A Two-Minute Digital Cognitive Task as a Pre-Enrichment Screening Method for Alzheimer's Disease Trials

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Introduction

- Traditional cognitive screeners such as MoCA and ADAS-Cog were not designed for early-stage Alzheimer's disease (AD) trials, where cognitive change is subtle, multidomain, and often obscured by education, practice effects, or compensatory strategies. Their limited dynamic range and ceiling effects reduce sensitivity in prodromal and preclinical populations, contributing to high screen-failure rates.
- Screen-failure rates can exceed 40% in mild AD studies and rise above 75–85% in prodromal and preclinical cohorts (Hampel 2023; Langbaum 2023; Aisen 2025).
- Scalable, low-cost tools are needed to identify individuals most likely to show early pathology or measurable decline before full clinical assessment, and PET or CSF screening.
- This multimodal assessment platform provides digital versions of validated tasks measuring cognition, memory, executive function, mood and sleep.
- We report interim data on a 2-minute tablet-based reimplementation of the digit symbol-substitution task (DSST) (Figure 1; Jaeger 2018; Dyer 2025) which measures executive function, comparing its pre-enrichment performance to traditional tests across one at-home study and two in-clinic studies (total N≈1,280). In one of those studies we also compare digital tasks in memory and language.

Methods

- Our digital version of the symbol-coding task requires participants to quickly match each digit to its corresponding symbol using a lookup key. Participants completed a guided practice task with onscreen instructions followed by a timed 90s task in which they completed as many matches as possible. Performance was quantified as the number of successful matches.
- Across three independent studies, a single administration of the digital symbol coding task was compared to a clinical benchmark assessment and the AUC-ROC rank association was calculated between performance on the digital task and phenotypes relevant to clinical trial recruitment. In Study 1, the task was delivered as part a year-long feasibility study of at home longitudinal use of a range of electrophysiological and neurocognitive measures in patients with mild AD. Participants received supervised baseline training on the platform at the seven study sites before at home use, followed by a two-week familiarisation stage in which they completed the task up to three times.
- We present the data from the subsequent testing stage following familiarisation, and the first completion of the task. In Studies 2 and 3 the task was administered as part of a combined electrophysiological and neurocognitive assessment lasting 20 minutes. Study 2 was conducted at the Cognitive Disorders Clinic at Southmead Hospital, Bristol, UK. Study 3 was conducted across 20 clinical sites in the United States, Canada, and Europe. AD and MCI patients were diagnosed according to NIA criteria across all studies.

	Study 1					Study 2					Study 3				
Title	**CNS-101**					**Fastball i4i**					**BioHermes-2**				
Funding	Cumulus Pharma Consortium and Innovate UK					NIHR					Global Alzheimer's Platform and Innovate UK				
Data collection location	At home (recruited through 7 UK sites)					2 UK clinical sites					20 clinical sites across the US, UK and Canada				
		n	age	no. of males	ADAS-Cog		n	age	no. of males	MoCA total score		n	age	no. of males	MMSE total score
Population	**Dementia**	46	71 (7)	26	8 (4)	**AD**	93	72 (9)	55	18 (7)	**AD**	147	76(7)	71	22 (3)
	Controls	54	73 (6)	29	24 (8)	**Controls**	114	69 (9)	48	27 (2)	**MCI**	226	73 (7)	108	27 (2)
	p-Tau217 +	52	74 (6)	34	19 (11)	**p-Tau217 +**	73	69 (10)	45	20 (8)	**Controls**	205	70 (7)	76	28 (1)
	p-Tau217 -	34	69 (7)	15	11(6)	**p-Tau217 -**	49	61 (9)	29	25 (4)					
Blood Biomarker	Pathology status used Alzpath phosphorylated-Tau 217					Pathology status used Alzpath phosphorylated-Tau 217 *					None**				
Clinical benchmark assessment	ADAS-Cog					MoCA					None**				

Table 1: Study characteristics and participant demographics

On Studies 1 and 2, pathology status was based on ALZpath phosphorylated-tau 217, with the single threshold from Ashton (2024).

* Blood biomarkers in Study 2 were collected from a diverse neurological cohort whose aetiologies included 21 AD, 2 Vascular Dementia, 5 Frontotemporal dementia, 7 Lewy Body dementia, 1 Progressive Supranuclear Palsy, 7 Parkinson's disease, 2 Mixed dementia, 2 Epilepsy, 6 Psychiatric, 10 Functional Cognitive Disorder, 2 Hydrocephalus, 1 Sleep Disorder, 1 Corticobasal degeneration, 2 Pain disorders, 3 Auto Immune disorders, 30 of unknown aetiology at the time of enrolment, and 19 healthy controls.

**End of study (2027) data release will include full neuropsychological scores, amyloid and tau PET and blood plasma biomarkers

Memory Match:
Visual associative memory

Symbol Swap:
Digit symbol substitution/coding task

Double Take:
N-back

Lingo:
Picture-description

Results

1. Detecting Dementia

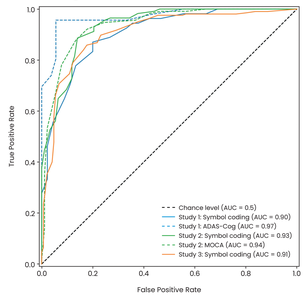

Figure 1: Receiver Operating Characteristic (ROC) curves comparing AD detection accuracy of the digital symbol coding task and clinical benchmark cognitive screeners. The task differentiated AD from controls across studies, comparably to the clinical benchmark.

