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ABSTRACT

Objective: Sensitive cognitive markers are still needed for frontotemporal dementia (FTD). The Benson Complex Figure Test (BCFT) is an interesting candidate test, as it assesses visuospatial, visual memory, and executive abilities, allowing the detection of multiple mechanisms of cognitive impairment. To investigate differences in BCFT Copy, Recall and Recognition in presymptomatic and symptomatic FTD mutation carriers, and to explore its cognitive and neuroimaging correlates.

Method: We included cross-sectional data from 332 presymptomatic and 136 symptomatic mutation carriers (*GRN*, *MAPT* or *C9orf72* mutations), and 290 controls in the GENFI consortium. We examined gene-specific differences between mutation carriers (stratified by CDR® NACC-FTLD score) and controls using Quade's / Pearson X^2 tests. We investigated associations with neuropsychological test scores and grey matter volume using partial correlations and multiple regression models respectively.

Results: No significant differences were found between groups at CDR® NACC-FTLD 0–0.5. Symptomatic *GRN* and *C9orf72* mutation carriers had lower Copy scores at CDR® NACC-FTLD ≥2. All three groups had lower Recall scores at CDR® NACC-FTLD ≥2, with *MAPT* mutation carriers starting at CDR® NACC-FTLD ≥1. All three groups had lower Recognition scores at CDR® NACC FTLD ≥2. Performance correlated with tests for visuoconstruction, memory, and executive function. Copy scores correlated with frontal-subcortical grey matter atrophy, while Recall scores correlated with temporal lobe atrophy.

Conclusions: In the symptomatic stage, the BCFT identifies differential mechanisms of cognitive impairment depending on the genetic mutation, corroborated by gene-specific cognitive and neuroimaging correlates. Our findings suggest that impaired performance on the BCFT occurs relatively late in the genetic FTD disease process. Therefore its potential as cognitive biomarker for upcoming clinical trials in presymptomatic to early-stage FTD is most likely limited.

1. Introduction

Frontotemporal dementia (FTD) is one of the most prevalent forms of early-onset dementia. Its clinical profile is typically characterized by disturbances in behaviour (behavioural variant; bvFTD) and language (primary progressive aphasia; PPA), with cognitive deficits in executive function and social cognition commonly seen. In contrast, episodic memory and visuospatial abilities are relatively spared [1–2]. FTD has an autosomal dominant inheritance pattern in around a third of cases, with mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), and chromosome 9 open reading frame 72 (*C9orf72*) the most common causes of familial FTD [3]. As the mutations cause brain atrophy in distinct as well as overlapping anatomical brain regions, the associated phenotypes are often rather heterogeneous [4]. The clinical presentation associated with *GRN* mutations includes bvFTD, nonfluent variant PPA, atypical parkinsonism, and corticobasal syndrome (CBS) [5,6]. The cognitive profile commonly shows executive dysfunction, speech and language disorders, amnestic deficits and apraxia, consistent with frontal, temporal and parietal lobe involvement [7,8]. Patients with *MAPT* mutations commonly present with bvFTD or atypical parkinsonism (CBS or progressive supranuclear palsy, PSP) [9], with early and prominent naming and memory recall deficits as a result of symmetrical anteromedial temporal lobe atrophy [4,8]. Lastly, the *C9orf72* repeat expansion is associated with a clinical phenotype of bvFTD, amyotrophic lateral sclerosis (ALS), and FTD-ALS [10,11]. The pattern of cognitive impairment is often widespread, including deficits in language, attention, mental processing speed, executive function and immediate memory recall [8], due to atrophy of the frontal and temporal, as well as posterior cortical and subcortical (e.g., cerebellum and thalamus) areas [12,13].

In recent years, research in the familial FTD field has increasingly focussed on the presymptomatic stage, as the critical time-window for treatment most likely lies prior to overt symptom onset, when the pathological damage is still low. With promising therapeutic avenues leading to disease-modifying therapy trials, the identification of robust clinical biomarkers is of utmost importance [12]. Interestingly, previous neuropsychological studies show that subtle cognitive decline is present in the presymptomatic stage of FTD (up to 10 years prior to overt disease onset), with gene-specific cognitive profiles for *GRN*, *MAPT* and *C9orf72* [14–17]. This suggests that presymptomatic neuropsychological assessment may provide sensitive cognitive markers indicative of disease, onset and progression.

One particular neuropsychological instrument, the Benson Complex Figure test (BCFT), is an interesting candidate for familial FTD. Being part of the National Alzheimer's Coordinating Centre (NACC) FTD-module neuropsychological battery [18], performance on the BCFT relies on multiple cognitive functions, including visuospatial abilities, visual memory, and executive functions such as organization and working memory. Most studies into the BCFT have looked into differences between patients with bvFTD, patients with AD, and healthy controls, demonstrating a trend for those with bvFTD to score lower on figure copying than controls [19–20]. Moreover, poor figure copy correlated with specific cognitive mechanisms (i.e. spatial planning and working memory) and neuroanatomical atrophy substrates (i.e. dorsolateral prefrontal cortex) in bvFTD [19]. Until now, research into the BCFT in presymptomatic FTD has been lacking.

The aim of the present study was therefore to: 1) investigate cross-sectional differences in the BCFT (copy, recall and recognition) between presymptomatic FTD mutation carriers, symptomatic FTD mutation carriers and cognitively unimpaired controls; 2) explore associations between the BCFT and other neuropsychological tests, and 3) examine associations between the BCFT and grey matter (GM) volume. Additionally, we investigated normative data and relationships with age, sex and education from the cognitively unimpaired control group.

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¹ See Appendix 1 for the full list of GENFI consortium members.

2. Method

2.1. Participants

We included baseline data of 758 participants from genetically confirmed FTD families with either a *GRN* or *MAPT* pathogenic variant, or *C9orf72* repeat expansion, recruited within the GENFI 2 fifth data freeze between March 2015 and May 2019. We determined clinical status according to established diagnostic criteria [1–2,21] and a standardized clinical assessment, including medical and family history taking, extensive neuropsychological assessment covering the major cognitive domains (see *Neuropsychological assessment* below), and MR imaging of the brain [14]. DNA genotyping was performed locally at each research site. >30 repeats in *C9orf72* was considered to be pathogenic [22]. The total sample consisted of 332 presymptomatic mutation carriers (*GRN* = 143; *MAPT* = 59; *C9orf72* = 130), 136 symptomatic mutation carriers (*GRN* = 41; *MAPT* = 23; *C9orf72* = 72), and 290 non-carriers that were used as reference group (*GRN* = 122; *MAPT* = 57; *C9orf72* = 111). The clinical diagnoses in symptomatic mutation carriers were as follows: bvFTD (*n* = 91), PPA (*n* = 21), ALS or FTD-ALS (*n* = 15), PSP (n = 2), dementia not otherwise specified (n = 2), and other (*n* = 5). We administered the global CDR® NACC-FTLD global score [23] as a measure of disease severity. Knowledgeable informants answered questions about behavioural and cognitive symptoms as well as the participant's activities of daily living in a structured interview which included two questionnaires (Cambridge Behavioural Inventory – Revised (CBI-R) [24] and Frontotemporal Dementia Rating Scale (FRS) [25]. Unless presymptomatic mutation carriers had undergone predictive testing at their own request, the clinical investigators were blinded to their genetic status. We obtained written informed consent from all participants at study enrolment. Ethical committees at each research site approved the study. This study was conducted in accordance with the declaration of Helsinki.

