Fig. 1 because only one mutation carrier had follow-up up to this point and this individual progressed to a CDR® plus NACC FTLD of ≥ 1. There was no significant difference between the progression rates of different genetic groups ($X^2(2) = 0.15$, $p = 0.93$). In the total group of mutation carriers, the probability of converting to a CDR® plus NACC FTLD of ≥ 1 was 26% after two years (SE = 0.08, 95% CI 0.14–0.44) and 55% after three years (SE = 0.15, 95% CI 0.30–0.83). This means that for a three year trial where drug treatment is assumed to have 20% effect (i.e. only 80% of the treated group will experience the change seen between CDR® plus NACC FTLD 0.5 and 1 groups) the sample size corresponding to a 10% effect in Table 3 needs to be included in order to demonstrate a treatment effect, because only ~ 50% of mutation carriers would be expected to progress from CDR® plus NACC FTLD 0.5 to 1 without treatment (i.e. effect size needs to be divided by 2).

Discussion

We have empirically developed gene-specific cognitive composite scores in *MAPT*, *GRN* and *C9orf72* mutation carriers (GENFI-Cog) and demonstrated that that they provide feasible sample sizes for clinical trials to evaluate the effect of treatment on clinical progression from the prodromal to the fully

symptomatic stage. Time-to-event analyses revealed that roughly 50% of the patients with a CDR® plus NACC FTLD of 0.5 progress to 1 or higher after a period of three years. The results from this study show that GENFI-Cog has potential as a cognitive endpoint in upcoming clinical trials and provide important guidelines on sample size recruitment and clinical trial duration.

The GENFI-Cog composites can be regarded as attractive clinical outcome measures because they produce substantially lower sample size estimates than most individual neuropsychological tests. Depending on the effect size (40–10%), sample size estimates ranged between 13–214 for *C9orf72*, 3–53 for *GRN* and 6–90 for *MAPT* per study arm for the weighted GENFI-Cog. A practical problem in trial design for FTD spectrum disorders is recruiting enough patients to test candidate therapeutics as FTD is ~ 200-fold less common than AD, with an estimated prevalence of 15/100,000 and approximately 10–20% of cases being caused by mutations in *C9orf72, GRN* and *MAPT* genes (4, 7, 41). It is therefore unlikely that a trial would be able to include many hundreds of patients per study arm, which our results show would be necessary for most individual neuropsychological tests. There were some individual neuropsychological tests that required reasonable sample sizes similar to that of GENFI-Cog, e.g. TMT and D-KEFS CWIT. These tests are typically included in clinical trials such as the current phase II study of AL001 (7). Yet, due to the heterogeneity in cognitive symptoms between individual patients even with the same genetic mutation, individually examining each cognitive test might not provide a sensitive and clinically meaningful primary outcome measure. Using GENFI-Cog will allow a single cognitive outcome to be used when analyzing treatment effect although validation in other large cohorts is warranted.

The CDR® plus NACC FTLD is currently often used as an inclusion criterion for clinical trials as well as for tracking disease progression. Results showed that roughly 50% of the patients with a CDR® plus NACC FTLD 0.5 progress to 1 or higher after a period of three years. This indicates that for trials with duration of three years around 50% of patients with CDR® plus NACC FTLD of 0.5 on entry to the trial would be expected to progress to CDR® plus NACC FTLD of 1 in the absence of effective disease modifying treatment. This means that if a treatment is expected to have a 20% effect the sample size corresponding to a 10% effect needs to be included per study arm to be able to demonstrate a treatment effect, because only half of the mutation carriers would be expected to progress from CDR® plus NACC FTLD 0.5 to 1 without treatment. This is important to consider when planning trial duration and recruitment with the current available clinical measures.

The optimal gene-specific cognitive composite score incorporated tests from different cognitive domains. For *GRN* mutation carriers, tests for executive function and social cognition contributed the most to the composite score, with the addition of tests for memory and language. In *MAPT* mutation carriers, there was a strong focus on semantic and episodic memory tests in the composite score with the addition of tests for attention and mental processing speed. A combination of tests from all cognitive domains was most sensitive in *C9orf72* mutation carriers, with the strongest contribution from tests within the domains of executive function, social cognition and memory. These results complement recent studies showing cognitive decline in the early stages of FTD with widespread cognitive impairment covering multiple domains in *C9orf72* (22, 42), dysexecutive functioning as the key feature in *GRN* (13, 22) and a specific

impairment in episodic and semantic memory in *MAPT*-associated FTD (13, 20, 22). Impairment of social cognition appears to be a key feature in all three genetic groups (38), which was probably due to the high number of bvFTD cases in the sample. Neuroimaging studies have indeed shown that the neurodegenerative process in *C9orf72* mutation carriers typically is reflected by widespread degeneration in frontal, temporal as well as cerebellar and subcortical structures (42), whereas focal atrophy of the anteromedial temporal lobe, an area important for memory and semantic functioning, is often seen in *MAPT*-associated FTD (43). In *GRN* mutation carriers the typical pattern of degeneration includes the inferior frontal regions as well as the cingulate cortex, areas known to be critical in executive function (43). Thus, although the GENFI-Cog was empirically derived, the selected tests are clinically meaningful and in line with a theoretically driven approach where the composite would be constructed a priori from cognitive tests that are known to decline in the early stages of each genetic group.

