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Abstract

Background: Ignite is an iPad-based cognitive assessment app designed to enhance the sensitivity of detecting early cognitive changes in presymptomatic frontotemporal dementia (FTD). It is intended for use as a remote outcome measure in future clinical trials. Before use in clinical trials, it is essential to establish the app's sensitivity for detecting cognitive impairment and to evaluate its performance relative to established clinical measures.

Methods: A total of 569 participants from the Genetic FTD Initiative who completed Ignite during their annual research visit were included. Each participant also underwent a clinical assessment and a standard neuropsychological battery. Ignite scores were z-scored against a normative sample, and cognitive composite scores were calculated across distinct domains. Disease stage was defined using the CDR+NACC-FTLD global score including neuropsychiatric and motor components (CDR+NACC-FTLD-NM), where 0=asymptomatic (N=190), 0.5=prodromal (N=110), 1=mildly symptomatic (N=27) and ≥ 2 =moderately/severely symptomatic (N=42). Linear regressions (adjusting for age, sex, and education) compared Ignite scores between healthy non-carriers (N=200) and mutation carriers stratified by disease stage, with further analyses also conducted by genetic group (*C9orf72*, *MAPT*, and *GRN*). Receiver operating characteristic (ROC) analyses were used to compare Ignite with standard neuropsychological composites.

Results: Ignite detected significant cognitive impairment in all symptomatic mutation carriers (CDR=1 and CDR ≥ 2) across all six cognitive domains compared with non-carriers ($p < 0.001$). Prodromal mutation carriers (CDR=0.5) showed impairments in all domains except social cognition, while asymptomatic carriers (CDR=0) demonstrated reduced performance in executive function, social cognition, and calculation ($p < 0.05$).

C9orf72 mutation carriers showed the earliest and broadest deficits across all cognitive domains, *MAPT* carriers exhibited pronounced impairments in semantic knowledge and social cognition, and *GRN* carriers demonstrated marked deficits in executive function and processing speed, particularly at symptomatic stages. ROC analyses demonstrated similarly good discrimination for Ignite and GENFI neuropsychology between symptomatic carriers and non-carriers across all cognitive domains (AUCs 0.91–0.92 for Ignite vs 0.89–0.93 for GENFI). Discrimination at the prodromal stage was lower for both measures, though Ignite showed higher AUCs across all domains (0.58–0.70 vs 0.55–0.64).

Conclusions: Ignite is a sensitive digital cognitive assessment capable of detecting early cognitive changes in genetic FTD and demonstrates improved discrimination compared with standard neuropsychological measures at milder disease severity. Its sensitivity to disease stage and gene-specific profiles, supports its potential utility as a scalable remote outcome measure for FTD clinical trials.

Keywords: cognitive, app, digital, frontotemporal dementia

Introduction

Frontotemporal dementia (FTD) is a clinically and genetically heterogeneous group of neurodegenerative disorders that primarily affect the frontal and temporal lobes of the brain. Clinically, FTD encompasses a spectrum of syndromes, including behavioural variant FTD (bvFTD), non-fluent/agrammatic and semantic variants of primary progressive aphasia (PPA), and, in some cases, movement disorders such as corticobasal syndrome, progressive supranuclear palsy, and motor neurone disease (Gorno-Tempini, 2011; Rascovsky et al., 2011). Genetically, approximately 20-30% of

FTD cases are familial, most commonly caused by mutations in the *C9orf72*, *GRN*, or *MAPT* genes (Baker et al., 2006; Cruts et al., 2006; DeJesus-Hernandez et al., 2011; Hutton et al., 1998; Renton et al., 2011). These mutations are associated with different patterns of clinical presentation, cognitive decline, and neurobiological progression.

As disease-modifying therapies begin to emerge, clinical trials in FTD face a critical bottleneck: the lack of sensitive outcome measures that can reliably detect subtle cognitive changes during the presymptomatic or prodromal phase and track progression over time (Desmarais et al., 2019; Panza et al., 2020; Tsai & Boxer, 2016). In Alzheimer's disease (AD), considerable progress has been made in the development of cognitive measures sensitive to the earliest stages of pathological change, including widely used tools such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), the Preclinical Alzheimer's Cognitive Composite (PACC), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Langbaum et al., 2014; Öhman et al., 2021; Silverberg et al., 2011). More recently, digital tools capturing both traditional cognitive domains and novel markers such as speech-based measures, have been deployed in large longitudinal cohorts and registries that include biomarker-characterised, cognitively unimpaired older adults (e.g., ADNI4, BioFINDER-2, DELCODE, PROSPECT-AD, RADAR-AD, REAL AD, SIDE-AD, SPeAk, WRAP, and the Brain Health Registry). Although several of these tools are still undergoing validation for use in preclinical AD, their inclusion in major collaborative research initiatives reflects increasing confidence in their potential to detect subtle cognitive changes prior to the onset of clinical symptoms (Polk et al., 2025).

In contrast to AD, relatively few digital cognitive assessment tools are currently available for FTD. Notable examples include the ALLFTD smartphone-based cognitive assessment (Wise et al., 2022), deployed within the ALLFTD study, and Ignite, an iPad-based platform used in the Genetic FTD Initiative (GENFI) study (Convery et al., 2025; Moore et al., 2022). The slower development of digital cognitive tools in FTD likely reflects the unique challenges posed by the disorder, including marked clinical and cognitive heterogeneity and prominent behavioural symptoms that place different demands on psychometric sensitivity and task design. Evidence from pen and paper neuropsychological assessments in large longitudinal cohorts such as GENFI and ALLFTD, has demonstrated that subtle cognitive decline across domains including executive function, social cognition, attention, language, and episodic memory can be detected in presymptomatic mutation carriers; however, these changes typically emerge only in the years immediately preceding symptom onset (Jiskoot et al., 2016; Poos et al., 2020; Rohrer, Nicholas, Cash, Cardoso, et al., 2015; Staffaroni et al., 2022). By contrast, biomarkers such as neurofilament light chain (NfL) and structural MRI often show abnormalities decades before clinical presentation, highlighting a substantial gap in the temporal sensitivity of currently available cognitive measures in FTD (Rohrer et al., 2015; Staffaroni et al., 2022).

Importantly, the trajectory and earliest manifestations of cognitive decline also vary by genetic mutation. For example, social cognition and verbal fluency impairments have been reported early in *C9orf72* expansion carriers (Jiskoot et al., 2016; Lule et al., 2020; Poos et al., 2022; Russell et al., 2021a), while memory and semantic impairments are more common in *MAPT* mutation carriers (Cheran et al., 2019; Jiskoot et al., 2016, 2018; Moore et al., 2020), and executive dysfunction tends to

appear earlier in *GRN* mutation carriers (Barandiaran et al., 2012, 2019; Hallam et al., 2014; Jiskoot et al., 2018). Therefore, this highlights an urgent need for digital cognitive tools in FTD that (i) are sensitive to early presymptomatic changes, (ii) reflect gene-specific impairment profiles, and (iii) are scalable for use in multi-site trials.

Ignite is an iPad-based cognitive app comprising 12 interactive tasks designed to assess domains commonly affected in genetic FTD, including executive function, processing speed, social cognition, visuospatial skills, arithmetic, and semantic knowledge (Moore et al., 2022). Designed for remote self-administration, it includes standardised instructions and practice trials with video demonstrations to ensure usability across a wide range of users. Ignite has been tested in over 2,000 healthy adults to establish normative data and has demonstrated good test-retest reliability and concurrent validity with gold-standard neuropsychological measures (Convery et al., 2025). The present study investigates the performance of Ignite in the GENFI cohort, with the primary aim of determining its sensitivity to early cognitive changes in presymptomatic mutation carriers, among genetic groups, and its association with established markers of disease severity.

Materials and methods

Participants

Participants were recruited from 24 different sites in the GENFI study. The study was approved by each local ethics committee and informed consent was obtained from all participants. The cohort included individuals with symptoms of FTD diagnosed by standard criteria and also presymptomatic mutation carriers and non-carriers, who are

first-degree relatives of individuals with a genetic mutation but do not carry a mutation themselves and therefore act as a natural control group.

Study design

Participants completed the Ignite assessment during their annual GENFI research visit. All participants entered basic demographic information into the app before completing each test in a predetermined order. They were told to read each test instruction carefully and watch the example videos as many times as they deemed necessary before attempting the test. No other instructions were provided. As per the standard GENFI protocol, participants also completed a standard clinical history (including the CDR+NACC-FTLD), and a neuropsychology battery. A blood sample was collected from all participants to genotype individuals into mutation carriers and non-carriers.

Materials

Ignite

Participants were presented with a short form within the app requiring them to enter basic demographic information, including age (years), education (years), sex (M/F), and country of residence. Participants then completed 12 separate cognitive tasks in a predetermined order: Think Back Level 1 and Level 2, Sum Up, Colour Mix Levels 1-4, Face Match, Mind Reading, Swipe Out, Card Sort, Line Judge, Balloon Fair, Time Tap, Path Finder Levels 1 and 2, and Picture Pair (Table 1). Detailed instructions were presented at the beginning of each test accompanied by an example video demonstrating how the task should be completed. No feedback was provided to participants on their performance, and on the final page of the assessment participants were required to select “Upload data”, which sent the results to a secure server.