2.2. Benson complex figure test

The BCFT [19] is part of the standardized GENFI neuropsychological battery and consists of 3 conditions: *Copy* (in which the figure has to be copied from an example – see Fig. 1), *Recall* (in which the figure has to be drawn from memory after a 10–15 min interval), and *Recognition* (in which the target figure has to be recognised amongst three distractor figures). Scoring follows the NACC FTD-criteria [18]. Total scores for both Copy and Recall range from 0 to 16; each of the eight elements can receive a maximum score of two when both accuracy and placement are correct. A bonus point – adding up to a maximum score of 17 – is given when the figure is well-drawn (i.e., each element must be accurately drawn, all elements must be properly placed, all elements must be drawn in proper proportions, all connections between elements must be clean, and no extraneous lines may be present). Recognition is either scored as correct (score 1) or incorrect (score 0).

2.3. Neuropsychological assessment

Global cognitive functioning was screened by means of the Mini-Mental State Examination (MMSE) [26], whilst other cognitive tests performed within the larger GENFI neuropsychological battery measured executive function (letter fluency [27]), Trail Making Test (TMT) [28], D-KEFS Color-Word Interference Test [29]), memory (Free and Cued Selective Reminding Test (FCSRT) [30]), and visuoconstructive abilities (WASI Block Design [31]).

2.4. MRI acquisition and (pre)processing

Volumetric T1-weighted MR images were acquired on a 3 T scanner in 698 participants (Philips Achieva *n* = 191, Siemens Prisma n = 191, Siemens Trio *n* = 178, Siemens Skyra *n* = 136, GE Discovery MR750 *n* = 2). All images were subjected to strict visual quality control, after which

Appendix 3. Neuroimaging correlates of the BCFT. Abbreviations: GRN, progranulin; MAPT, microtubule-associated protein tau; C9orf72, chromosome 9 open reading frame 72; BCFT, Benson Complex Figure Test; L, left; R, right. *only clusters >50 voxels were reported; **uncorrected $p < 0.001$.

Gene	BCFT	Cluster	T	P_FWE-corrected	MNI coordinates			Region
					x	y	z	
GRN	Copy	4	5.15	0.031	-20	−22	10	Thalamus L
	Recall*	7354	6.82	<0.001	2	32	27	Anterior cingulate R
		2964	7.00	<0.001	−33	−28	−10	Hippocampus L
		1726	6.35	<0.001	−15	−58	39	Precuneus L
		1605	6.45	<0.001	−40	15	2	Frontal operculum L
		1542	6.57	<0.001	44	2	2	Anterior insula R
		943	6.13	<0.001	20	−22	−20	Parahippocampal gyrus R
		637	5.72	<0.001	−32	−63	−38	Cerebellum L
		590	5.77	<0.001	−22	3	−16	Basal forebrain L
		238	6.33	<0.001	2	10	−12	Subcallosal area R
		216	5.96	<0.001	33	14	−24	Temporal pole R
		206	5.45	<0.001	22	−70	−36	Cerebellum R
		191	5.54	<0.001	−26	40	−12	Anterior orbital gyrus L
		128	5.95	<0.001	−50	39	−8	Inferior frontal gyrus L
		128	5.55	<0.001	51	−57	−12	Inferior temporal gyrus R
		117	5.59	0.001	−2	−88	14	Cuneus L
		113	5.58	0.001	−39	−16	45	Precentral gyrus L
		82	5.52	0.001	−44	26	10	Inferior frontal gyrus L
		62	5.43	0.003	−34	18	−16	Posterior orbital gyrus L
		50	5.50	0.004	−8	−96	18	Occipital pole L
		50	5.26	0.004	24	58	4	Superior frontal gyrus R
MAPT	Copy**	57	3.74	<0.001	46	−70	−22	Cerebellum R
		44	3.69	<0.001	52	−45	−40	Cerebellum R
	Recall*	185	6.41	<0.001	−21	4	−38	Temporal pole L
		89	6.08	<0.001	−18	−36	3	Hippocampus L
		85	5.80	<0.001	−33	−32	−2	Hippocampus L
		67	6.29	0.001	24	30	−9	Hippocampus R
		57	5.75	0.001	33	−18	−12	Hippocampus R
C9orf72	Copy**	22	3.26	0.001	−26	12	30	Middle frontal gyrus L
	Recall*	593	6.34	<0.001	−28	−20	−14	Hippocampus L
		100	5.49	<0.001	27	−22	−12	Hippocampus R
		58	5.56	0.002	18	−12	−12	Hippocampus R

15 participants were excluded from further analysis due to inadequate image quality. The DICOM images were subsequently corrected for gradient nonlinearity distortions and converted to NifTI format. These images were then analysed using the standard Voxel-Based Morphometry (VBM) pipeline in Statistical Parametric Mapping 12 (SPM12; Functional Imaging Laboratory, University College London, London, UK; www.fil.ion.ucl.ac.uk/spm) implemented in Matlab R2018a (Mathworks, USA). In the first pre-processing step, the T1-weighted images were normalized to a template space and segmented into GM, white matter (WM) and cerebrospinal fluid (CSF), after which they were rigidly aligned. We calculated total intracranial volume (TIV) by adding GM, WM and CSF. Secondly, the segmentations were spatially normalized to a DARTEL template by applying the flow fields of all the individual scans. Images were smoothed using a 6 mm full width at half maximum (FWHM) isotropic Gaussian kernel. At every preprocessing step, images were visually inspected.

2.5. Statistical analysis

We performed statistical analyses using SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 5 (La Jolla, California, USA). Alpha was set at 0.05 across all comparisons, unless otherwise specified, and two-tailed analyses were performed. We compared continuous demographic data between groups by means of one-way ANOVA with post hoc Bonferroni comparisons for normally distributed data, or Kruskal-Wallis tests with post hoc Mann-Whitney U tests in case of non-normally distributed data. Between-group differences in sex distribution were analysed using Pearson X^2 tests. In our reference (healthy control) group, we calculated cumulative frequencies, percentile scores, and performance across age, sex and education for BCFT Copy, Recall and Recognition. We used Spearman rank correlations to explore the relationships between the BCFT Copy and Recall, and age and education. The square root of eta squared ($\sqrt{\eta^2}$) was used to investigate the relationship between age and education, and BCFT Recognition. We explored the differences in BCFT Copy and Recall and sex by means of Mann-Whitney U tests, and sex differences in BCFT Recognition by means of a Pearson X^2 test. As BCFT Copy and Recall scores were non-normally distributed, we examined gene-specific (*GRN*, *MAPT*, *C9orf72*) differences between presymptomatic mutation carriers (CDR® NACC-FTLD global score 0 and 0.5), symptomatic mutation carriers (CDR® NACC-FTLD global score $\geq$ 1) and controls by means of Quade's rank analysis of covariance – adjusting for the effect of age, sex, years of education, and family clustering. We performed Pearson X^2 tests to compare BCFT Recognition scores between groups. We investigated associations between BCFT Copy and Recall with neuropsychological test scores per mutation by means of partial correlations, controlling for the effect of age, sex, years of education, and family

clustering. We explored the relationship between each BCFT test score and GM volume by means of multiple regression models in SPM12 (University College London, London, UK). Age, sex, scanner and TIV were entered as covariates. We set the statistical threshold at $p < 0.05$, adjusted for multiple comparisons with familywise error (FWE) correction. The uncorrected statistical threshold was set at $p < 0.001$ (minimum cluster size $\geq$10 voxels).