This is to our knowledge the first study that has created cognitive composites for genetic forms of FTD by selecting the most sensitive combinations of cognitive variables based on systematic comparisons with controls. A major strength of this study is the use of a large cohort of genetic FTD mutation carriers allowing gene-specific analyses, but also the use of a matched control group of mutation negative family members. Another strength is the use of LASSO with cross-validation to avoid overfitting bias to ensure that results have generalizability (40).

Limitations

There are some limitations to the present study however. Results from the logistic regression analysis revealed two neuropsychological tests in *GRN* mutation carriers with a positive coefficient, indicating better performance compared to controls, and were excluded from the composite scores. Development of GENFI-Cog was constrained by the neuropsychological test battery that is used in the GENFI cohort (14) and validation in other cohorts (such as ALLFTD (44) or DINAD) is therefore recommended. The sample size estimates serve as a guide on the sensitivity and power of GENFI-Cog compared to individual cognitive tests and should be interpreted with caution as they were calculated from the cross-sectional difference between patients with CDR® plus NACC FTLD 0.5 and 1, assuming that the difference between these groups is representative of the change over time that would be seen in longitudinal scores in a clinical trial as patients progress from a score of 0.5 to 1 i.e. prodromal to fully symptomatic. Future research using longitudinal data is necessary to examine the validity of this assumption and to examine if the cognitive composites presented in the current study are similar to those derived using longitudinal change in scores.

Conclusions

In summary, we examined cognitive data from the GENFI cohort and conducted a search for the combination of cognitive assessments most sensitive to differentiate *MAPT*, *GRN* and *C9orf72* mutation carriers from non-carriers. As a result, we created three gene-specific cognitive composite scores, GENFI-Cog, that were sensitive to track progression on the clinical progression of the CDR® plus NACC FTLD 0.5

to 1 stage as it resulted in smaller sample sizes than most individual neuropsychological tests. To conclude, GENFI-Cog has the potential to be a primary cognitive outcome measure in upcoming clinical trials for *C9orf72, GRN* and *MAPT* mutation carriers.

Abbreviations

AD = Alzheimer's disease

ADAS-Cog = Alzheimer's Disease Assessment Scale cognitive subscale

ALLFTD = ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration study

BNT = Boston Naming Test

bvFTD = behavioural variant frontotemporal dementia

C9orf72 = chromosome 9 open reading frame 72

CDR plus NACC-FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center – Frontotemporal Lobar Degenaration

CWIT = Color Word Interference Test

DINAD = Dominantly Inherited Non-Alzheimer Dementias

D-KEFS = Delis-Kaplan Execution Function System

FCSRT = Free and Cued Selective Reminding Test

FTD = frontotemporal dementia

FTD-ALS = frontotemporal dementia with amyotrophic lateral sclerosis

GENFI = Genetic FTD Initiative

GRN = progranulin

HD = Huntington's disease

LASSO = least absolute shrinkage and selection operator

MAPT = microtubule-associated protein tau

MMSE = Mini-Mental State Examination

PD = Parkinson's disease

PPA = primary progressive aphasia

TMT = Trail Making Test

UPDRS = Unified Parkinson's Disease Rating Scale

UHDRS = Unified Huntington's Disease Rating Scale

WAIS-R = Wechsler Adult Intelligence Scale - Revised

WMS-R = Wechsler Memory Scale - Revised

Declarations

- Ethics approval and consent to participate

All GENFI sites had local ethical approval for the study and all participants gave written informed consent.

- Consent for publication

Not applicable

- Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

- Competing interest

The authors declare that they have no competing interests

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- Authors’ contributions

JMP, KMM, JN and JDR contributed to the conception and design of the work and the analysis of the data. JMP drafted the original work. All authors contributed to the acquisition and interpretation of data and revised the work. All authors read and approved the final manuscript.

