

Cognitive differences in presymptomatic *C9orf72* expansion carriers versus familial non-carriers across adulthood

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Background

C9orf72 repeat expansions represent the most common genetic cause of frontotemporal dementia (FTD). In symptomatic disease, *C9orf72* carriers may show a broad cognitive profile including executive dysfunction, social-emotional disturbance, language impairment, and episodic and working memory difficulties.

Increasing evidence from familial cohorts indicate that subtle cognitive features can emerge during the presymptomatic or asymptomatic stage, with limited longitudinal decline. Neuroimaging studies similarly

demonstrate early subcortical and whole-brain differences in carriers, detectable decades before expected symptom onset.

Together, these findings raise the possibility that early cognitive differences may reflect longstanding neurodevelopmental traits in addition to progressive presymptomatic neurodegenerative.

Methods

Participants were drawn from the Genetic Frontotemporal dementia Initiative (GENFI). Cross-sectional baseline data were analysed for 542 presymptomatic participants (all CDR® plus NACC FTLD-NM global score ≤0.5; *Table 1*), comprising 285 *C9orf72* expansion carriers (*C9* Carriers) and 257 familial non-carriers (*GRN-MAPT* non-carriers; controls).

To examine the timing of presymptomatic cognitive differences, participants were stratified into age deciles ('20s', '30s', '40s', and '50s+').

Group differences on neuropsychology tasks (Figure 1) were examined using linear regression models with bootstrapped confidence intervals (2,000 replications), adjusting for sex and years of education.

To complement mean-level analyses, participants were classified as scoring <10th percentile on each task using control-derived norms, to quantify the proportion of individuals with atypical performance.

Results

Across age deciles, presymptomatic *C9orf72* expansion carriers showed measurable cognitive differences relative to familial non-carriers, emerging from the thirties. Early effects were most consistent for processing speed and executive function.

Percentile analyses (<10th percentile) converged with mean-level findings, showing a higher frequency of atypical performance in carriers, particularly on executive and memory measures (*Figures 2-3*).

