A Brief Digital Symbol-Coding Task Outperforms Clinical Benchmarks For Alzheimer's Trial Pre-enrichment

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Memory Match (left): Visual associative memory



Symbol Swap (right): Digit symbol substitution/coding task

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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.
- NeuLogiq is a multimodal endpoint platform deployed today in CNS trials, featuring patient-friendly digital versions of well validated tasks that measure cognition, memory, executive function, mood & sleep.
- We report interim data (further updated relative to the abstract) on Symbol Swap, a 2-minute tablet-based Symbol Coding Task (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

- Symbol Swap is a digital Digit Symbol Substitution Task which 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, Symbol Swap was administered once and compared to a clinical benchmark assessment and the AUC-ROC rank association was calculated between performance on Symbol Swap and phenotypes relevant to clinical trial recruitment. In Study 1, Symbol Swap was delivered as part a year-long feasibility study of at home longitudinal use of the Cumulus NeuLogiq Platform for 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 Symbol Swap 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

Results

1. Detecting Dementia

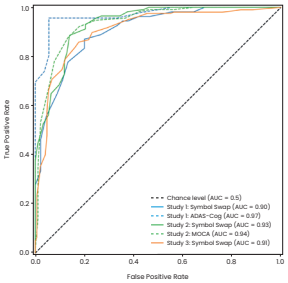


Figure 1: Receiver Operating Characteristic (ROC) curves comparing AD detection accuracy of Symbol Swap and clinical benchmark cognitive screeners. Symbol Swap showed excellent detection of AD from controls across studies, with performance comparable to clinical benchmark cognitive screeners.

2. Detecting MCI

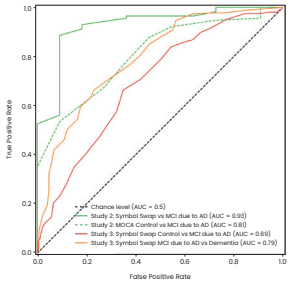


Figure 2: Receiver Operating Characteristic (ROC) curves comparing MCI due to AD detection accuracy of Symbol Swap and clinical benchmark cognitive screeners. Symbol Swap showed good to excellent detection of MCI due to AD from controls across studies.

3. Detecting Pathology

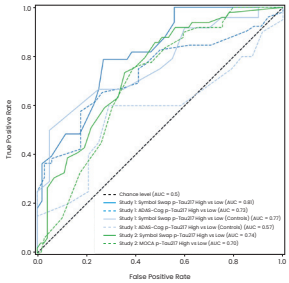


Figure 3: Receiver Operating Characteristic (ROC) curves comparing AD biomarker (blood plasma p-Tau217) detection accuracy of Symbol Swap and clinical benchmark cognitive screeners. Symbol Swap showed good to excellent detection of biomarker positivity across studies, with performance consistently exceeding that of clinical benchmark cognitive screeners.

		AUC accuracy per study and cohort contrast		
		Symbol Swap (digital DSST)	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: Symbol Swap 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: 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, Symbol Swap generally matched or 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 dramatically reducing participant and site burden.
- Symbol Swap showed robust associations 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, automated scoring and high-resolution performance metrics, reducing variability introduced by rater expertise, site differences or administration time. These operational advantages support scalable deployment across large, multi-site trials and make Symbol Swap suitable for both in-clinic and at-home pre-screening workflows.
- Integrating Symbol Swap into multimodal enrichment pipelines could substantially reduce screen-failure rates and accelerate recruitment into AD trials. Its brevity, patient acceptability and sensitivity to pathology make it an attractive 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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Disclosures: Murphy, Stothart, Nolan, Barbey and Rueda-Delgado are all employees and hold shares in Cumulus Neuroscience.

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