206 **Table 1: Descriptions of Ignite tests and cognitive domains, with corresponding GENFI neuropsychology tests mapping onto the same domains. D-**
207 **KEFS = Delis=Kaplan Executive Function System.**

Cognitive domain	Ignite test	Task description	GENFI Neuropsychology test
Processing Speed	Colour Mix (Level 1)	Participants are required to tap the name of a colour that matches the colour of a circle.	D-KEFS Colour Naming
	Colour Mix (Level 2)	Participants are required to match the name of a colour that matches a colour word.	D-KEFS Word Reading
	Path Finder (Level 1)	Participants are required to tap from one number to the next in sequential order.	Trail Making Test Part A
	Think Back (Level 1)	Participants must indicate whether a shape presented exactly matches (including colour) the shape that preceded it.	
Executive Function	Think Back (Level 2)	Participants must indicate whether a shape presented exactly matches (including colour) the shape that came two before it.	Digit Span Backwards
	Colour Mix (Level 3)	Participants are presented with a colour word written in different coloured ink. They are required to choose the name of the colour that matches the colour of the ink.	D-KEFS Ink Naming
	Path Finder (Level 2)	Participants are required to alternate between tapping from numbers to letters in sequence (i.e., 1, A, 2, B).	Trails Part B
	Colour Mix (Level 4)	Participants are presented with a colour word written in different coloured ink. They are required to complete the task as in Level 3, unless a black border appears around the word in which case, they should match the written word rather than the ink colour.	WAIS-R Digit Symbol Test

	Card Sort	Participants are presented with four cards, one in each corner of the screen, and one card in the middle. They are required to match the card in the middle to one of the four cards according to a secret rule (e.g., Colour, Shape or Number).	
	Swipe Out	Participants are presented with arrows pointing in a given direction. They are required to swipe on the screen, in the direction of the central arrow. Flanking arrows are either facing in the same (congruent) or different (incongruent) direction.	
	Balloon Fair	Participants are required to pump a balloon to win money. The more the balloon is inflated the more money there is available to collect, however, if the balloon is pumped too much it can burst.	
Calculation	Sum Up	Participants are required to select the correct answer (from four options) to different calculations including additions, subtractions, multiplications, and divisions.	
Social Cognition	Face Match	Participants are required to tap the faces displaying a target emotion that match a word written at the top of the screen (e.g., Happy, Surprise, Anger, Fear, Sadness, Disgust).	Facial Emotion Recognition Test
	Mind Reading	Participants are required to tap the pair of eyes (from four options) that match a target emotion written at the top of the screen (e.g., reflective, contemplative).	

Visuospatial Function	Line Judge	Participants are required to select two lines that match with the orientation of two target lines presented above.	Benson Complex Figure Copy
Semantic Knowledge	Picture Pair	Participants are required to select an image (from four options) that best matches with a target image.	Modified Camel and Cactus Test

209 **Neuropsychology**

210 Participants completed a comprehensive GENFI neuropsychological battery, including
211 the WMS-R Digit Span Forward and Backward (Morris et al., 2006), Trail-Making Test
212 (Parts A and B) (Corrigan & Hinkeldey, 1987), WAIS-R Digit Symbol Test (Morris et
213 al., 2006), D-KEFS Color-Word Interference Test (colour, word, and ink naming) (Delis
214 et al., 2007), Modified Camel and Cactus Test (Moore et al., 2020), Benson Complex
215 Figure (copy and recall) (Jiskoot et al., 2023), and the Facial Emotion Recognition Test
216 (Russell et al., 2020), see Table 1.

217 **Statistical analysis**

218 Statistical analyses were performed using Stata version 19 (StataCorp). For several
219 tests, including Think Back, Colour Mix, Mind Reading, Face Match, Sum Up, Picture
220 Pair, and Line Judge, a speed-accuracy trade-off score (SAT = total correct/average
221 reaction time) was calculated. Average reaction time was also calculated for the Swipe
222 Out task along with the Flanker effect measure (average reaction time of incongruent
223 trials - average reaction time of congruent trials). The total completion time (in
224 seconds) was calculated for Path Finder Levels 1 and 2. The total number of correct
225 categories achieved was the measure of interest for the Card Sort task, and the total
226 amount of money won was calculated for the Balloon Fair test. Age, sex, and
227 education adjusted z-scores were calculated for each Ignite outcome measure from a
228 normative population of over 2,000 healthy controls (Convery et al., 2025). To assess
229 performance by cognitive domain, individual test z-scores were averaged across
230 cognitive domains that they each tap into (Table 1), to create six individual cognitive
231 composites: Processing Speed, Executive Function, Social Cognition, Semantic
232 Knowledge, Calculation, and Visuospatial Function. The same approach was applied

to the GENFI neuropsychology tests, with composites generated for each cognitive domain (Table 1); however, z-scores were calculated relative to the performance of the non-carrier group.

Demographic data were compared between groups using ANOVAs except for sex, which was compared using a chi-square test. Linear regression models were used to examine group differences between non-carriers and mutation carriers, stratified by CDR+NACC-FTLD-NM global scores, first for individual Ignite tests and then for composite scores. All models were adjusted for age, sex, and years of education. When residuals violated normality assumptions, bootstrapped regression estimates were obtained. Additional linear regressions were conducted to assess associations between genetic group (*C9orf72*, *GRN*, and *MAPT*) and CDR+NACC-FTLD-NM global scores on Ignite composite scores.

To evaluate the ability of the Ignite battery to discriminate mutation status, receiver operating characteristic (ROC) analyses were conducted comparing Ignite and GENFI neuropsychology composite scores for processing speed, executive function, and social cognition. These domains were selected because they are among the earliest and most affected in FTD, are represented by multiple tests within each composite, and were therefore considered the most robust for this analysis. Separate analyses were conducted for (1) symptomatic mutation carriers ($CDR \geq 1$, $N=69$) and (2) prodromal mutation carriers ($CDR=0.5$, $N=110$) versus non-carriers, within each cognitive domain. Logistic regression models were fitted for the corresponding Ignite and GENFI composite scores, adjusting for age, sex, and education. Adjusted predicted probabilities from these models were used to generate ROC curves, from

which area under the curve (AUC) values and 95% confidence intervals were derived to quantify classification accuracy.

Results

Demographic data

Demographic data are displayed in Table 2. Symptomatic groups were significantly older than controls and presymptomatic groups ($p=0.003$) and had significantly lower years in education ($p=0.031$). There were no significant differences in sex between the groups $X^2(6, N = 569) = 10.4$ ($p=0.057$). All symptomatic mutation carriers performed significantly lower on the GENFI Neuropsychology tests and had higher CDR+NACC-FTLD-NM sum of boxes scores than presymptomatic mutation carriers (all $p < 0.001$).

Table 2: Demographic information and GENFI neuropsychology scores. All data are shown as mean $\pm$ standard deviation. NCs= non-carriers, SOB=sum of boxes. Bold values represent ($p<0.05$) in comparison to non-carriers.

CDR+NACC-FTLDNM global	0	0.5	1	≥ 2	NCs
<i>N</i>	190	110	27	42	200
Sex (% male)	41.6	38.2	44.4	64.2	41.5
Age, y	44.6 $\pm$ 12.4	47.8 $\pm$ 12.0	59.4 $\pm$ 9.38	60.2 $\pm$ 8.76	49.4 $\pm$ 13.0
Education, y	15.8 $\pm$ 3.01	15.4 $\pm$ 2.70	13.9 $\pm$ 2.89	13.8 $\pm$ 3.16	15.7 $\pm$ 3.21
CDR+NACC-FTLDNM SOB	0 $\pm$ 0	1.11 $\pm$ 0.74	4.74 $\pm$ 1.90	12.61 $\pm$ 4.34	0.23 $\pm$ 0.68
Neuropsychology					
Processing Speed	-0.28 $\pm$ 1.01	-0.62 $\pm$ 1.22	-2.44 $\pm$ 2.48	-3.80 $\pm$ 2.96	-0.00 $\pm$ 0.82
Executive function	-0.07 $\pm$ 0.71	-0.51 $\pm$ 1.09	-2.03 $\pm$ 1.64	-2.23 $\pm$ 1.46	-0.03 $\pm$ 0.71
Social cognition	-0.11 $\pm$ 0.98	-0.04 $\pm$ 0.94	-2.38 $\pm$ 2.22	-3.47 $\pm$ 2.19	-0.00 $\pm$ 0.98
Visuo-construction	0.07 $\pm$ 0.91	-0.59 $\pm$ 1.36	-1.87 $\pm$ 1.60	-2.71 $\pm$ 1.84	-0.00 $\pm$ 1.00
Semantic Knowledge	-0.12 $\pm$ 1.14	-0.35 $\pm$ 1.33	-5.30 $\pm$ 4.64	-6.56 $\pm$ 5.40	-0.00 $\pm$ 1.00

Sensitivity to disease stage

All symptomatic mutation carriers performed significantly worse than non-carriers on 15 of the 16 Ignite tests (all $p < 0.01$), with the exception of the Think Back Level 2 task at the mildly symptomatic level (CDR=1) (see Table 3). Prodromal carriers (CDR = 0.5) showed poorer performance than non-carriers on 10 tests ($p < 0.05$), and asymptomatic carriers (CDR = 0) showed impairments on 8 tests ($p < 0.05$). At the cognitive domain level, symptomatic carriers demonstrated significantly lower performance across all six domains ($p < 0.001$), prodromal carriers were impaired in all domains except social cognition, and asymptomatic carriers showed reduced performance in executive function, social cognition, and calculation (see Table 3 and Figure 1).