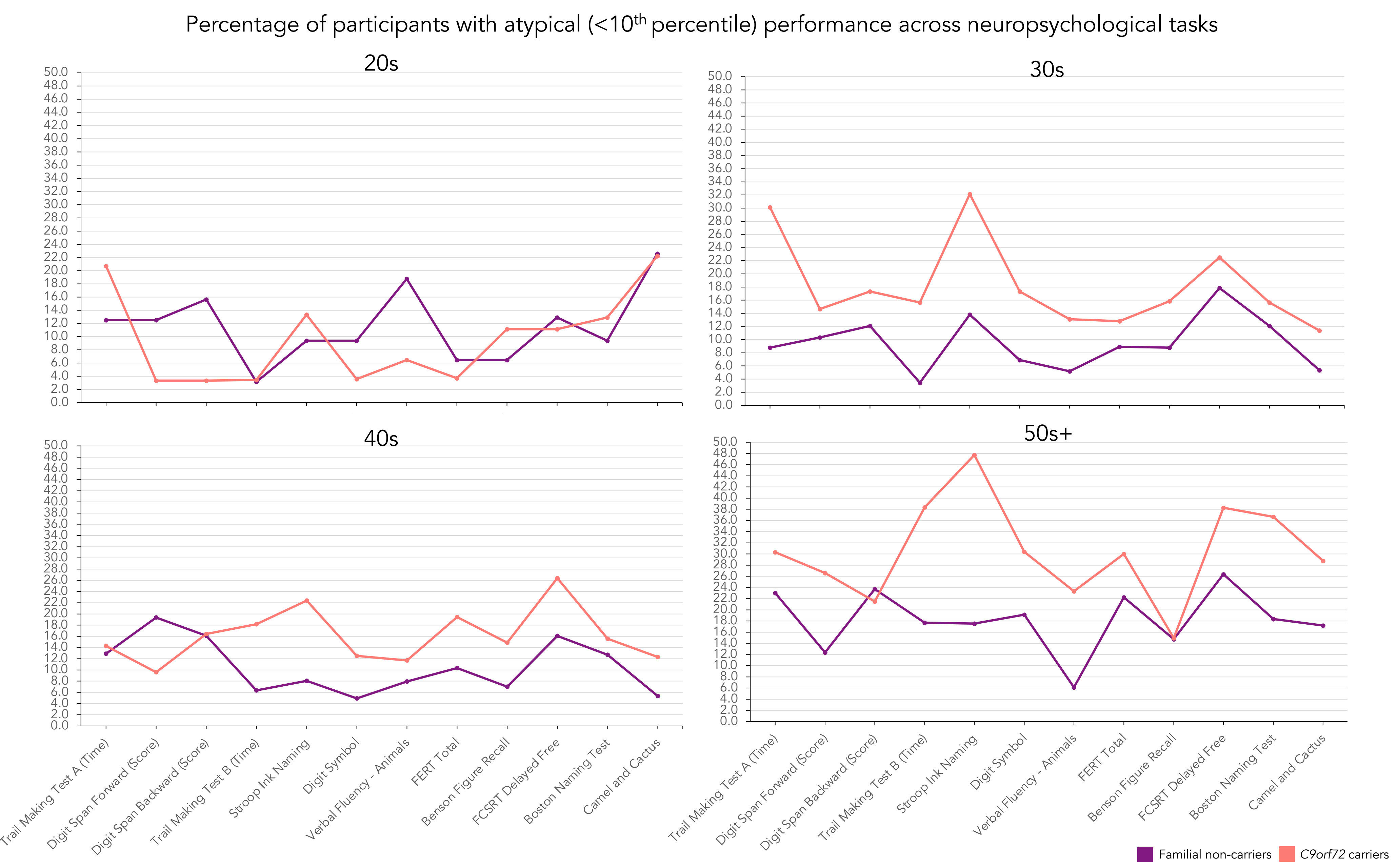
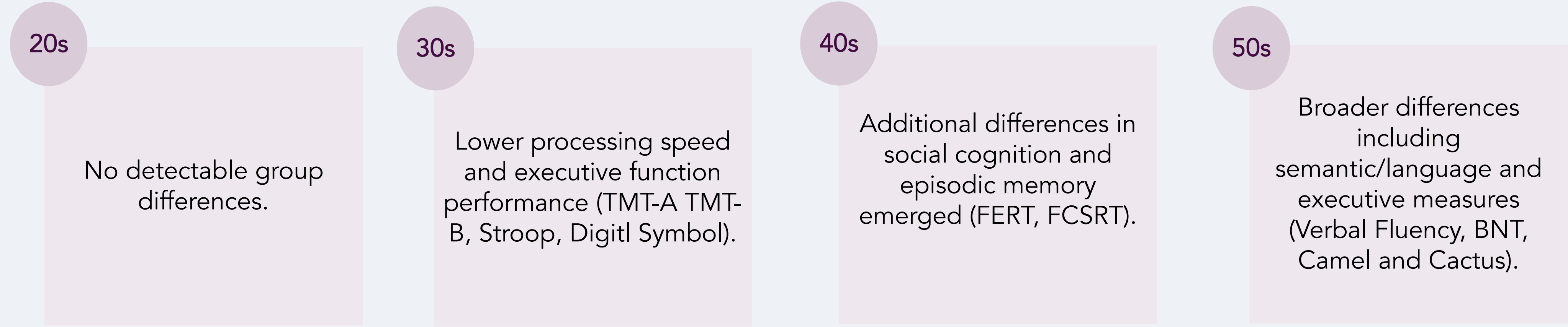


Figure 2. Percentage of participants scoring below the 10th percentile (control-derived norms) across neuropsychology tasks, shown by age decile. Higher values represent a greater proportion of atypical performance.