2. Detecting MCI

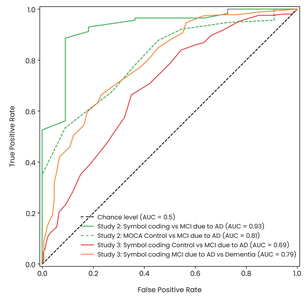

Figure 2: Receiver Operating Characteristic (ROC) curves comparing MCI due to AD detection accuracy of the digital symbol coding task and clinical benchmark cognitive screeners. The task differentiated MCI due to AD from controls across studies.

3. Detecting Pathology

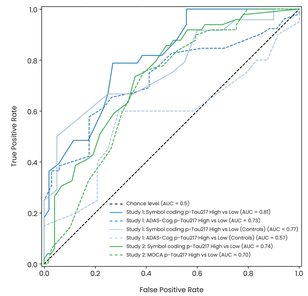

Figure 3: Receiver Operating Characteristic (ROC) curves comparing AD biomarker (blood plasma p-Tau217) detection accuracy of the digital symbol coding task and clinical benchmark cognitive screeners. The task detected biomarker positivity across studies, with higher AUC than the clinical benchmark in the p-tau217 contrasts.

		AUC accuracy per study and cohort contrast		
		Digital symbol-coding task	**Clinical benchmark**	
Study 1	Controls (n=54) vs Dementia (n=46)*	0.91	0.97	ADAS-Cog
	p-Tau217+ (n=20) vs p-Tau217- (n=24), Controls only	0.77	0.57	ADAS-Cog
	p-Tau217+ (n=52) vs p-Tau217- (n=34), All Participants*	0.81	0.73	ADAS-Cog
Study 2	Controls (n=114) vs MCI due to AD and AD Dementia (n=93)	0.93	0.94	MoCA**
	Controls (n=114) vs MCI due to AD (n=11)	0.93	0.81	MoCA**
	p-Tau217+ (n=73) vs p-Tau217- (n=49)	0.74	0.70	MoCA**
Study 3	Controls (n=205) vs MCI (n=226)	0.69	-	-
	Controls (n=205) vs AD (n=147)	0.91	-	-
	MCI (n=226) vs AD (n=147)	0.79	-	-

Table 2 (left, top): Digital symbol-coding task performance vs clinical benchmark in clinical and biomarker-derived contrasts

*One p-Tau217- AD patient did not complete Symbol Swap

**The MoCA was a part of diagnostic workup for patients, alongside clinical interview, neuropsychological testing and available biomarkers. 4 p-Tau217+ participants did not complete a MoCA

		AUC accuracy		
		Episodic memory (visual associative)	**language (picture-description speech rate)**	**working memory (n-back)**
Study 1	Controls (n=54) vs Dementia (n=46)	0.87	0.76	0.66
	p-Tau217+ (n=52) vs p-Tau217- (n=34), All Participants	0.67	0.62	0.53

Table 3 (left, bottom): Additional cognitive task performance vs Clinical Benchmark in clinical and biomarker derived contrasts

In addition to Symbol Swap, several other cognitive tasks were completed in Study 1 and demonstrated meaningful discrimination accuracy for identifying both clinical status (controls vs. AD) and biomarker-defined groups (p-Tau217 positive vs. negative). Episodic memory, language, and working memory tasks achieved AUC values up to 0.87, with episodic memory showing the best performance. These data show the potential in developing composite indices of cognitive performance that integrate multiple task domains, which may prove more sensitive than any single measure alone.

Conclusions

- Across three independent studies, the symbol coding task performed comparably, and in some cases exceeded the pre-enrichment performance of established clinical screeners, despite requiring only two minutes. This demonstrates that brief, well-designed digital tasks can deliver clinically meaningful discrimination between control, MCI and AD groups while reducing participant and site burden.
- The digital symbol coding task was associationed with biomarker-defined AD pathology, including in clinically normal individuals who would typically score well on standard cognitive tests. This sensitivity to early cognitive deficits suggests the task may help identify individuals at highest likelihood of amyloid or tau positivity, improving the efficiency and value of downstream plasma-based screening, PET or CSF.
- The task's digital format enables standardised administration and automated scoring - potentially reducing variability introduced by rater expertise, site differences or administration time. These operational characteristics are consistent with deployment across large, multi-site trials for both in-clinic and at-home pre-screening workflows.
- Within a multimodal enrichment pipeline, such tools could substantially reduce screen-failure rates and accelerate recruitment into AD trials. Brief patient-friendly and pathology-sensitive assessments could function as first-line filter, either preceding plasma biomarkers or contributing to composite digital endpoints that capture complementary cognitive and language-based signatures of early disease.
- Beyond AD, the same low-burden pre-screening principle should extend to other CNS indications where cognition is impaired (e.g. major depressive disorder, schizophrenia), where novel treatments may have benefits beyond core symptoms.

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