3. Results

3.1. Demographic and clinical data

Demographic and clinical data are shown in Table 1. Controls were significantly younger than symptomatic mutation carriers (*GRN* U = 1655.5, *MAPT* U = 1374.5; *C9orf72* U = 3190.5; all $p < 0.001$), while presymptomatic *MAPT* mutation carriers were younger than controls (U = 6043, p < 0.001). All presymptomatic mutation carriers were younger than symptomatic mutation carriers (p < 0.001). There were fewer females in the symptomatic *C9orf72* group than in the control (X(1) = 9.69, p < 0.001) or presymptomatic groups (*GRN* X(1) = 13.21, *MAPT* X (1) = 7.18; *C9orf72* X(1) = 9.40; all $p < 0.007$). Symptomatic *GRN* and symptomatic *C9orf72* were lower educated than controls [F(6,751) = 5.74, $p \leq$0.001]. MMSE scores were lower in symptomatic mutation carriers than in controls (*GRN* U = 949, *MAPT* U = 654; *C9orf72* U = 1909; all p < 0.001) and all presymptomatic groups (all p < 0.001). No differences were found amongst the symptomatic or presymptomatic groups (all $p > 0.05$). CDR® NACC-FTLD scores were higher in symptomatic mutation carriers than in presymptomatic mutation carriers and controls (all $p < 0.001$), and presymptomatic mutation carriers also had higher CDR® NACC-FTLD scores than controls (*GRN* U = 15,660, *MAPT* U = 6380; *C9orf72* U = 13,050; all p < 0.001). Behavioural symptoms were higher in symptomatic mutation carriers than in presymptomatic mutation carriers and controls (all p < 0.001), but also higher in presymptomatic *C9orf72* mutation carriers compared to controls (CBI-R U = 12,625.5, $p = 0.053$; FRS U = 10,677.5, $p < 0.001$) and presymptomatic *GRN* mutation carriers (CBI-R U = 6121.5, $p = 0.008$; FRS U = 4967.5, $p = 0.004$).

3.2. Normative data non-carriers (reference group)

Appendix 2 shows the reference groups' cumulative frequencies (Appendix 2.1), percentile scores (Appendix 2.2), and performance across age, sex and education (Appendix 2.3) for the BCFT Copy, Recall and Recognition. Scores for Copy ranged between 9 and 17; scores for Recall ranged between 6 and 17. 94.5% of controls were able to identify the correct figure in the Recognition trial. Performance below 14 for the Copy trial and below 8 for the Recall trial would be considered outside

Table 1

Demographic and clinical data of the mutation carriers and controls. Values indicate: count (percentage) or mean (standard deviation). Abbreviations: *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; *C9orf72*, chromosome 9 open reading frame 72; MMSE, Mini-Mental State Examination; CDR, clinical dementia rating; NACC, National Alzheimer's Coordinating Center; FTLD, frontotemporal lobar degeneration; CBI-R, Cambridge Behavioural Inventory – Revised; FRS, Frontotemporal Dementia Rating Scale; BCFT, Benson Complex Figure Test.

Mutation	*GRN*		*MAPT*		*C9orf72*		Controls
Clinical status	Presymptomatic	Symptomatic	Presymptomatic	Symptomatic	Presymptomatic	Symptomatic	
n	143	41	59	23	130	72	290
Age, y [range]	46.4 (12.4)	64.0 (8.7)	39.6 (10.6)	59.0 (7.1)	44.7 (13.4)	62.5 (7.7)	46.2 (12.9)
Sex, female	91 (63.6)	19 (46.3)	36 (61.0)	10 (43.5)	78 (60.0)	27 (37.5)	168 (57.9)
Education, y	14.8 (3.5)	11.9 (3.5)	14.4 (3.0)	13.8 (3.9)	14.4 (3.0)	13.0 (3.6)	14.5 (3.4)
MMSE	29.4 (1.1)	22.1 (6.2)	29.5 (0.9)	23.8 (6.3)	29.2 (1.2)	24.2 (5.0)	29.4 (1.1)
CDR© NACC-FTLD	0.2 (0.3)	1.7 (0.9)	0.2 (0.3)	1.8 (0.9)	0.2 (0.3)	2.0 (0.9)	0 (0)
CBI-R	4.5 (6.9)	52.3 (28.8)	7.1 (10.2)	59.0 (36.6)	7.4 (9.2)	65.3 (31.3)	5.4 (7.9)
FRS, percentage	96.7 (8.3)	51.7 (27.9)	94.4 (9.4)	44.5 (26.9)	93.8 (9.7)	36.8 (29.4)	96.2 (7.9)
BCFT - copy	16.5 (1.0)	14.2 (3.7)	16.1 (1.1)	14.3 (3.5)	16.0 (1.5)	13.6 (3.5)	16.3 (1.3)
BCFT - recall	12.9 (2.7)	7.7 (4.5)	12.9 (2.8)	5.9 (5.3)	12.8 (2.8)	8.1 (4.4)	13.2 (2.8)
BCFT – recognition, % correct	94.4	65.8	96.6	65.2	93.1	66.7	94.5

the normal range (i.e. ≤5th percentile). Age ($r_s(288) = -0.09$, $p = 0.125$) and education ($r_s(288) = 0.11$, $p = 0.068$) were not significantly associated with BCFT Copy. However, there was a significant correlation between both age ($r_s(288) = -0.45$, $p < 0.001$) and education ($r_s(288) = 0.13$, $p = 0.031$) and BCFT Recall. There was a strong positive correlation between BCFT Recognition and age ($\sqrt{\eta^2} = 0.88$); the correlation with education was weak ($\sqrt{\eta^2} = 0.26$). Women had higher BCFT Copy scores than men (mean rank women: 153.9 vs. men: 133.87; U = 8829.5, $p = 0.014$), whereas there were no sex differences in Recall (U = 9233.5, $p = 0.147$). Also BCFT Recognition scores did not differ between males and females (X(1) = 1.40, $p = 0.237$).

3.3. Group differences of the BCFT

Figure 1 shows the group differences in the BCFT Copy, Recall and Recognition between *GRN*, *MAPT* and *C9orf72* mutation carriers according to CDR® NACC-FTLD global score.

For the BCFT Copy, no significant differences were found between groups at CDR® NACC-FTLD global score = 0 [F(3,529) = 1.170, $p = 0.321$] or 0.5 [F(3,370) = 0.751, $p = 0.522$]. However, there were significant differences between groups at CDR® NACC-FTLD global score ≥ 1 [F(3,426) = 10.128, $p < 0.001$], with both *GRN* and *C9orf72* mutation carriers having lower Copy scores than controls ($p = 0.001$ and $p < 0.001$, respectively). No differences were seen in the *MAPT* mutation group. Performing a sub-analysis in the CDR® NACC-FTLD global score ≥ 1 group (stratifying into scores of 1, 2 and 3) demonstrated significant differences from a score of 2 onwards in both *GRN* and *C9orf72* (but not *MAPT*) mutation carriers: at CDR® NACC-FTLD global scores of both 2 and 3 *GRN* and *C9orf72* mutation carriers had lower Copy scores than controls (all $p < 0.001$).