Conclusions & Future Directions

Presymptomatic *C9orf72* expansion carriers showed detectable cognitive differences relative to familial non-carriers from the thirties, substantially preceding expected symptom onset. Early effects were concentrated in processing speed and executive function, with later broadening across domains.

The elevated frequency of <10th percentile performance suggests that group differences are partly driven by a subset of individuals with atypical scores.

Future analyses will integrate longitudinal modelling, neuroimaging correlates, neuropsychiatric associations, and extension into earlier development (GENFI Neuro-Dev).

The temporal emergence of presymptomatic cognitive differences in *C9orf72* remains poorly defined, particularly in younger adulthood.

- 1 Do presymptomatic *C9orf72* carriers differ from familial non-carriers, and how early do differences emerge across age bands?
- 2 Are group effects explained by mean-level shifts, or by a subset of individuals with atypical performance?



Figure 1. GENFI neuropsychology battery grouped by cognitive domain.

Table 1. Demographic characteristics of presymptomatic participants (mean [SD] unless stated) and distribution across the age deciles.

	Demographic Characteristics				N per Age Decile			
	N	Sex (F:M)	Education (Years)	Age (Years)	20s	30s	40s	50s
Familial non-carriers	257	134:123	14.63 (3.42)	46.43 (13.52)	32	59	66	100
<i>C9orf72</i> carriers	285	173:112	14.78 (3.15)	44.08 (12.30)	31	86	77	91

Table 2. Linear regression results comparing presymptomatic *C9orf72* expansion carriers versus familial non-carriers across age bands. Values represent adjusted mean difference between groups, with *p*-values shown.

Cognitive Domain	Neuropsychology Task	<i>C9orf72</i> carriers vs familial non-carriers			
		20s	30s	40s	50s+
Processing speed and attention	Trail Making Test A (Time)	0.69 (p=.790)	4.76 (p=.001)	4.16 (p=.022)	3.25 (p=.176)
	Digit Span Forward (Score)	0.20 (p=.443)	-0.26 (p=.145)	-0.01 (p=.951)	0.02 (p=.916)
Executive function	Digit Span Backward (Score)	0.78 (p=.097)	-0.23 (p=.537)	0.48 (p=.203)	-0.54 (p=.070)
	Trail Making Test B (Time)	1.68 (p=.779)	11.35 (p=.001)	9.79 (p=.145)	33.58 (p<.001)
	Stroop Ink Naming (Time)	-2.32 (p=.387)	6.45 (p=.001)	6.09 (p=.006)	14.06 (p<.001)
	Digit Symbol	-0.10 (p=.971)	-4.71 (p=.009)	-4.00 (p=.038)	-6.43 (p<.001)
	Verbal Fluency - Animals	0.62 (p=.689)	-0.40 (p=.702)	-1.39 (p=.129)	-2.15 (p=.015)
	Verbal Fluency - Letter F	0.02 (p=.987)	-0.78 (p=.307)	-0.93 (p=.219)	-2.49 (p<.001)
Social cognition	FERT (Total)	0.91 (p=.196)	0.37 (p=.483)	-1.14 (p=.020)	-1.28 (p=.017)
Memory	Benson Figure (Recall)	-1.11 (p=.102)	-0.22 (p=.594)	-0.85 (p=.077)	-0.14 (p=.736)
	FCSRT (Delayed Free Recall)	-0.30 (p=.610)	-0.68 (p=.080)	-1.21 (p=.013)	-1.08 (p=.013)
Language	Boston Naming Test	-0.10 (p=.795)	-0.32 (p=.397)	-0.40 (p=.250)	-1.17 (p=.002)
	Camel and Cactus	0.02 (p=.970)	-0.15 (p=.576)	-0.57 (p=.148)	-0.76 (p=.008)