283 Table 3: Differences on a) individual Ignite test scores and b) cognitive composites in FTD mutation carriers, stratified by CDR+NACC-FTLD-NM
284 global scores, compared to non-carriers. Adj. mean diff = adjusted mean difference between groups, LCI = lower 95% confidence interval, UCI =
285 upper 95% confidence interval.

a)

Cognitive domain	Ignite test	0				0.5				1				≥2			
		Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI
Processing speed	<i>Colour Mix Level 1</i>	-0.08	0.422	-0.28	0.12	-0.26	0.038	-0.50	-0.01	-1.04	0.000	-1.41	-0.67	-1.43	0.000	-1.76	-1.02
	<i>Colour Mix Level 2</i>	-0.13	0.216	-0.34	0.08	-0.32	0.011	-0.56	-0.07	-1.01	0.000	-1.44	-0.59	-1.53	0.000	-1.97	-1.14
	<i>Path Finder Level 1</i>	-0.14	0.157	-0.34	0.05	-0.43	0.000	-0.66	-0.20	-1.00	0.000	-1.40	-0.61	-1.57	0.000	-1.88	-1.10
	<i>Think Back Level 1</i>	-0.19	0.072	-0.40	0.02	-0.22	0.074	-0.46	0.02	-0.85	0.000	-1.27	-0.43	-1.17	0.000	-1.53	-0.71
Executive function	<i>Colour Mix Level 3</i>	-0.28	0.007	-0.48	-0.08	-0.59	0.000	-0.83	-0.34	-1.26	0.000	-1.62	-0.90	-1.50	0.000	-1.85	-1.05
	<i>Colour Mix Level 4</i>	-0.25	0.020	-0.46	-0.04	-0.33	0.009	-0.58	-0.08	-0.94	0.000	-1.38	-0.49	-1.38	0.000	-1.82	-1.14
	<i>Path Finder Level 2</i>	-0.26	0.003	-0.44	-0.09	-0.50	0.000	-0.74	-0.26	-1.27	0.000	-1.69	-0.84	-1.69	0.000	-2.01	-1.22
	<i>Think Back Level 2</i>	-0.17	0.159	-0.41	0.07	-0.18	0.201	-0.46	0.10	0.20	0.550	-0.46	0.86	-0.80	0.006	-1.49	-0.09
	<i>Balloon Fair</i>	-0.28	0.008	-0.49	-0.07	-0.20	0.117	-0.45	0.05	-0.88	0.000	-1.28	-0.48	-1.00	0.000	-1.34	-0.46
	<i>Swipe Out</i>	-0.32	0.023	-0.59	-0.04	-0.50	0.007	-0.87	-0.13	-1.70	0.000	-2.46	-0.94	-2.52	0.000	-2.97	-1.55
	<i>Card Sort</i>	-0.10	0.330	-0.32	0.11	-0.20	0.105	-0.45	0.04	-0.53	0.018	-0.96	-0.09	-0.79	0.000	-1.18	-0.33
Social cognition	<i>Mind Reading</i>	-0.39	0.001	-0.61	-0.16	-0.16	0.239	-0.42	0.11	-0.70	0.004	-1.18	-0.23	-1.08	0.000	-1.41	-0.46
	<i>Face Match</i>	-0.20	0.042	-0.40	-0.01	-0.18	0.126	-0.41	0.05	-1.12	0.000	-1.53	-0.71	-1.63	0.000	-2.00	-1.22
Semantic knowledge	<i>Picture Pair</i>	-0.35	0.115	-0.78	0.09	-0.83	0.002	-1.34	-0.32	-2.67	0.000	-3.52	-1.83	-3.71	0.000	-4.38	-3.05
Visuospatial function	<i>Line Judge</i>	-0.21	0.056	-0.42	0.01	-0.35	0.012	-0.63	-0.08	-1.86	0.000	-2.57	-1.16	-2.58	0.000	-3.19	-1.87
Calculation	<i>Sum Up</i>	-0.20	0.046	-0.39	0.00	-0.44	0.000	-0.68	-0.20	-1.13	0.000	-1.61	-0.65	-1.70	0.000	-1.87	-1.22

286b)

Cognitive domain	0				0.5				1				≥2			
	Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI	Adj. mean diff	p-value	LCI	UCI
<i>Processing speed</i>	-0.14	0.114	-0.31	0.03	-0.37	0.000	-0.57	-0.18	-1.01	0.000	-1.35	-0.66	-1.54	0.000	-1.83	-1.24
<i>Executive function</i>	-0.28	0.000	-0.41	-0.14	-0.43	0.000	-0.62	-0.24	-1.13	0.000	-1.48	-0.79	-1.56	0.000	-1.83	-1.28
<i>Social cognition</i>	-0.30	0.001	-0.48	-0.12	-0.17	0.114	-0.38	0.04	-0.83	0.000	-1.22	-0.45	-1.35	0.000	-1.66	-1.04
<i>Semantic knowledge</i>	-0.35	0.115	-0.78	0.09	-0.83	0.002	-1.34	-0.32	-2.67	0.000	-3.52	-1.83	-3.71	0.000	-4.38	-3.05
<i>Visuospatial function</i>	-0.21	0.056	-0.42	0.01	-0.35	0.012	-0.63	-0.08	-1.86	0.000	-2.57	-1.16	-2.58	0.000	-3.19	-1.87
<i>Calculation</i>	-0.20	0.046	-0.39	0.00	-0.44	0.000	-0.68	-0.20	-1.13	0.000	-1.61	-0.65	-1.70	0.000	-1.87	-1.22

287

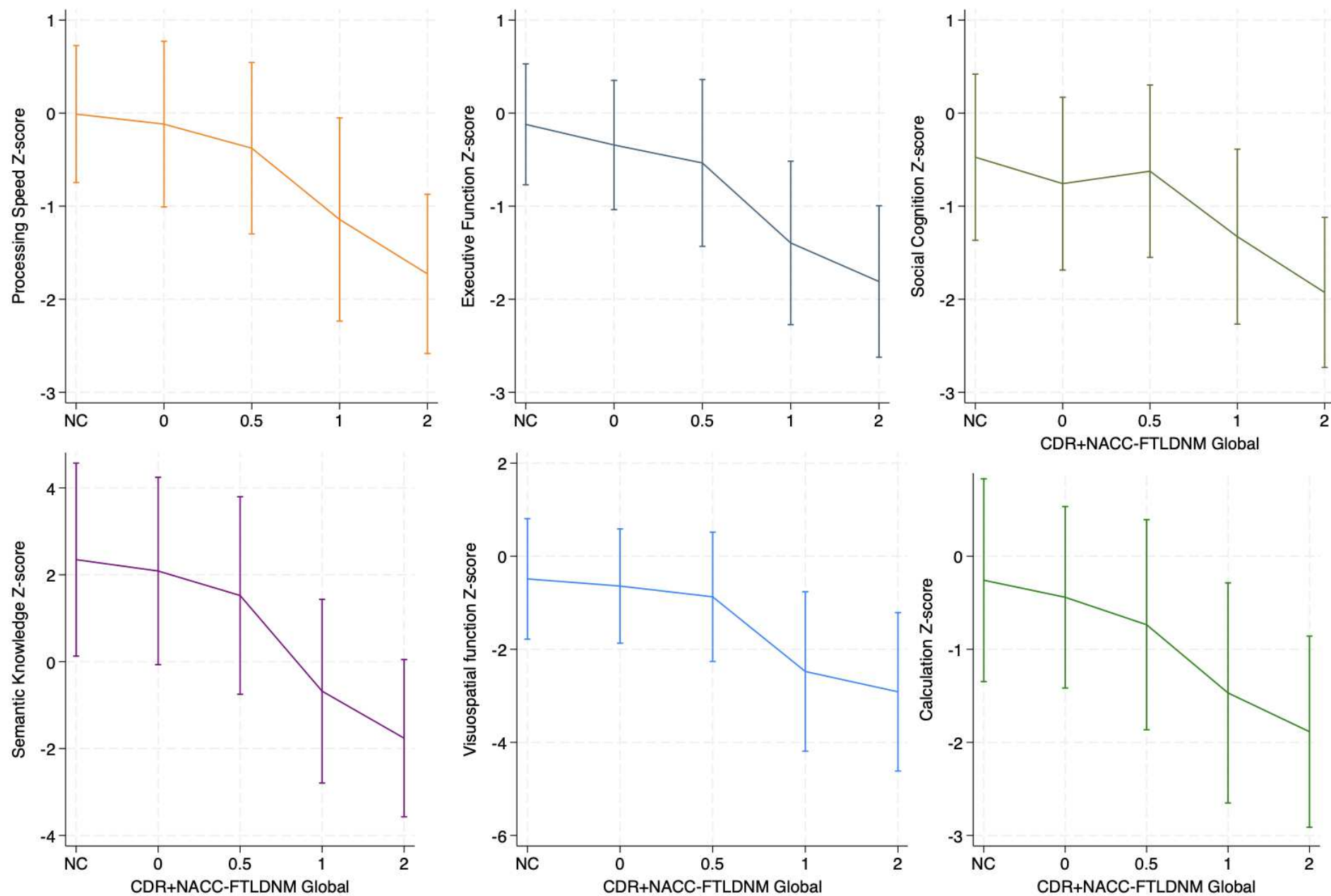


Figure 1: Line graphs displaying mean Ignite cognitive domain z-scores by CDR+NACC-FTLD-NM global scores. Bars represent standard deviations.