For the BCFT Recall, there were similarly no significant differences between groups at CDR® NACC-FTLD global score = 0 [F(3,529) = 2.390, p = 0.068] or 0.5 [F(3,370) = 1.279, $p = 0.281$]. However, significant differences were seen between groups at CDR® NACC-FTLD global score ≥ 1 [F(3,426) = 20.469, $p < 0.001$]: all mutation carrier groups (*GRN*, *MAPT* and *C9orf72*) had significantly lower Recall scores than controls (all $p < 0.001$). Performing additional sub-analyses in the CDR® plus NACC FTLD score ≥ 1 group (stratified into scores of 1, 2 and 3) demonstrated significant differences in the CDR® NACC-FTLD global score = 1 group in the *MAPT* mutation carriers only (lower Recall scores than controls: $p = 0.024$). At CDR® NACC-FTLD global scores of 2 and 3, all mutation carrier groups had lower Recall scores than controls (p-values for scores 2 and 3 respectively: *GRN*, $p = 0.007$, $p < 0.001$; *MAPT*, $p = 0.065$, $p < 0.001$; *C9orf72*, p = 0.024, $p < 0.001$). No significant differences at any time point were found between mutation carrier

groups (*GRN* vs. *MAPT*, $p = 0.872$; *MAPT* vs. *C9orf72*, $p = 0.608$; *C9orf72* vs. *GRN*, $p = 1.000$).

For the BCFT Recognition, there were no significant differences between groups at CDR® NACC-FTLD global score = 0 [X(3) = 2.982, $p = 0.394$] or 0.5 [X(3) = 4.381, $p = 0.223$]. Significant differences between groups were seen at CDR® NACC-FTLD global score ≥ 1 [X(3) = 52.924, $p < 0.001$], with all mutation carrier groups having significantly lower Recognition scores than controls (all $p < 0.001$), although no significant differences were found between mutation carrier groups (*GRN* vs. *MAPT*, $p = 0.830$; *MAPT* vs. *C9orf72*, $p = 0.794$; *C9orf72* vs. *GRN*, $p = 0.974$). Additional sub-analyses in the CDR® NACC-FTLD global score ≥ 1 group (stratified into scores of 1, 2 and 3) demonstrated no significant differences at CDR® NACC-FTLD global score = 1, but significant differences were seen between all mutation carrier groups and controls at a score of 2 (*GRN* vs. control, $p < 0.001$; *MAPT* vs. control, $p = 0.038$; *C9orf72* vs. controls, $p < 0.001$) and a score of 3 (all comparisons $p < 0.001$).

3.4. Cognitive correlates of the BCFT

Partial correlation coefficients between the BCFT Copy and Recall test score and other relevant neuropsychological tests within the GENFI battery are shown in Table 2. Irrespective of the underlying mutation, both BCFT Copy and Recall test scores correlated significantly with TMT part B and WASI Block Design ($p < 0.05$). FCSRT immediate and delayed recall also correlated significantly with both BCFT Copy and Recall in every genetic group ($p < 0.01$), apart from Copy in *C9orf72* mutation carriers. In this mutation, but not in *GRN* and *MAPT*, significant correlations were found between BCFT Copy and Recall test scores and D-KEFS Color-Word Interference Test card III and the letter fluency test ($p < 0.05$).

3.5. Neuroimaging correlates of the BCFT

The relationships between BCFT Copy and Recall and GM volume are displayed in Fig. 2 and Appendix 3. VBM analyses demonstrated different structures to be involved in BCFT Copy depending on the mutation involved: in *GRN* mutation carriers worse performance correlated with GM atrophy of the left thalamus ($p < 0.05$ FWE corrected), in *MAPT* mutation carriers with atrophy of the right cerebellum, and in *C9orf72* repeat expansion carriers with atrophy of the left middle frontal gyrus (both $p < 0.001$ uncorrected). In all mutation carriers, worse BCFT Recall score correlated with atrophy of the temporal lobe, especially the hippocampus ($p < 0.05$ FWE corrected). In *MAPT* mutation carriers there was additional involvement of the left temporal pole,
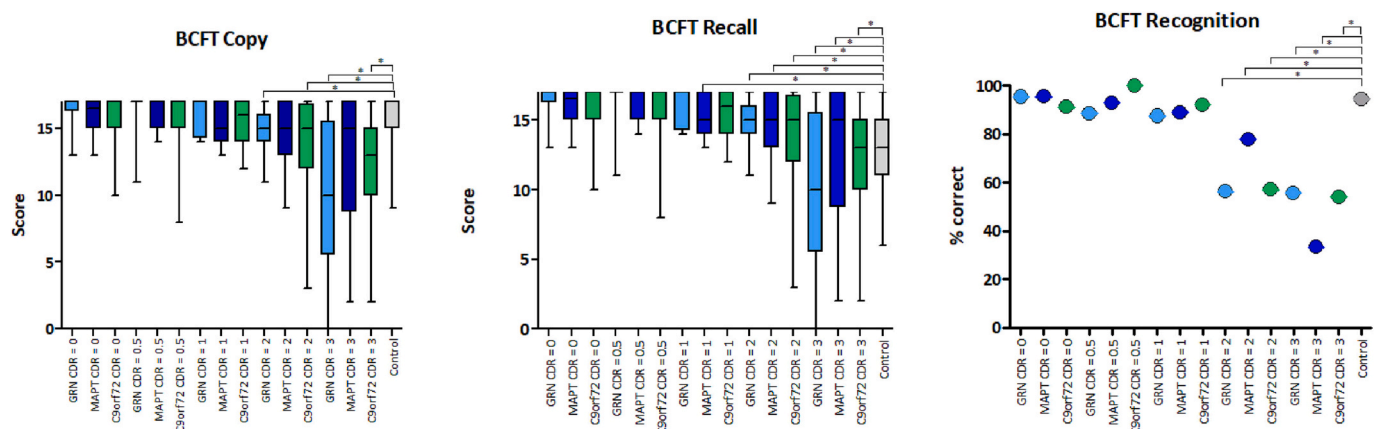

Fig. 1. BCFT Copy, Recall and Recognition data stratified by CDR plus NACC FTLD global score (0, 0.5, 1, 2 and 3) in *GRN*, *MAPT* and *C9orf72* mutation carriers. Boxplots (for BCFT Copy and Recall) visualize mean (with whiskers representing min-max) scores per clinical group. * $p < 0.05$. Abbreviations: BCFT, Benson Complex Figure Test; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; *C9orf72*, Chromosome 9 open reading frame 72; CDR, Clinical Dementia Rating Scale.

Table 2

Partial correlation coefficients (corrected for age, sex, years of education, and family clustering) in *GRN*, *MAPT* and *C9orf72* mutation carriers between Benson Complex Figure Copy and Recall and other neuropsychological test scores. Significant correlations are displayed in bold; * p < 0.05, ** p < 0.01, *** p < 0.001. Abbreviations: BCFT, Benson Complex Figure Test; *GRN*, progranulin, *MAPT*, microtubule-associated protein tau; *C9orf72*, Chromosome 9 open reading frame 72; TMT, Trailmaking Test; FCSRT, Free and Cued Selective Reminding Test, D-KEFS, Delis-Kaplan Executive Function System; WASI, Wechsler Abbreviated Scale of Intelligence.