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Figures

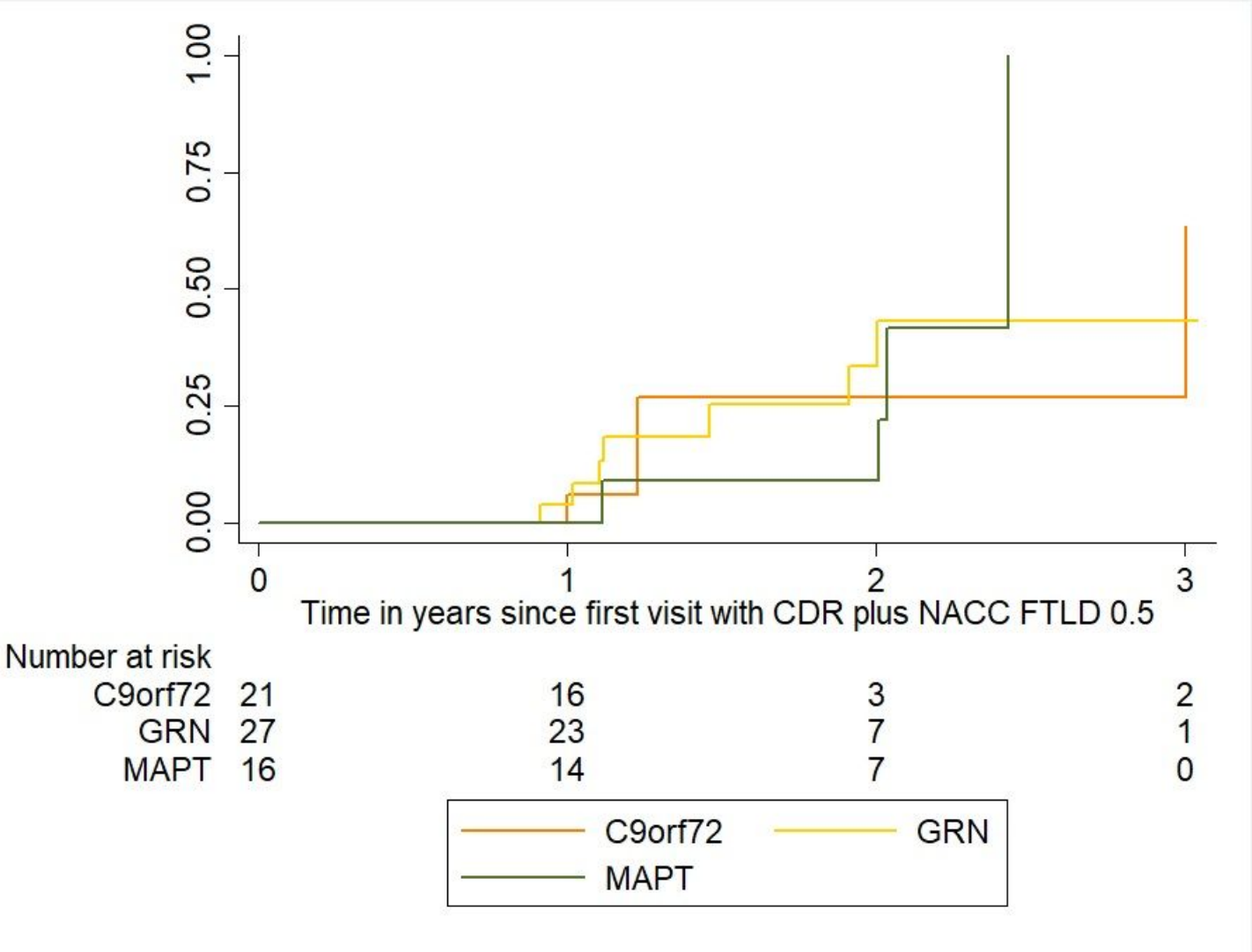

Figure 1

Kaplan-Meier estimates of mutation carriers that converted from CDR® plus NACC FTLD 0.5 to ≥1. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; CDR plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

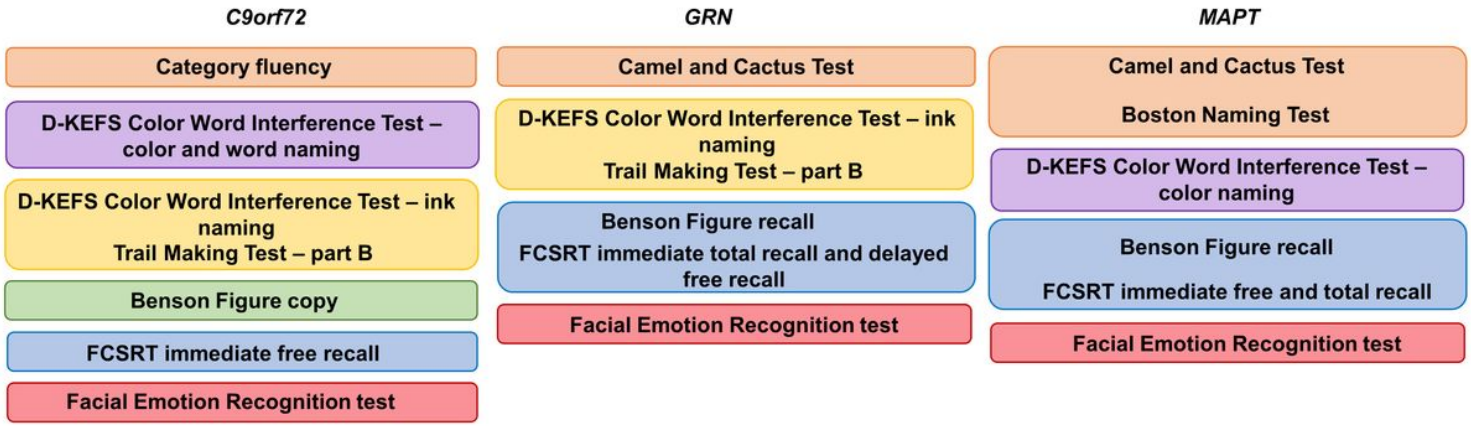

Figure 2

Overview of the neuropsychological tests included in the GENFI-Cog scores per cognitive domain. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau

Supplementary Files

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