Genetic groups

Groups were stratified by CDR+NACC-FTLD-NM: *C9orf72* (0=95, 0.5=68, 1=18, $\geq 2=27$), *MAPT* (0=29, 0.5=19, 1=6, $\geq 2=9$), and *GRN* (0=66, 0.5=22, 1=4, $\geq 2=6$). Across all disease stages, *C9orf72* expansion carriers performed significantly worse than non-carriers across all six Ignite cognitive domains (all $p < 0.05$; Table 4, Figure 2). For *MAPT*, moderately to severely symptomatic carriers (CDR ≥ 2) showed significantly poorer performance across all six cognitive domains compared with non-carriers ($p < 0.001$). Mildly symptomatic carriers (CDR=1) also performed worse across domains ($p < 0.05$), with the exception of processing speed, which did not differ from non-carriers ($p = 0.157$). At the asymptomatic stage (CDR=0), significant differences were observed in social cognition ($p = 0.011$) and semantic knowledge ($p = 0.001$); however, no significant differences were detected between carriers and non-carriers at the prodromal stage (CDR=0.5). Moderately to severely symptomatic *GRN* carriers performed significantly worse than non-carriers across all six cognitive domains (all $p < 0.001$). In the prodromal and mildly symptomatic stages, significant differences were observed in executive function and semantic knowledge ($p < 0.05$). No significant differences were detected at the asymptomatic stage.

Table 4: Ignite performance by cognitive domain and CDR+NACC-FTLD-NM by each genetic group, a) *C9orf72*, b), *GRN*, and c) *MAPT*.

a)

Cognitive domain	<i>C9orf72</i>															
	0				0.5				1				≥2			
	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI
<i>Processing speed</i>	-0.31	0.003	-0.52	-0.11	-0.50	0.000	-0.73	-0.27	-1.26	0.000	-1.67	-0.86	-1.55	0.000	-1.90	-1.20
<i>Executive function</i>	-0.46	0.000	-0.63	-0.28	-0.58	0.000	-0.78	-0.39	-1.31	0.000	-1.67	-0.95	-1.71	0.000	-2.02	-1.39
<i>Social cognition</i>	-0.41	0.000	-0.63	-0.19	-0.25	0.049	-0.49	0.00	-0.82	0.000	-1.27	-0.37	-1.46	0.000	-1.83	-1.09
<i>Semantic</i>	-0.57	0.033	-1.10	-0.05	-0.74	0.014	-1.32	-0.15	-2.67	0.000	-3.71	-1.63	-3.21	0.000	-4.11	-2.32
<i>Visuospatial</i>	-0.47	0.001	-0.75	-0.19	-0.62	0.000	-0.94	-0.31	-2.27	0.000	-2.82	-1.71	-2.67	0.000	-3.16	-2.18
<i>Calculation</i>	-0.37	0.002	-0.61	-0.13	-0.61	0.000	-0.88	-0.35	-1.38	0.000	-1.86	-0.91	-1.82	0.000	-2.21	-1.42

b)

Cognitive domain	<i>GRN</i>															
	0				0.5				1				≥2			
	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI
<i>Processing speed</i>	0.04	0.714	-0.19	0.27	-0.32	0.084	-0.67	0.04	-0.69	0.152	-1.64	0.26	-1.19	0.001	-1.87	-0.51
<i>Executive function</i>	-0.14	0.168	-0.34	0.06	-0.33	0.042	-0.64	-0.01	-1.01	0.016	-1.82	-0.19	-1.26	0.000	-1.85	-0.67
<i>Social cognition</i>	-0.11	0.388	-0.36	0.14	-0.29	0.146	-0.67	0.10	-0.53	0.401	-1.78	0.71	-0.69	0.043	-1.42	-0.04
<i>Semantic</i>	0.34	0.256	-0.25	0.93	-1.27	0.007	-2.19	-0.36	-1.65	0.031	-4.08	-1.78	-4.32	0.000	-6.06	-2.59
<i>Visuospatial</i>	-0.02	0.908	-0.33	0.30	0.16	0.532	-0.33	0.65	0.00	0.999	-1.30	1.30	-2.48	0.000	-3.41	-1.55
<i>Calculation</i>	-0.04	0.762	-0.31	0.23	-0.04	0.863	-0.45	0.38	-0.06	0.908	-1.16	1.04	-1.28	0.001	-2.07	-0.50

c)

Cognitive domain	<i>MAPT</i>															
	0				0.5				1				≥2			
	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI	Mean diff	p-value	LCI	UCI
<i>Processing speed</i>	-0.18	0.281	-0.51	0.15	-0.15	0.444	-0.54	0.24	-0.49	0.157	-1.16	0.19	-1.85	0.000	-2.41	-1.29
<i>Executive function</i>	-0.14	0.350	-0.42	0.15	-0.12	0.469	-0.46	0.21	-0.71	0.028	-1.34	-0.08	-1.42	0.000	-1.96	-0.88
<i>Social cognition</i>	-0.46	0.011	-0.82	-0.11	0.17	0.415	-0.25	0.60	-1.04	0.010	-1.83	-0.25	-1.50	0.000	-2.10	-0.91
<i>Semantic</i>	-1.43	0.001	-2.28	-0.59	-0.75	0.143	-1.75	0.25	-3.07	0.001	-4.79	-1.35	-4.66	0.000	-6.08	-3.23
<i>Visuospatial</i>	-0.07	0.751	-0.52	0.38	-0.24	0.386	-0.77	0.30	-1.65	0.000	-2.57	-0.73	-2.50	0.000	-3.30	-1.69
<i>Calculation</i>	-0.05	0.805	-0.43	0.33	-0.34	0.136	-0.80	0.11	-0.83	0.037	-1.61	-0.05	-1.59	0.000	-2.23	-0.94

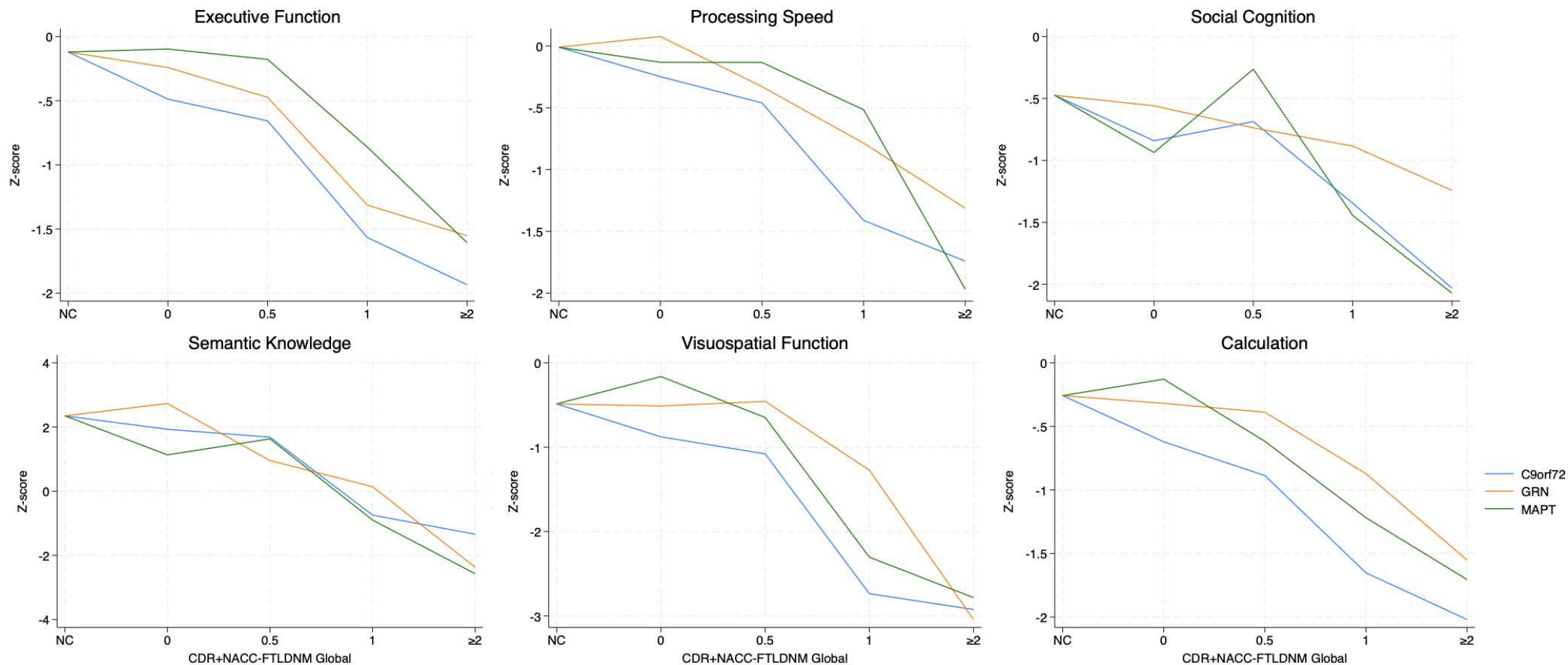


Figure 2: Line graphs displaying mean Ignite cognitive domain z-scores by CDR+NACC-FTLD-NM global scores and genetic group.