Mutation	*GRN*		*MAPT*		*C9orf72*	
BCFT	Copy	Recall	Copy	Recall	Copy	Recall
TMT part B	**−0.18***	**−0.49*****	**−0.45*****	**−0.35****	**−0.40*****	**−0.31*****
FCSRT immediate recall	**0.41*****	**0.54*****	**0.43*****	**0.72*****	0.06	**0.26****
FCSRT delayed recall	**0.40*****	**0.54*****	**0.52*****	**0.76*****	0.04	**0.33*****
D-KEFS Color-Word Interference Test card III	−0.06	**−0.21***	−0.13	−0.21	**−0.25****	**−0.28*****
Letter fluency	0.15	0.13	−0.04	0.14	**0.19***	**0.22****
WASI Block Design	**0.28****	**0.37*****	**0.33****	**0.32****	**0.31*****	**0.31*****
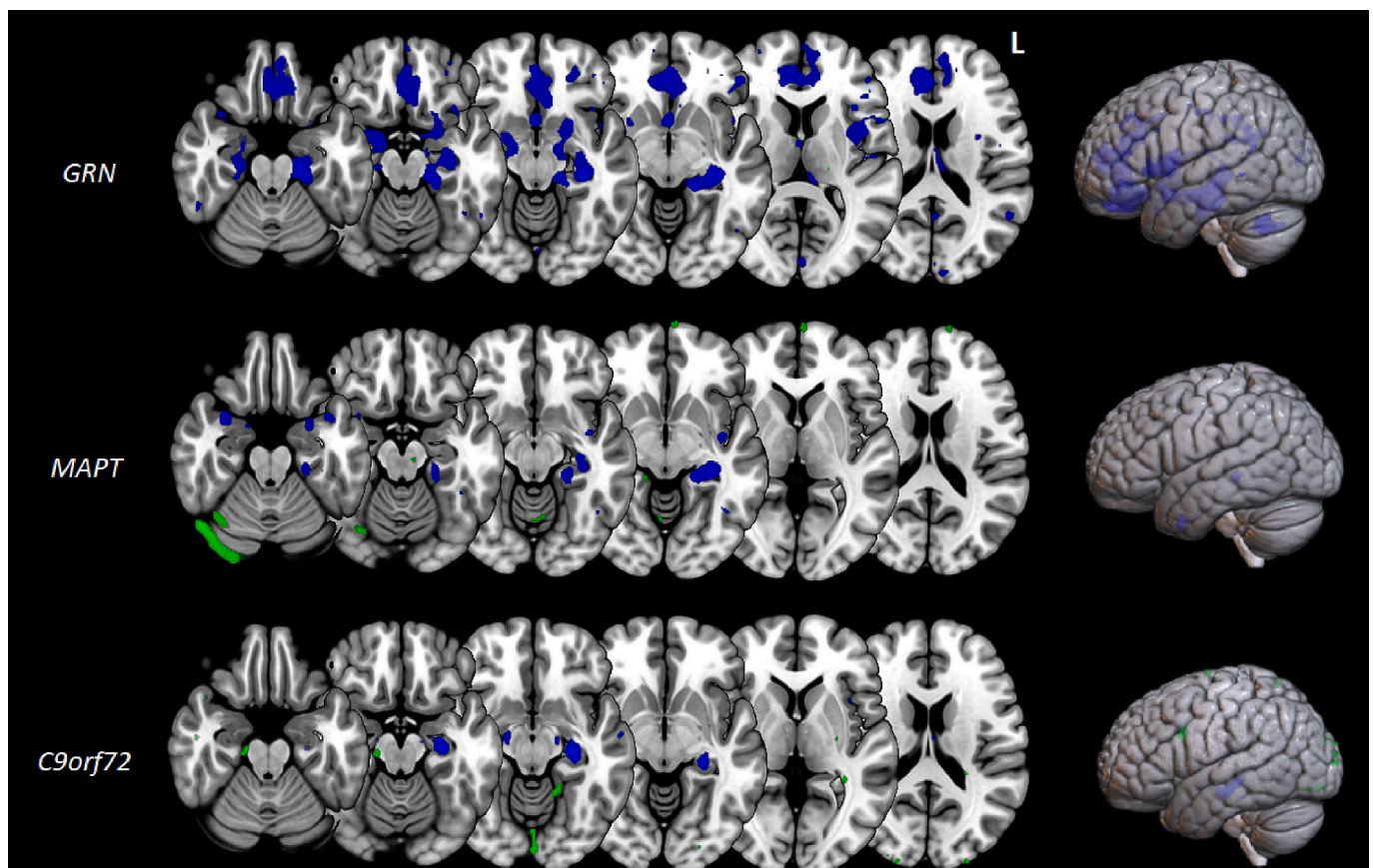
Fig. 2. Neuroimaging correlates of the BCFT Copy and Recall. VBM analyses demonstrated lower scores in BCFT Copy (in green) and BCFT Recall (in blue) to be correlated with lower grey matter volume in *GRN* mutation carriers (top), *MAPT* mutation carriers (middle) and *C9orf72* repeat expansion carriers (bottom). We set the statistical threshold at *p* < 0.05 (FWE-corrected) for *GRN* copy and all recall conditions, and *p* < 0.001 (uncorrected) for *MAPT* and *C9orf72* copy. Abbreviations: L, left; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; *C9orf72*, chromosome 9 open reading frame 72. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

whilst in *GRN* mutation carriers, there was also involvement outside of the temporal lobe, including the anterior cingulate, anterior insula, frontal and parietal lobes in particular (both *p* < 0.05 FWE corrected).

4. Discussion

In this study of a large cohort of participants from genetic FTD families, we have shown lower scores compared to healthy controls in the BCFT Copy, Recall and Recognition abilities of symptomatic mutation carriers, with different profiles depending on the genetic mutation involved. *GRN* and *C9orf72* – but not *MAPT* – mutation carriers had lower BCFT Copy performance at a CDR® NACC-FTLD global scores of 2

and 3 whereas all mutation carriers had lower BCFT Recall and Recognition scores than controls at those stages, with the addition of earlier impairment of Recall in *MAPT* mutation carriers (from CDR® NACC-FTLD global score of 1). Cognitive correlates of the BCFT Copy and Recall included tests for visuoconstruction, verbal memory, and executive function. Furthermore, lower BCFT Copy score was associated with atrophy of fronto-subcortical areas, while lower BCFT Recall score correlated with predominantly (medial) temporal lobe atrophy.

