Ignite: A digital cognitive outcome measure for early detection across *C9orf72*-related FTD-ALS.

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Background

Expansions in C9orf72 are the most common genetic cause of behavioural variant frontotemporal dementia (bvFTD) and amyotrophic lateral sclerosis (ALS). Emerging evidence suggests that in carriers of this expansion, disease-related cognitive and neuropsychiatric vulnerability may begin decades before clinical onset. As such, there is a growing need for sensitive, scalable tools capable of detecting early cognitive change across the FTD–MND spectrum. Within the Genetic FTD Initiative (GENFI), the Ignite app was developed as a remote, computerised cognitive assessment with potential application as a digital outcome measure in clinical trials. This study aimed to evaluate the sensitivity of Ignite to early cognitive differences in C9orf72 carriers and to pilot its validity in individuals with ALS.

Methods

A total of 208 GENFI participants with C9orf72 expansions, including symptomatic (n=45; mean age = 60.2 [9.0]) and presymptomatic carriers (n=163; mean age = 44.7 [12.3]), and 200 mutation negative controls (mean age = 49.1 [13.0]) completed Ignite alongside standard clinical assessments. Carriers were stratified by disease stage using the CDR plus NACC FTLD-NM scale. Ignite outcomes were z-scored relative to a normative population and aggregated by cognitive domain (executive function, processing speed, social cognition, semantic knowledge, visuospatial function, and arithmetic skills). Linear regression models adjusted for age, sex, and education examined group differences. In a complementary pilot study, 10 individuals with ALS (mean age = 60.6, SD=10.2, mean years of education = 15.2, 50% female) completed Ignite and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (mean total ECAS score= 105, SD= 24.5). A composite Ignite score was derived and correlated with ECAS total scores to assess validity in this cohort.

Genetic status	*N*	Age (*SD*)	*Mean Years of Education*	Sex in % Female
Non-carriers	200	49.4 (13.0)	15.8	58.5
Mutation carriers				
Asymptomatic (CDR = 0)	95	43.2 (11.9)	15.7	61.0
Prodromal (CDR = 0.5)	68	46.6 (10.5)	15.7	61.7
Symptomatic (CDR ≥ 1)	45	60.2 (9.0)	13.4	37.8
Total	408	49.75 (11.1)	15.1	54.7

Table 1. Participant demographics.

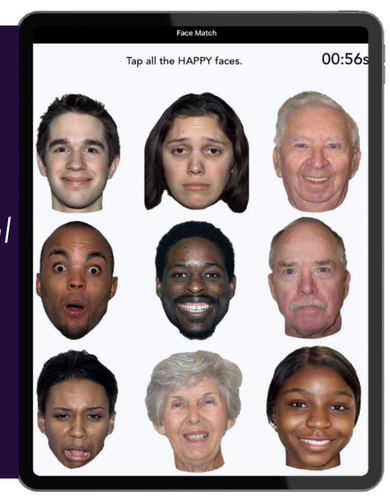
Ignite

12 computerised tasks measuring cognition:

Including executive function, processing speed, social cognition, semantic knowledge, visuospatial function and arithmetic skills.

Outcome measures:

Z-scores relative to a normative population and aggregated by cognitive domain.