313 **ROC analyses**

314 Across cognitive domains, Ignite and the GENFI neuropsychology composites showed
 315 robust discrimination between symptomatic mutation carriers ($CDR \geq 1$) and non-
 316 carriers. For executive function, Ignite achieved an AUC of 0.92 while the GENFI
 317 composite yielded an AUC of 0.90 (Figure 3, Table 5). Discrimination was similarly
 318 high for processing speed (Ignite AUC = 0.92; GENFI AUC = 0.93) and social cognition
 319 (Ignite AUC = 0.91; GENFI AUC = 0.92). In contrast, discrimination between prodromal
 320 carriers ($CDR = 0.5$) and non-carriers was consistently lower across domains. For
 321 executive function, AUCs were 0.66 for Ignite and 0.60 for GENFI. For processing
 322 speed, Ignite demonstrated an AUC of 0.70, compared with 0.64 for GENFI.
 323 Discrimination was weakest for social cognition, with AUCs of 0.58 for Ignite and 0.55
 324 for GENFI.

325 **Table 5: ROC analyses between Ignite and GENFI neuropsychology composites for**
 326 **classification of symptomatic and prodromal mutation carriers across multiple cognitive**
 327 **domains. AUC=Area under the curve, CIs=95% confidence intervals.**

Groups	Cognitive domain	GENFI Neuropsychology		Ignite	
		AUC	CIs	AUC	CIs
Symptomatic ($CDR \geq 1$) carriers	Executive function	0.904	0.84-0.95	0.922	0.87-0.97
	Processing speed	0.929	0.89-0.97	0.918	0.86-0.97
	Social cognition	0.920	0.87-0.96	0.906	0.86-0.96
Prodromal ($CDR = 0.5$) carriers	Executive function	0.609	0.54-0.69	0.661	0.55-0.70
	Processing speed	0.640	0.63-0.76	0.696	0.57-0.70

328

	Social cognition	0.551	0.48-0.62	0.577	0.49-0.63
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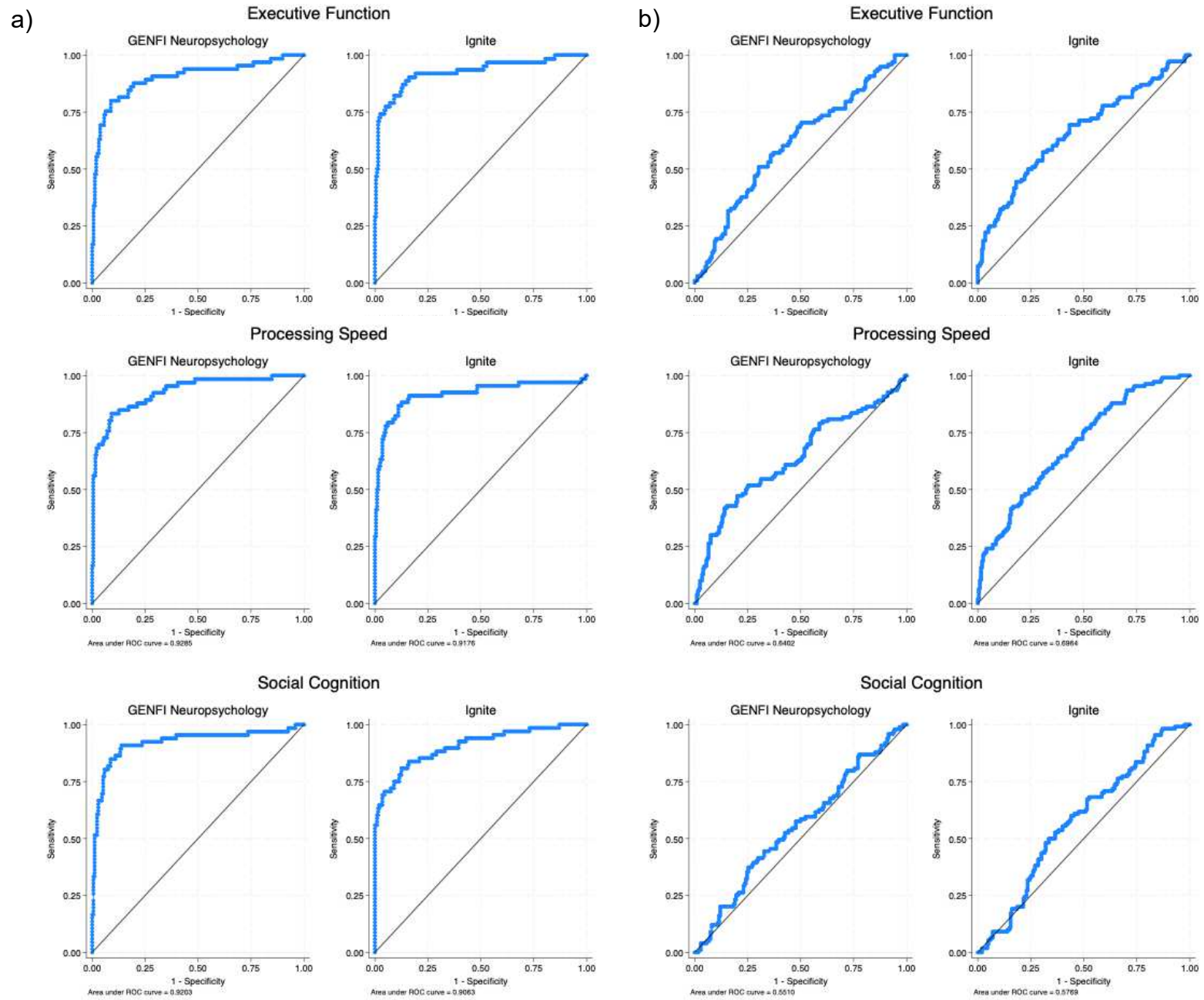


Figure 3: ROC curves comparing Ignite and GENFI neuropsychology measures in distinguishing a) symptomatic and b) prodromal mutation carriers from non-carrier controls across cognitive domains.

Discussion

The present study evaluated the sensitivity of the Ignite app for detecting early cognitive impairment in a large cohort of individuals from the GENFI study. Our findings demonstrate that Ignite is sensitive to cognitive deficits associated with genetic FTD and is able to distinguish symptomatic and prodromal mutation carriers from non-carriers across multiple cognitive domains, and even asymptomatic carriers from non-carriers in domains known to be affected early in the disease course. Across genes, Ignite revealed distinct patterns of cognitive impairment that varied by disease stage. *C9orf72* expansion carriers showed widespread deficits across all Ignite domains, including detectable impairments at the asymptomatic stage, indicating particular sensitivity of Ignite to very early cognitive changes in this group. In contrast, *MAPT* and *GRN* mutation carriers demonstrated more stage-dependent and domain specific impairments, consistent with differing cognitive profiles across genetic forms of FTD. Importantly, Ignite showed comparable discriminative performance compared with standard pen-and-paper neuropsychological assessments at the symptomatic level, and mildly superior discriminative abilities during the prodromal phase, supporting its potential utility as a digital cognitive outcome measure for future clinical trials. Over time, integrating digital tools like Ignite into routine assessments may allow for more continuous and ecologically valid tracking of cognitive trajectories, supporting a shift towards more personalised and responsive care pathways.

Sensitivity of Ignite to cognitive impairment

At the individual test level, nearly all Ignite tasks were sensitive to cognitive impairment in symptomatic mutation carriers; however, not all measures demonstrated equivalent sensitivity across disease stages. Notably, the Think Back Level 2 task did not

differentiate mildly symptomatic carriers from non-carriers, suggesting that this task may be less sensitive to early or moderate disease related changes. This may reflect limited task complexity or relatively preserved working memory function in early FTD. As such, certain individual tasks, particularly those that do not show consistent group separation, may be candidates for exclusion or modification in future analyses to optimise the sensitivity of the Ignite battery.

Importantly, domain level analyses suggest that executive function, social cognition, and calculation may represent the earliest cognitive domains detectable using Ignite. Impairments in these domains were evident in asymptomatic carriers, supporting their potential utility as early digital biomarkers of disease related change. Previous work from GENFI using standard neuropsychometry demonstrated subtle cognitive decline, but only prior to clinical symptom onset, particularly in the years immediately preceding conversion (Jiskoot et al., 2016; Poos et al., 2020). The ability of Ignite to detect impairments at the asymptomatic stages suggests that digitally derived measures, such as reaction times and speed–accuracy trade-offs, that capture more detailed aspects of performance variability may be more sensitive to early disease related changes than traditional neuropsychological tests. Together, these findings highlight the value of focusing on domain- and task-level sensitivity when refining digital cognitive batteries and suggest that prioritising the most responsive measures may enhance the ability of Ignite to detect subtle presymptomatic changes.