Our results demonstrate visuoconstructive deficits in FTD mutation carriers only from the moderate dementia stage onwards, reflected in lower BCFT Copy performance at CDR® NACC-FTLD global score of 2 and 3. This is in contrast with a previous study, that showed progressive

decline in BCFT Copy after the CDR = 0.5 stage in patients with bvFTD [32]. A potential explanation for this discrepancy is the use of the original CDR [33], which does not include the behaviour and language domains, and therefore is likely less sensitive for early changes in FTD, i. e. patients with original CDR = 0.5 potentially score higher on the CDR® NACC-FTLD [23], which was used in our study. In our patient sample, BCFT Copy performance was not affected in asymptomatic and pro-dromal mutation carriers (i.e. CDR® NACC-FTLD global scores 0 and 0.5), which is in line with an earlier study that did not find visuocon-structive decline in presymptomatic mutation carriers [15]. Interest-ingly, our findings also suggest gene-specific patterns in BCFT Copy performance, in that both *GRN* and *C9orf72* mutation carriers, but not *MAPT* mutation carriers, had lower scores than controls in the moderate to severe dementia stages. Deficits in visuoconstructive functioning have been described in both symptomatic *GRN* and *C9orf72*-related FTD previously [34–36]. Results in the presymptomatic stage have been mixed, with some studies showing early decline [22,37], but not others [38–39]. A recent study into cognitive composites for familial FTD suggested BCFT Copy as part of the neuropsychological battery best discriminating *C9orf72* mutation carriers from controls, whereas BCFT Recall was amongst the tests best differentiating *MAPT* mutation carriers from controls [40]. The latter, as well as our findings, confirms the presence of early memory decline in particularly *MAPT* mutations, as has also been found in previous studies [8,41]. In contrast to studies demonstrating verbal memory deficits in presymptomatic *MAPT* [15–16,42], we only found significant differences in BCFT Recall (i.e. visual memory) from CDR® NACC-FTLD global score of 1. A potential explanation for this discrepancy could be the difference between per-formances on verbal versus visual memory tests. Because of the early semantic memory involvement in *MAPT*-related FTD [43], language-led tests could be more sensitive to change in the presymptomatic stage than visuoconstructive-mediated tests.

The cognitive and neuroimaging correlates of the BCFT Copy and Recall showed both cross-mutation as well as mutation-specific patterns. Irrespective of the underlying mutation, BCFT scores correlated with tests for visuoconstruction, verbal memory, and executive function, with stronger executive function involvement in *C9orf72*. These findings suggest two important aspects about the BCFT, namely that it – as pre-vious research suggested [19–20] – assess multiple cognitive functions, allowing the exploration of differential mechanisms of cognitive impairment in familial FTD, and also specifically taps into frontally-mediated skills in *C9orf72*. This is an interesting finding, as BCFT Copy performance indeed correlated with atrophy of the left middle frontal gyrus in this mutation. Although early atrophy of the thalamus and cerebellum is commonly regarded as the neuroimaging signature of *C9orf72* [14,44], the associations we found with the thalamus (in *GRN*) and cerebellar (in *MAPT*) atrophy confirm that subcortical involvement is also present in the other two FTD genetic groups [45], and leads to lower visuoconstructive scores. In all mutation carriers, worse BCFT Recall score correlated with atrophy of the (medial) temporal lobe. This is not a surprising finding, given the pivotal role of the hippocampus in memory recall, and indeed previous studies into the Rey Complex Figure Test, similar to the BCFT, have related recall performance to medial temporal lobe structures including the hippocampus [46]. In *MAPT* mutation carriers there was specific involvement of the temporal pole. This finding coincides with the lower BCFT Recall performance relatively early in the disease process of this mutation, confirming *MAPT*-FTD as a predominantly temporal-predominant disease [14].

Key strengths of our study are the large sample sizes of presymp-tomatic and symptomatic *GRN*, *MAPT* and *C9orf72* mutation carriers and non-carriers from the same families. Not only is the non-carrier group an ideal control group as they have the same genetic and social background as the mutation carriers, we were also able to generate new normative data and relationships with age, sex and education for the BCFT. Despite large numbers, some groups (especially *MAPT* mutation carriers) remain relatively small when dividing the sample according to

CDR® NACC-FTLD global scores, so that replication in other familial FTD cohorts (e.g., ALLFTD, DINAD) is warranted. We were unable to detect any changes in the CDR® NACC-FTLD global score = 0.5 group, which might have been the result of the heterogeneous nature of this category, likely including mutation carriers without overt dementia symptoms as well as people with primary psychiatric disorders and early-stage PPA, in which it is difficult to detect clinical features [23]. Directions for future research include modifications to traditional scoring methods (i.e., accuracy and placement), such as incorporating process (e.g., direction and order of drawing) and/or digital scoring methods to increase test sensitivity in early disease stages [47] and to allow the measurement of the different cognitive processes that the BCFT relies on (i.e., visuospatial abilities, visual memory, and executive functions such as organization and working memory) but currently cannot be separated.

5. Conclusion

Our study showed lower BCFT Copy, Recall and Recognition per-formance in symptomatic FTD mutation carriers in comparison to non-carriers. We demonstrated copy deficits in symptomatic *GRN* and *C9orf72* mutation carriers, whereas recall was affected in the early-symptomatic period in *MAPT* mutation carriers, suggesting differential mechanisms of cognitive impairment depending on the genetic mutation involved, which was corroborated by specific cognitive and neuro-imaging correlates. Performance on this brief and easy-to-apply test may aid in differential diagnosis in genetic FTD, but its potential as candidate cognitive biomarker for upcoming clinical trials is most likely limited as impaired performance on the BCFT occurs relatively late in the genetic FTD disease process.

Declaration of Competing Interest

RSV has served in Advisory boards Meetings for Wave Life Sciences, Ionis and Novo Nordisk and received personal fees for participating in educational activities from Janssen, Roche Diagnostics, and Neuraxpharma and funding to her institution for research projects from Biogen and Sage Pharmaceuticals. The other authors declare that they have no competing interests.

Acknowledgements

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Appendix B. Cumulative frequencies, percentile scores, and performance across age, sex and education for the Benson Complex Figure Test (BCFT) in the reference (non-carrier) group ($n = 290$)

Appendix 2.1 – Cumulative frequencies for the BCFT Copy, Recall and Recognition in the reference group.

BCFT Copy			BCFT Recall		
Score	n	Cumulative frequency (%)	Score	n	Cumulative frequency (%)
9	1	0.3	6	4	1.4
11	1	0.7	7	5	3.1
12	1	1.0	8	14	7.9
13	8	3.8	9	10	11.4
14	18	10.0	10	20	18.3
15	49	26.9	11	22	25.9
16	13	31.4	12	30	36.2
17	199	100	13	41	50.3
BCFT Recognition			14	41	64.5
Score	**n**	**Cumulative frequency (%)**	15	46	80.3
0	16	5.5	16	10	83.8
1	274	100	17	47	100

Appendix 2.2 – Percentile scores of the BCFT Copy and Recall in the reference group.

Percentile	BCFT Copy	BCFT Recall
5th	14	8
10th		9
20th	15	11
30th	16	12
40th	17	13
50th		
60th		14
70th		15
80th		
90th		17

Appendix 2.3 – BCFT performance across age, sex, and education in the reference group. Abbreviation: SD, standard deviation.

	BCFT Copy		BCFT Recall		BCFT Recognition
	n	Mean (SD); [range]	n	Mean (SD); [range]	n (% correct)
Age group (years)					
18.1–29.9	33	16.4 (1.2); [13–17]	33	15.0 (2.4); [6–17]	32 (97.0)
30.0–39.9	68	16.1 (1.5); [9–17]	68	13.6 (2.4); [8–17]	65 (95.6)
40.0–49.9	83	16.5 (1.1); [12–17]	83	13.2 (2.7); [6–17]	78 (94.0)
50.0–59.9	54	16.5 (0.9); [14–17]	54	13.2 (2.7); [7–17]	51 (94.4)
60.0–69.9	42	15.9 (1.3); [13–17]	42	11.7 (2.7); [7–17]	40 (95.2)
70.0–85.0	10	15.6 (2.0); [11–17]	10	10.2 (3.2); [7–17]	8 (80.0)
Education (years)					
0–9	24	16.1 (1.2); [14–17]	24	12.1 (2.8); [8–17]	23 (95.8)
10–12	60	16.1 (1.2); [13–17]	60	13.2 (2.6); [7–17]	54 (90.0)
13–16	135	16.2 (1.5); [9–17]	135	13.1 (2.9); [6–17]	129 (95.6)
≥17	71	16.5 (0.9); [14–17]	71	13.6 (2.6); [6–17]	68 (95.8)
Sex					
Female	168	16.4 (1.1); [12–17]	168	13.0 (2.7); [6–17]	161 (95.8)
Male	122	16.0 (1.5); [9–17]	122	13.4 (2.9); [6–17]	113 (92.6)

References

[1] M.L. Gorno-Tempini, A.E. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S.F. Cappa, M. Grossman, Classification of primary progressive aphasia and its variants, Neurology 76 (11) (2011) 1006–1014, https://doi.org/10.1212/WNL.0b013e31821103e6.