Results

Ignite in C9orf72 expansion carriers

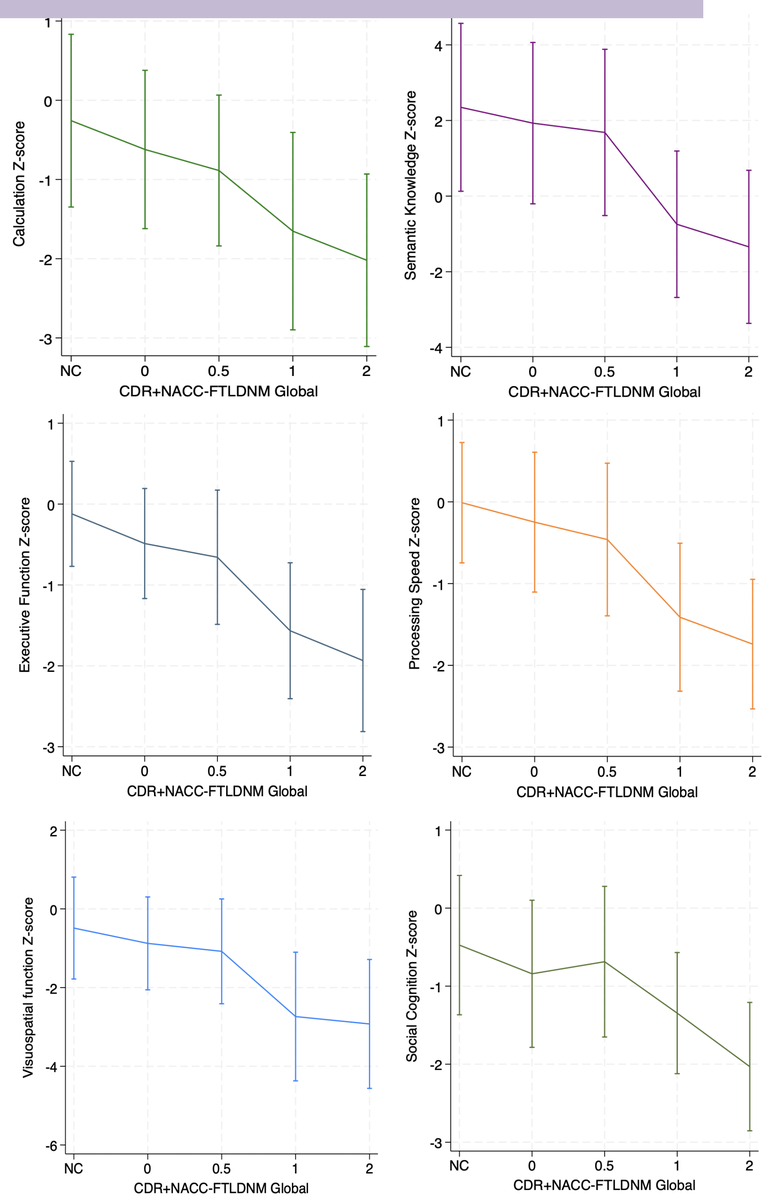


Figure 1. Performance across Ignite tasks (z-scores relative to normative population) stratified by CDR plus NACC FTLD-NM.

Across all disease stages, C9orf72 expansion carriers showed significant differences compared with controls on all Ignite cognitive domains. All mutation carrier groups, including asymptomatic, prodromal and symptomatic C9orf72 expansion carriers, scored significantly lower as a group in all cognitive domains.

	0				*0.5*				*>1*			
Composites	*Adj. mean diff*	*p*	*LCI*	*UCI*	*Adj. mean diff*	*p*	*LCI*	*UCI*	*Adj. mean diff*	*p*	*LCI*	*UCI*
Processing speed	-0.30	0.002	-0.49	-0.12	-0.40	<0.001	-0.60	-0.19	-1.29	<0.001	-1.55	-1.03
Executive Function	-0.39	<0.001	-0.54	-0.24	-0.52	<0.001	-0.73	-0.32	-1.20	<0.001	-1.46	-0.95
Social Cognition	-0.41	<0.001	-0.63	-0.19	-0.25	0.049	-0.49	0.00	-1.21	<0.001	-1.52	-0.90
Semantic Knowledge	-0.58	0.038	-1.12	-0.03	-0.74	0.017	-1.35	-0.13	-2.98	<0.001	-3.70	-2.26
Visuospatial function	-0.47	<0.001	-0.73	-0.22	-0.62	<0.001	-0.95	-0.30	-2.49	<0.001	-2.97	-2.02
Arithmetic	-0.39	<0.001	-0.63	-0.15	-0.63	<0.001	-0.88	-0.38	-1.66	<0.001	-2.00	-1.32

Table 2. Adjusted mean difference in Ignite performance stratified by CDR plus NACC FTLD-NM disease stage.

Ignite in an ALS Cohort

In the ALS pilot, the Ignite composite score demonstrated a significant positive correlation with ECAS total score (r = 0.65, p = 0.041), supporting convergent validity.

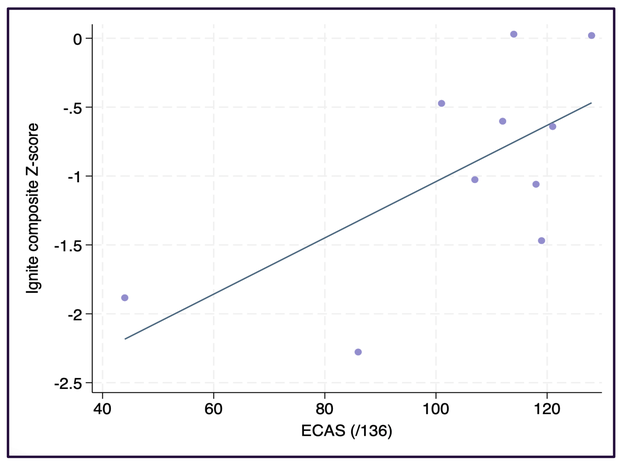


Figure 2. Performance across Ignite composite z-score correlated with ECAS total scores.

Conclusion

Ignite is sensitive to early, multi-domain cognitive differences in C9orf72 expansion carriers and shows promising validity in ALS. Together, these findings support Ignite as a feasible and scalable digital cognitive outcome measure across the FTD–ALS spectrum, with potential utility in research and future clinical trials.

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