Gene-specific cognitive profiles

Distinct patterns of cognitive impairment were observed across genetic subgroups, in keeping with established genotype phenotype associations in FTD. For instance, *C9orf72* expansion carriers exhibited impairments across all cognitive domains at

every disease stage, consistent with the broad and heterogeneous cognitive phenotype associated with this mutation(Jiskoot et al., 2023; Mahoney et al., 2012; Poos et al., 2020), and with early, widespread cortical and subcortical atrophy (Saracino et al., 2025; Cash et al., 2018; Mahoney et al., 2012). *MAPT* mutation carriers demonstrated early impairments in social cognition and semantic knowledge at the asymptomatic stage, with broader cognitive deficits emerging as the disease progressed, consistent with findings from pen-and-paper neuropsychological assessments (Jiskoot et al., 2018; Moore et al., 2020; Poos et al., 2020, 2022) and evidence of early temporal lobe involvement (Rohrer & Warren, 2011). This effect did not persist at the prodromal phase, but this variability in performance is likely due to the small numbers in this group. *GRN* mutation carriers exhibited prominent executive and semantic impairments in the prodromal and mildly symptomatic stages, aligning with the characteristic cognitive profile (Barandiaran et al., 2012, 2019; Hallam et al., 2014; Jiskoot et al., 2018; Moore et al., 2020; Poos et al., 2020, 2022) and pattern of neurodegeneration seen in this group (Cash et al., 2018; Rohrer, Nicholas, Cash, Cardoso, et al., 2015). However, early changes were not detected, again consistent with the relatively well-preserved cognitive performance we see in this group followed by a more rapid decline following symptoms (Poos et al., 2022; Staffaroni et al., 2022). These findings indicate that Ignite is sensitive not only to disease severity but also to gene-specific cognitive signatures.

Comparison with standard neuropsychology

ROC analyses demonstrated that Ignite showed comparable discriminative performance relative to the GENFI neuropsychology composites across multiple cognitive domains for symptomatic carriers. Ignite moderately outperformed GENFI in distinguishing symptomatic mutation carriers from non-carriers on executive function

tasks but achieved similarly high AUCs across other domains. In contrast, discrimination between prodromal carriers and non-carriers was consistently poorer across all domains for both Ignite and GENFI, reflecting the subtle and heterogeneous nature of cognitive impairment at this early disease stage. However, Ignite demonstrated modestly higher AUCs than GENFI for all cognitive domains in prodromal carriers. Together, these findings indicate that Ignite demonstrates robust classification accuracy in established symptomatic disease and may offer improved sensitivity during the prodromal phase. With further validation, these findings have potential implications for future patient pathways. In clinical settings, tools such as Ignite could complement or enhance standard neuropsychological assessments by providing a more sensitive and granular measure of cognitive change, particularly in the earliest stages of disease where traditional measures may lack precision, supporting earlier identification of subtle cognitive decline.

An important methodological consideration is that z-scores for the two assessments were derived from different reference populations. GENFI neuropsychology composites are standardised relative to non-carrier family members within the cohort, whereas Ignite z-scores are derived from a large normative dataset of over 2,000 healthy controls (Convery et al., 2025). This difference in normative anchoring may contribute to observed differences in discriminative performance, particularly by reducing variance and increasing sensitivity in the Ignite metrics. Nevertheless, the consistent performance of Ignite across domains, coupled with its slightly superior discrimination in early symptomatic and prodromal stages, supports its potential utility as a sensitive outcome measure for clinical trials targeting early disease progression.

Implications for clinical trials and remote assessment

The development of sensitive, scalable cognitive outcome measures is critical for the success of disease-modifying trials in genetic FTD, particularly in presymptomatic and prodromal populations. Ignite offers several advantages in this context, including self-administration, standardised instructions, and suitability for remote deployment. Its sensitivity to early cognitive change and ability to capture gene-specific impairment profiles suggest that it may be particularly useful as a cognitive endpoint in multisite and prevention-focused trials.

Limitations and future directions

Several limitations should be acknowledged. First, the analyses were cross-sectional, limiting inferences about within-person cognitive change over time. Longitudinal studies will be essential to determine the sensitivity of Ignite to subtle cognitive decline and its utility for tracking disease progression. In addition, the prodromal phase of disease is characterised by substantial inter-individual variability in both duration and clinical expression, and the relatively small sample sizes within prodromal subgroups may have reduced statistical power to detect subtle effects in this group. Heterogeneity in the severity and profile of cognitive impairment within this group further complicates discrimination at this early stage and likely contributes to the modest classification performance observed.

Second, the current version of Ignite does not include an episodic memory task, although recent evidence has emerged showing episodic memory may be affected early in FTD, particularly in *MAPT* mutation carriers (Poos et al., 2021; Rohrer, Nicholas, Cash, van Swieten, et al., 2015b), nor does it incorporate a performance validity measure or collect detailed demographic information on ethnicity within the

app. To address these limitations, a revised version of the battery (Ignite+) has been developed, incorporating episodic memory and performance validity tasks alongside enhanced demographic data capture, and will be deployed within future GENFI studies. Further work should assess the robustness of Ignite+ across sites and culturally diverse samples, and evaluate its integration with fluid biomarkers and neuroimaging measures to enhance early disease detection and improve characterisation of disease stage.

Conclusion

In summary, this study demonstrates that Ignite is a sensitive digital cognitive assessment capable of detecting early cognitive impairment in genetic FTD. Ignite showed good discriminative performance and demonstrated sensitivity to disease severity and gene-specific cognitive profiles. These findings support the use of Ignite as a promising cognitive outcome measure for future clinical trials and remote monitoring in genetic FTD.

Declarations

Ethics approval and consent to participate

All participants signed informed consent before information collection and the study has full ethical approval under the GENetic Frontotemporal dementia (GENFI) where ethics committees approved the study at each site. The study was conducted according to the Declaration of Helsinki.

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. The normative calculator is available for use on the GENFI website (www.genfi.org/ignite). The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

Competing Interests

No competing interests.

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Author contributions

R.C designed and executed the study, recruited participants, analysed the data, and wrote the main manuscript text. K.AC, A.B, S.G, E.L, and S.F, helped with the recruitment of participants and study visits. E.FB and A.B helped to pre-process the data for analysis. J.DR and L.R supervised this project. J.DR reviewed and edited the manuscript. H.S, J.BR, B.B, M.M., C.MT, E.CF, B.N, A.GT, A.G, T.L, R.J.L, R.SV, A.M, F.M, M.S, R.V, S.D, R.B, E.S, J.K, P.K, M.O, G.L, I.IG and E.RR reviewed and commented on the manuscript.

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500 **References**

- 501 Baker, M., Mackenzie, I. R., Pickering-Brown, S. M., Gass, J., Rademakers, R.,
502 Lindholm, C., Snowden, J., Adamson, J., Sadovnick, A. D., Rollinson, S., Cannon,
503 A., Dwosh, E., Neary, D., Melquist, S., Richardson, A., Dickson, D., Berger, Z.,
504 Eriksen, J., Robinson, T., ... Hutton, M. (2006). Mutations in progranulin cause
505 tau-negative frontotemporal dementia linked to chromosome 17. *Nature*,
506 442(7105), 916–919. <https://doi.org/10.1038/nature05016>
- 507 Barandiaran, M., Estanga, A., Moreno, F., Indakoetxea, B., Alzualde, A., Balluerka,
508 N., Massó, J. F. M., & De Munain, A. L. (2012). Neuropsychological Features of
509 Asymptomatic c.709-1G>A Progranulin Mutation Carriers*. *Journal of the*
510 *International Neuropsychological Society*, 18(6), 1086–1090.
511 <https://doi.org/10.1017/S1355617712000823>
- 512 Barandiaran, M., Moreno, F., De Arriba, M., Indakoetxea, B., Boda, I., Gabilondo, A.,
513 Tainta, M., & López De Munain, A. (2019). Longitudinal Neuropsychological Study
514 of Presymptomatic c.709-1G>A Progranulin Mutation Carriers. *Journal of the*
515 *International Neuropsychological Society*, 25(1), 39–47.
516 <https://doi.org/10.1017/S1355617718000735>
- 517 Cash, D. M., Bocchetta, M., Thomas, D. L., Dick, K. M., van Swieten, J. C., Borroni,
518 B., Galimberti, D., Masellis, M., Tartaglia, M. C., Rowe, J. B., Graff, C., Tagliavini,
519 F., Frisoni, G. B., Laforce, R., Finger, E., de Mendonça, A., Sorbi, S., Rossor, M.
520 N., Ourselin, S., & Rohrer, J. D. (2018). Patterns of gray matter atrophy in genetic

frontotemporal dementia: results from the GENFI study. *Neurobiology of Aging*,
62, 191–196. <https://doi.org/10.1016/j.neurobiolaging.2017.10.008>

Cheran, G., Wu, L., Lee, S., Manoochchri, M., Cines, S., Fallon, E., Lynch, T.,
Heidebrink, J., Paulson, H., Goldman, J., Huey, E., & Cosentino, S. (2019).
Cognitive Indicators of Preclinical Behavioral Variant Frontotemporal Dementia in
MAPT Carriers. *Journal of the International Neuropsychological Society*, 25(2),
184–194. <https://doi.org/10.1017/S1355617718001005>

Convery, R. S., Adams-Carr, K., Nicholas, J. M., Moore, K. M., Goldsmith, S.,
Bocchetta, M., Russell, L. L., & Rohrer, J. D. (2025). Concurrent Validity, Test–
Retest Reliability, and Normative Properties of the Ignite App: A Cognitive
Assessment for Frontotemporal Dementia. *Neuropsychology*, 39(5), 402–421.
<https://doi.org/10.1037/NEU0001005>