[2] K. Rascovsky, J.R. Hodges, D. Knopman, M.F. Mendez, J.H. Kramer, J. Neuheus, B. L. Miller, Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia, Brain 134 (2011) 2456–2477, https://doi.org/10.1093/brain/awr179.

[3] J.D. Warren, J.D. Rohrer, M.N. Rossor, Clinical review. Frontotemporal dementia, BMJ 347 (2013), f4827, https://doi.org/10.1136/bmj.f4827.

[4] J.D. Rohrer, G.R. Ridgway, M. Modat, S. Ourselin, S. Mead, N.C. Fox, J.D. Warren, Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations, NeuroImage 53 (3–3) (2010) 1070–1076, https://doi.org/10.1016/j.neuroimage.2009.12.088.

[5] M. Baker, I.R. Mackenzie, S.M. Pickering-Brown, J. Gass, R. Rademakers, C. Lindholm, M. Hutton, Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17, Nature 442 (7105) (2006) 916–919, https://doi.org/10.1038/nature05016.

[6] J.C. van Swieten, P. Heutink, Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia, Lancet Neurol. 7 (10) (2008) 965–974, https://doi.org/10.1016/S1474-4422(08)70194-7.

[7] I. Le Ber, A. Camuzat, D. Hannequin, F. Pasquier, E. Guedj, A. Rovelet-Lecrux, V. Hahn-Barma, J. van der Zee, French research network on FTD/FTD-MND, Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study, Brain 131 (3) (2008) 732–746, https://doi.org/10.1093/brain/awn012.

[8] J.M. Poos, L.C. Jiskoot, S.M.J. Leijdesdorff, H. Seelaar, J.L. Panman, E.L. van der Ende, E. van den Berg, Cognitive profiles discriminate between genetic variants of behavioral variant of frontotemporal dementia, J. Neurol. 267 (2020) 1603–1612, https://doi.org/10.1007/s00415-020-09738-y.

[9] J.C. van Swieten, M.G. Spillantini, Hereditary frontotemporal dementia caused by tau gene mutations, Brain Pathol. 17 (1) (2007) 63–73, https://doi.org/10.1111/j.1750-3639.2007.00052.x.

[10] S.J. Sha, L.T. Takada, K.P. Rankin, J.S. Yokoyama, N.J. Rutherford, J.C. Fong, A. L. Boxer, Frontotemporal dementia due to C9ORF72 mutations: clinical and imaging features, Neurology 79 (10) (2012) 1002–1011, https://doi.org/10.1212/WNL.0b013e318268452e.

[11] J.S. Snowden, S. Rollinson, J.C. Thompson, J.M. Harris, C.L. Stopford, A.M. T. Richardson, S.M. Pickering-Brown, Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9orf72 mutations, Brain 135 (Pt 3) (2012) 693–708, https://doi.org/10.1093/brain/awr355.

[12] J.D. Rohrer, J.D. Warren, N.C. Fox, M.N. Rossor, Presymptomatic studies in genetic frontotemporal dementia, Rev. Neurol. 169 (10) (2013) 820–824, https://doi.org/10.1016/j.neurol.2013.07.010.

[13] C.J. Mahoney, J. Beck, J.D. Rohrer, T. Lashley, K. Mok, T. Shakespeare, J. D. Warren, Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features, Brain 135 (2012) 736–750, https://doi.org/10.1093/brain/awr361.

[14] J.D. Rohrer, J.M. Nicolas, D.M. Cash, J.C. van Swieten, E.G.P. Dopper, L.C. Jiskoot, M.N. Rossor, Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the genetic frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis, Lancet Neurol. 14 (2015) 253–262, https://doi.org/10.1016/S1474-4422(14)70324-2.

[15] L.C. Jiskoot, E.G.P. Dopper, T. den Heijer, R. Timman, R. van Minkelen, J.C. van Swieten, J.M. Papma, Presymptomatic cognitive decline in familial frontotemporal dementia: a longitudinal study, Neurology 87 (4) (2016) 384–391, https://doi.org/10.1212/WNL.0000000000002895.

[16] L.C. Jiskoot, J.L. Panman, L. van Asseldonk, S. Franzen, L.H.H. Meeter, L. Donker Kaat, J.M. Papma, Longitudinal cognitive biomarkers predicting symptom onset in presymptomatic frontotemporal dementia, J. Neurol. 265 (6) (2018) 1381–1392, https://doi.org/10.1007/s00415-018-8850-7.

[17] M. Barandiaran, A. Estanga, F. Moreno, B. Indakoetxea, A. Alzualde, N. Balluerka, A. López de Munain, Neuropsychological features of asymptomatic c.709-1G>a progranulin carriers, J. Int. Neuropsychol. Soc. 18 (6) (2012) 1086–1090, https://doi.org/10.1017/S1355617712000823.

[18] S. Weintraub, L. Besser, H.H. Dodge, M. Teylan, S. Ferris, F.C. Goldstein, J. C. Morris, Version 3 of the Alzheimer disease Centers' neuropsychological test Battery in the uniform data set (UDS), Alzheimer Dis. Assoc. Disord. 32 (2018) 10–17, https://doi.org/10.1097/WAD.0000000000000223.

[19] K.L. Possin, V.R. Laluz, O.Z. Alcantar, B.L. Miller, J.H. Kramer, Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia, Neuropsychologia 49 (2011) 43–48, https://doi.org/10.1016/j.neuropsychologia.2010.10.026.

[20] K. Rascovsky, E. Moran, L. Baehr, D. Irwin, C. McMillan, M. Grossman, Utility and neuroanatomical correlates of the FTLD-NACC neuropsychology module in the differential diagnosis of behavioural variant frontotemporal dementia and Alzheimer's disease, Neurology 84 (14 Supplement) (2015).

[21] B.R. Brooks, R.G. Miller, M. Swash, T.L. Munsat, World Federation of Neurology Research Group on motor neuron diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotrop. Later. Scler. Other Motor Neuron Disord. 1 (5) (2000) 293–299, https://doi.org/10.1080/146608200300079536.

[22] J.D. Rohrer, A.M. Isaacs, S. Mizielinska, S. Mead, T. Lashley, S. Wray, J.D. Warren, C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis, Lancet Neurol. 14 (2015) 291–301, https://doi.org/10.1016/S1474-4422(14)70233-9.

[23] T. Miyagawa, D. Brushaber, J. Syrjanen, W. Kremers, J. Fields, L.K. Forsberg, Z. Wszolek, Utility of the global CDR® plus NACC FTLD rating and development of scoring rules: data from the ARTFL/LEFFTDS consortium, Alzheimer's Dement. 16 (1) (2020) 106–117, https://doi.org/10.1002/alz.12033.