Percentage of participants scoring <10th percentile on >1 neuropsychology task

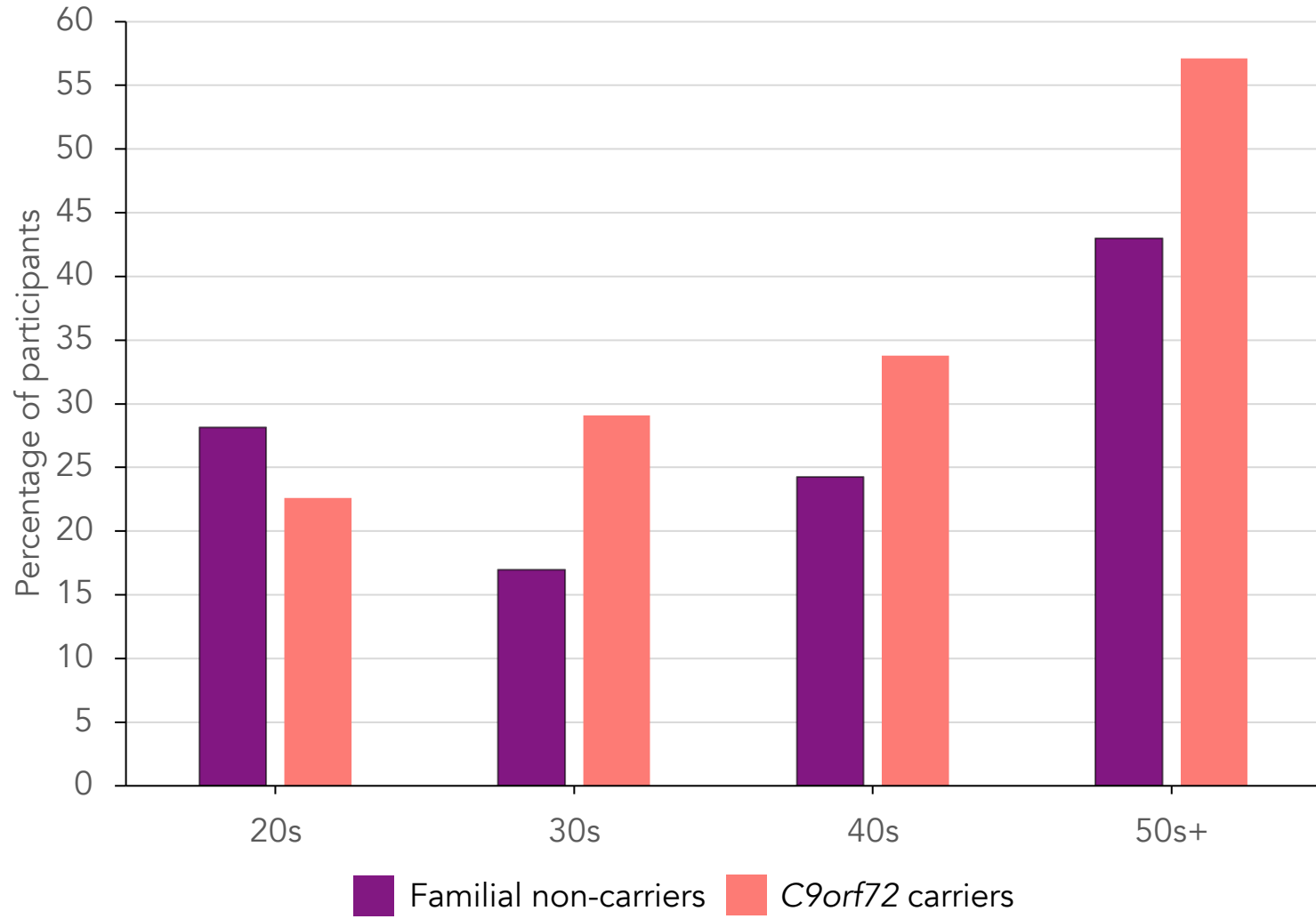


Figure 3. Percentage of participants scoring below the 10th percentile threshold on more than 1 task by participant group and age decile.