Corrigan, J. D., & Hinkeldey, N. S. (1987). Relationships between Parts A and B of the
Trail Making Test. *Journal of Clinical Psychology*, 43(4), 402–409.
[https://doi.org/10.1002/1097-4679\(198707\)43:4<402::AID-](https://doi.org/10.1002/1097-4679(198707)43:4<402::AID-JCLP2270430411>3.0.CO;2-E)
[JCLP2270430411>3.0.CO;2-E](https://doi.org/10.1002/1097-4679(198707)43:4<402::AID-JCLP2270430411>3.0.CO;2-E)

Cruts, M., Gijselinck, I., van der Zee, J., Engelborghs, S., Wils, H., Pirici, D.,
Rademakers, R., Vandenberghe, R., Dermaut, B., Martin, J.-J., van Duijn, C.,
Peeters, K., Sciot, R., Santens, P., De Pooter, T., Mattheijssens, M., Van den
Broeck, M., Cuijt, I., Vennekens, K., ... Van Broeckhoven, C. (2006). Null
mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked
to chromosome 17q21. *Nature*, 442(7105), 920–924.
<https://doi.org/10.1038/nature05017>

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M.,
Rutherford, N. J., Nicholson, A. M., Finch, N. A., Flynn, H., Adamson, J., Kouri,

546 N., Wojtas, A., Sengdy, P., Hsiung, G.-Y. R., Karydas, A., Seeley, W. W.,
 547 Josephs, K. A., Coppola, G., Geschwind, D. H., ... Rademakers, R. (2011).
 548 Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72
 549 Causes Chromosome 9p-Linked FTD and ALS. *Neuron*, 72(2), 245–256.
 550 <https://doi.org/10.1016/J.NEURON.2011.09.011>
 551 Delis, D. C., Kaplan, E., & Kramer, J. (2007). *Delis-Kaplan executive function system:*
 552 *color-word interference test: handling*. Pearson.
 553 Desmarais, P., Rohrer, J. D., Nguyen, Q. D., Herrmann, N., Stuss, D. T., Lang, A. E.,
 554 Boxer, A. L., Dickerson, B. C., Rosen, H., van Swieten, J. C., Meeter, L. H.,
 555 Borroni, B., Tartaglia, M. C., Feldman, H. H., Black, S. E., & Masellis, M. (2019).
 556 Therapeutic trial design for frontotemporal dementia and related disorders.
 557 *Journal of Neurology, Neurosurgery & Psychiatry*, 90(4), 412–423.
 558 <https://doi.org/10.1136/JNNP-2018-318603>
 559 Gorno-Tempini, M. (2011). Classification of primary progressive aphasia and its
 560 variants. *Neurology*, 76(11), 1006–1014.
 561 Hallam, B. J., Jacova, C., Hsiung, G. Y. R., Wittenberg, D., Sengdy, P., Bouchard-
 562 Kerr, P., Slack, P., Rademakers, R., Baker, M., Chow, T. W., Levine, B., Feldman,
 563 H. H., & Mackenzie, I. R. (2014). Early Neuropsychological Characteristics of
 564 Progranulin Mutation Carriers. *Journal of the International Neuropsychological*
 565 *Society*, 20(7), 694–703. <https://doi.org/10.1017/S1355617714000551>
 566 Hutton, M., Lendon, C. L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., Pickering-
 567 Brown, S., Chakraverty, S., Isaacs, A., Grover, A., Hackett, J., Adamson, J.,
 568 Lincoln, S., Dickson, D., Davies, P., Petersen, R. C., Stevens, M., de Graaff, E.,
 569 Wauters, E., ... Heutink, P. (1998). Association of missense and 5'-splice-site

mutations in tau with the inherited dementia FTDP-17. *Nature*, 393(6686), 702–
 705. <https://doi.org/10.1038/31508>

Jiskoot, L. C., Dopper, E. G. P., Heijer, T. Den, Timman, R., Van Minkelen, R., Van
 Swieten, J. C., & Papma, J. M. (2016). Presymptomatic cognitive decline in
 familial frontotemporal dementia: A longitudinal study. *Neurology*, 87(4), 384–
 391. <https://doi.org/10.1212/WNL.0000000000002895>

Jiskoot, L. C., Panman, J. L., van Asseldonk, L., Franzen, S., Meeter, L. H. H., Donker
 Kaat, L., van der Ende, E. L., Dopper, E. G. P., Timman, R., van Minkelen, R.,
 van Swieten, J. C., van den Berg, E., & Papma, J. M. (2018). Longitudinal
 cognitive biomarkers predicting symptom onset in presymptomatic frontotemporal
 dementia. *Journal of Neurology*, 265(6), 1381–1392.
<https://doi.org/10.1007/s00415-018-8850-7>

Jiskoot, L. C., Russell, L. L., Peakman, G., Convery, R. S., Greaves, C. V., Bocchetta,
 M., Poos, J. M., Seelaar, H., Giannini, L. A. A., van Swieten, J. C., van Minkelen,
 R., Pijnenburg, Y. A. L., Rowe, J. B., Borroni, B., Galimberti, D., Masellis, M.,
 Tartaglia, C., Finger, E., Butler, C. R., ... Rohrer, J. D. (2023). The Benson
 Complex Figure Test detects deficits in visuoconstruction and visual memory in
 symptomatic familial frontotemporal dementia: A GENFI study. *Journal of the
 Neurological Sciences*, 446, 120590. <https://doi.org/10.1016/J.JNS.2023.120590>

Langbaum, J. B., Hendrix, S. B., Ayutyanont, N., Chen, K., Fleisher, A. S., Shah, R.
 C., Barnes, L. L., Bennett, D. A., Tariot, P. N., & Reiman, E. M. (2014). An
 empirically derived composite cognitive test score with improved power to track
 and evaluate treatments for preclinical Alzheimer's disease. *Alzheimer's &
 Dementia*, 10(6), 666–674. <https://doi.org/10.1016/J.JALZ.2014.02.002>

594 Lule, D. E., Müller, H. P., Finsel, J., Weydt, P., Knehr, A., Winroth, I., Andersen, P.,
 595 Weishaupt, J., Uttner, I., Kassubek, J., & Ludolph, A. C. (2020). Deficits in verbal
 596 fluency in presymptomatic C9orf72 mutation gene carriers—a developmental
 597 disorder. *Journal of Neurology, Neurosurgery & Psychiatry*, 91(11), 1195–1200.
 598 <https://doi.org/10.1136/JNNP-2020-323671>

599 Mahoney, C. J., Downey, L. E., Ridgway, G. R., Beck, J., Clegg, S., Blair, M.,
 600 Finnegan, S., Leung, K. K., Yeatman, T., Golden, H., Mead, S., Rohrer, J. D., Fox,
 601 N. C., & Warren, J. D. (2012). Longitudinal neuroimaging and neuropsychological
 602 profiles of frontotemporal dementia with C9ORF72 expansions. *Alzheimer's*
 603 *Research and Therapy*, 4(5), 1–10.
 604 <https://doi.org/10.1186/ALZRT144/FIGURES/3>

605 Moore, Convery, R., Bocchetta, M., Neason, M., Cash, D. M., Greaves, C., Russell, L.
 606 L., Clarke, M. T. M., Peakman, G., van Swieten, J., Jiskoot, L., Moreno, F.,
 607 Barandiaran, M., Sanchez-Valle, R., Borroni, B., Laforce, R., Doré, M.-C.,
 608 Masellis, M., Tartaglia, M. C., ... Rohrer, J. D. (2020). A modified Camel and
 609 Cactus Test detects presymptomatic semantic impairment in genetic
 610 frontotemporal dementia within the GENFI cohort. *Applied*
 611 *Neuropsychology:Adult*. <https://doi.org/10.1080/23279095.2020.1716357>

612 Moore, Convery, R. S., & Rohrer, J. D. (2022). Study protocol: computerised cognitive
 613 testing in a cohort of people with frontotemporal dementia. *BMJ Open*, 12, 55211.
 614 <https://doi.org/10.1136/bmjopen-2021-055211>

615 Morris, J. C., Weintraub, S., Chui, H. C., Cummings, J., DeCarli, C., Ferris, S., Foster,
 616 N. L., Galasko, D., Graff-Radford, N., Peskind, E. R., Beekly, D., Ramos, E. M.,
 617 & Kukull, W. A. (2006). The Uniform Data Set (UDS): Clinical and cognitive
 618 variables and descriptive data from Alzheimer disease centers. *Alzheimer*

619 *Disease and Associated Disorders*, 20(4), 210–216.
620 <https://doi.org/10.1097/01.WAD.0000213865.09806.92>

621 Öhman, F., Hassenstab, J., Berron, D., Schöll, M., & Papp, K. V. (2021). Current
622 advances in digital cognitive assessment for preclinical Alzheimer's disease.
623 *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 13(1),
624 e12217. <https://doi.org/10.1002/DAD2.12217>