[24] H.J. Wear, C.J. Wedderburn, E. Mioshi, C.H. Williams-Gray, S.L. Mason, R. A. Barker, J.R. Hodges, The Cambridge Behavioural inventory revised, Dementia Neuropsychol. 2 (2) (2008) 102–107, https://doi.org/10.1590/S1980-57642009DN20200005.

[25] E. Mioshi, S. Hsieh, S. Savage, M. Hornberger, J.R. Hodges, Clinical staging and disease progression in frontotemporal dementia, Neurology 75 (20) (2010) 1591–1597, https://doi.org/10.1212/WNL.0b013e3181e04070.

[26] M.F. Folstein, S.E. Folstein, P.R. McHugh, Mini-mental state. A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198, https://doi.org/10.1016/0022-3956(75)90026-6.

[27] L.L.T. Thurstone, T.G. Thurstone, Primary Mental Abilities, Science Research Associates, Chicago, 1962.

[28] Army Individual Test Battery, Manual of Directions and Scoring, War Department, Adjutant General's office, Washington DC, 1994.

[29] J.R. Stroop, Studies of interference in serial verbal reactions, J. Exp. Psychol. 18 (1935) 643–662, https://doi.org/10.1037/h0054651.

[30] D. Wechsler, WAIS-R: Wechsler Adult Intelligence Scale-Revised, N.Y. Psychological Corporation, New York, 1981.

[31] H. Buschke, Cued recall in amnesia, J. Int. Neuropsychol. Soc. 6 (4) (1984) 433–440, https://doi.org/10.1080/01688638408401233.

[32] K.G. Ranasinghe, K. Rankin, I.V. Lobach, J.H. Kramer, V.E. Sturm, B.M. Bettcher, B. L. Miller, Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage, Neurology 86 (2016) 600–610, https://doi.org/10.1212/WNL.0000000000002373.

[33] J.C. Morris, The clinical dementia rating (CDR): current version and scoring rules, Neurology 43 (1993) 2412–2414, https://doi.org/10.1212/wnl.43.11.2412-a.

[34] G. Floris, G. Borghero, A. Cannas, F. Di Stefano, E. Ruiu, M.R. Murru, F. Marrosu, Constructional apraxia in frontotemporal dementia associated with the C9orf72 mutation: broadening the clinical and neuropsychological phenotype, Amyotrop. Later. Scleros. Frontotemp. Degener. 16 (1–2) (2015) 8–15, https://doi.org/10.3109/21678421.2014.959450.

[35] E. Devenney, M. Hornberger, M. Irish, E. Mioshi, J. Burrell, R. Tan, J.R. Hodges, Frontotemporal dementia associated with the C9orf72 mutation: a unique clinical profile, JAMA Neurol. 71 (3) (2014) 331–339, https://doi.org/10.1001/jamaneurol.2013.6002.

[36] V.M. Van Deerlin, E. McCarty Wood, P. Moore, W. Yuan, M.S. Forman, C.M. Clark, M. Grossman, Clinical, genetic, and pathological characteristics of patients with frontotemporal dementia and progranulin mutations, JAMA Neurol. 64 (8) (2007) 1148–1153, https://doi.org/10.1001/archneur.64.8.1148.

[37] B.J. Hallam, C. Jacova, G.R. Hsiung, D. Wittenberg, P. Sengdy, P. Bouchard-Kerr, I. R. Mackenzie, Early neuropsychological characteristics of progranulin mutation carriers, J. Int. Neuropsychol. Soc. 20 (7) (2014) 694–703, https://doi.org/10.1017/S1355617714000551.

[38] S.E. Lee, A.C. Sias, M.L. Mandelli, J.A. Brown, A.B. Brown, A.M. Khazenzon, W. W. Seeley, Network degeneration and dysfunction in presymptomatic C9orf72 mutation carriers, NeuroImage: Clin. 14 (2017) 286–297, https://doi.org/10.1016/j.nicl.2016.12.006.

[39] J.M. Papma, L.C. Jiskoot, J.L. Panman, E.G.P. Dopper, T. den Heijer, L. Donker Kaat, J.C. van Swieten, Cognition and gray and white matter characteristics of presymptomatic C9orf72 repeat expansion, Neurology 89 (12) (2017) 1256–1264, https://doi.org/10.1212/WNL.0000000000004393.

[40] J.M. Poos, K.M. Moore, J.M. Nicholas, L.L. Russell, G. Peakman, R.S. Convery, Genetic F.T.D. Initiative, GENFI., Cognitive composites for genetic frontotemporal dementia: GENFI-cog, Alzheimers Res. Ther. 14 (2022) 10, https://doi.org/10.1186/s13195-022-00958-0.

[41] J.M. Poos, L.L. Russell, G. Peakman, M. Bocchetta, C.V. Greaves, L.C. Jiskoot, Genetic F.T.D. Initiative, GENFI., Impairment of episodic memory in genetic frontotemporal dementia: a GENFI study, Alzheimer's Dement. 13 (1) (2021), e12185, https://doi.org/10.1002/dad2.12185.

[42] G. Cheran, L. Wu, S. Lee, M. Manoochehri, S. Cines, E. Fallon, S. Cosentino, Cognitive indicators of preclinical behavioral variant frontotemporal dementia in MAPT carriers, J. Int. Neuropsychol. Soc. 25 (2) (2019) 184–194, https://doi.org/10.1017/S1355617718001005.

[43] K. Moore, R. Convery, M. Bocchetta, M. Neason, D.M. Cash, C. Greaves, Genetic F. T.D. Initiative, GENFI., A modified camel and Cactus test detects presymptomatic semantic impairment in genetic frontotemporal dementia within the GENFI cohort, Appl. Neuropsychol.: Adult 1-8 (2020), https://doi.org/10.1080/23279095.2020.1716357.

[44] D.M. Cash, M. Bocchetta, D.L. Thomas, K.M. Dick, J.C. van Swieten, B. Borroni, Genetic FTD Initiative, GENFI, Patterns of gray matter atrophy in genetic

frontotemporal dementia: results from the GENFI study, Neurobiol. Aging 62 (2018) 191–196, https://doi.org/10.1016/j.neurobiolaging.2017.10.008.

[45] M. Bocchetta, E. Gordon, M.J. Cardoso, M. Modat, S. Ourselin, J.D. Warren, J. D. Rohrer, Thalamic atrophy in frontotemporal dementia — not just a *C9orf72* problem, NeuroImage: Clin. 18 (2018) 675–681, https://doi.org/10.1016/j.nicl.2018.02.019.

[46] F. L'Ecuyer-Giguère, S. Greffou, S. Tabet, L.C. Frenette, S. Tinawi, M. Feyz, E. de Guise, Visual memory performance following mild traumatic brain injury and its relationship with intellectual functioning, Appl. Neuropsych.: Adult 27 (3) (2020) 219–231, https://doi.org/10.1080/23279095.2018.1528263.

[47] X. Zhang, L. Lv, G. Min, Q. Wang, Y. Zhao, Y. Li, Overview of the complex figure test and its clinical application in neuropsychiatric disorders, including copying and recall, Front. Neurol. 12 (2021), 680474, https://doi.org/10.3389/fneur.2021.680474.