625 Panza, F., Lozupone, M., Seripa, D., Daniele, A., Watling, M., Giannelli, G., &
626 Imbimbo, B. P. (2020). Development of disease-modifying drugs for
627 frontotemporal dementia spectrum disorders. *Nature Reviews Neurology* 2020
628 16:4, 16(4), 213–228. <https://doi.org/10.1038/s41582-020-0330-x>

629 Polk, S. E., Öhman, F., Hassenstab, J., König, A., Papp, K. V., Schöll, M., & Berron,
630 D. (2025). A scoping review of remote and unsupervised digital cognitive
631 assessments in preclinical Alzheimer's disease. *Npj Digital Medicine* 2025 8:1,
632 8(1), 266-. <https://doi.org/10.1038/s41746-025-01583-5>

633 Poos, J. M., Jiskoot, L. C., Leijdesdorff, S. M. J., Seelaar, H., Panman, J. L., van der
634 Ende, E. L., Mol, M. O., Meeter, L. H. H., Pijnenburg, Y. A. L., Donker Kaat, L.,
635 de Jong, F. J., van Swieten, J. C., Papma, J. M., & van den Berg, E. (2020).
636 Cognitive profiles discriminate between genetic variants of behavioral
637 frontotemporal dementia. *Journal of Neurology*, 267(6), 1603–1612.
638 <https://doi.org/10.1007/S00415-020-09738-Y/FIGURES/1>

639 Poos, J. M., Macdougall, A., Van Den Berg, E., Jiskoot, L. C., Papma, J. M., Van Der
640 Ende, E. L., Seelaar, H., Russell, L. L., Peakman, G., Convery, R., Pijnenburg, Y.
641 A. L., Moreno, F., Sanchez-Valle, R., Borroni, B., Laforce, R., Dore, M. C.,
642 Masellis, M., Tartaglia, M. C., Graff, C., ... Rohrer, J. D. (2022). Longitudinal
643 Cognitive Changes in Genetic Frontotemporal Dementia Within the GENFI

644 Cohort. *Neurology*, 99(3), e281–e295.
645 <https://doi.org/10.1212/WNL.0000000000200384>

646 Poos, J. M., Russell, L. L., Peakman, G., Bocchetta, M., Greaves, C. V., Jiskoot, L. C.,
647 van der Ende, E. L., Seelaar, H., Papma, J. M., van den Berg, E., Pijnenburg, Y.
648 A. L., Borroni, B., Sanchez-Valle, R., Moreno, F., Laforce, R., Graff, C., Synofzik,
649 M., Galimberti, D., Rowe, J. B., ... Rollin, A. (2021). Impairment of episodic
650 memory in genetic frontotemporal dementia: A GENFI study. *Alzheimer's &*
651 *Dementia: Diagnosis, Assessment & Disease Monitoring*, 13(1), e12185.
652 <https://doi.org/10.1002/DAD2.12185>

653 Rascovsky, K., Hodges, J. R. J. R., Knopman, D., Mendez, M. F. M. F., Kramer, J. H.
654 J. H., Neuhaus, J., van Swieten, J. C. J. C., Seelaar, H., Dopper, E. G. P. E. G.
655 P., Onyike, C. U. C. U., Hillis, A. E., Josephs, K. A., Boeve, B. F., Kertesz, A.,
656 Seeley, W. W., Rankin, K. P., Johnson, J. K., Gorno-Tempini, M.-L. M.-L., Rosen,
657 H., ... Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the
658 behavioural variant of frontotemporal dementia. *Brain: A Journal of Neurology*,
659 134(Pt 9), 2456–2477. <https://doi.org/Doi 10.1093/Brain/Awr179>

660 Renton, A. E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J. R.,
661 Schymick, J. C., Laaksovirta, H., van Swieten, J. C., Myllykangas, L., Kalimo, H.,
662 Paetau, A., Abramzon, Y., Remes, A. M., Kaganovich, A., Scholz, S. W.,
663 Duckworth, J., Ding, J., Harmer, D. W., ... Traynor, B. J. (2011). A Hexanucleotide
664 Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-
665 FTD. *Neuron*, 72(2), 257–268. <https://doi.org/10.1016/J.NEURON.2011.09.010>

666 Rohrer, J. D., Nicholas, J. M., Cash, D. M., Cardoso, M. J., Clegg Bsc, S., Espak, M.,
667 Thomas, D. L., Warren, J. D., Ourselin, S., Fox, N. C., Thomas, L., De Vita, E.,
668 Van Swieten, J., Rohrer, J. D., Nicholas, J. M., Cash, D. M., Van Swieten, J.,

Dopper, E., Jiskoot, L., ... Rossor, M. N. (2015). Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *The Lancet Global Health*. [https://doi.org/10.1016/S1474-4422\(14\)70324-2](https://doi.org/10.1016/S1474-4422(14)70324-2)

Rohrer, J. D., Nicholas, J. M., Cash, D. M., van Swieten, J., Dopper, E., Jiskoot, L., van Minkelen, R., Rombouts, S. A., Cardoso, M. J., Clegg, S., Espak, M., Mead, S., Thomas, D. L., De Vita, E., Masellis, M., Black, S. E., Freedman, M., Keren, R., MacIntosh, B. J., ... Rossor, M. N. (2015a). Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *The Lancet Neurology*, 14(3), 253–262. [https://doi.org/10.1016/S1474-4422\(14\)70324-2](https://doi.org/10.1016/S1474-4422(14)70324-2)

Rohrer, J. D., Nicholas, J. M., Cash, D. M., van Swieten, J., Dopper, E., Jiskoot, L., van Minkelen, R., Rombouts, S. A., Cardoso, M. J., Clegg, S., Espak, M., Mead, S., Thomas, D. L., De Vita, E., Masellis, M., Black, S. E., Freedman, M., Keren, R., MacIntosh, B. J., ... Rossor, M. N. (2015b). Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: A cross-sectional analysis. *The Lancet Neurology*, 14(3). [https://doi.org/10.1016/S1474-4422\(14\)70324-2](https://doi.org/10.1016/S1474-4422(14)70324-2)

Rohrer, J. D., & Warren, J. D. (2011). Phenotypic signatures of genetic frontotemporal dementia. *Current Opinion in Neurology*, 24(6), 542–549. <https://doi.org/10.1097/WCO.0b013e32834cd442>

Russell, L. L., Greaves, C. V., Convery, R. S., Nicholas, J., Warren, J. D., Kaski, D., & Rohrer, J. D. (2021). Novel instructionless eye tracking tasks identify emotion

recognition deficits in frontotemporal dementia. *Alzheimer's Research and Therapy*, 13(1). <https://doi.org/10.1186/s13195-021-00775-x>

Russell, L. L., Greaves, C. V., Bocchetta, M., Nicholas, J., Convery, R. S., Moore, K., Cash, D. M., van Swieten, J., Jiskoot, L., Moreno, F., Sanchez-Valle, R., Borroni, B., Laforce, R., Masellis, M., Tartaglia, M. C., Graff, C., Rotondo, E., Galimberti, D., Rowe, J. B., ... Anderl-Straub, S. (2020). Social cognition impairment in genetic frontotemporal dementia within the GENFI cohort. *Cortex*, 133, 384–398. <https://doi.org/10.1016/J.CORTEX.2020.08.023>

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology*, 5(JUL), 89695. <https://doi.org/10.3389/FPSYG.2014.00772/BIBTEX>

Silverberg, N. B., Ryan, L. M., Carrillo, M. C., Sperling, R., Petersen, R. C., Posner, H. B., Snyder, P. J., Hilsabeck, R., Gallagher, M., Raber, J., Rizzo, A., Possin, K., King, J., Kaye, J., Ott, B. R., Albert, M. S., Wagster, M. V., Schinka, J. A., Cullum, C. M., ... Ferman, T. J. (2011). Assessment of cognition in early dementia. *Alzheimer's & Dementia*, 7(3), e60–e76. <https://doi.org/10.1016/J.JALZ.2011.05.001>

Staffaroni, A. M., Quintana, M., Wendelberger, B., Heuer, H. W., Russell, L. L., Cobigo, Y., Wolf, A., Matt Goh, S.-Y., Petrucelli, L., Gendron, T. F., Heller, C., Clark, A. L., Carson Taylor, J., Wise, A., Ong, E., Forsberg, L., Brushaber, D., Rojas, J. C., VandeVrede, L., ... Afonso, S. (2022). Temporal order of clinical and biomarker changes in familial frontotemporal dementia. *Nature Medicine* 2022 28:10, 28(10), 2194–2206. <https://doi.org/10.1038/s41591-022-01942-9>

Tsai, R. M., & Boxer, A. L. (2016). Therapy and clinical trials in frontotemporal dementia: past, present, and future. *Journal of Neurochemistry*, 138, 211–221. <https://doi.org/10.1111/JNC.13640>

Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult*, 23(1), 29–34. <https://doi.org/10.1080/23279095.2015.1004574>

Wise, A. B., Clark, A. L., Taylor, J. C., Heuer, H. W., Mester, C. T., Rao, M., Brushaber, D., Boeve, B. F., Forsberg, L. K., Kramer, J. H., Rosen, H. J., Boxer, A. L., & Staffaroni, A. M. (2022). ALLFTD Mobile App Balance and Finger Tapping Tasks: Task Description and Initial Reliability and Validity Findings. *Alzheimer's & Dementia*, 18(S7). <https://doi.org/10.1002/ALZ.069454;WGROU:STRING:PUBLICATION>