Validating a Multi-Domain Digital Endpoint Platform (NeuLogiq®) for Decentralized Alzheimer's Trials: Results from the CNS-101 Study

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Introduction

- AD trial endpoints that are sampled infrequently in clinics are subject to white-coat effects and day-to-day variability (Binder et al., 2009)
- Limited sensitivity of endpoints require long-duration and large-N trials to detect response to treatment
- Repeated longitudinal measurements can improve endpoint reliability, and increase statistical power to detect progression (Öhman et al., 2021)
- CNS-101 is a non-interventional observational study designed by a consortium of 10 pharmaceutical companies to test the feasibility and evidential power of the NeuLogiq® platform (McWilliams et al., 2021)
- NeuLogiq at-home digital tools may be more sensitive to cohort progression than current endpoints (e.g. ADAS-Cog)
- Sensitive digital endpoints could deliver streamlined trial designs (e.g. smaller cohorts), reducing burden on patients and clinical teams, saving time and money

Methods

- Mild dementia patients (n=59, ACE-III scores >60 and ≤88) and controls (n=60, ACE-III scores >88) recruited at 7 UK sites
- Dementia patients had clinician opinion of AD, with subsequent evaluation on basis of p-Tau 217 plasma biomarker (Quanterix Simoa), using Ashton et al.'s single threshold (2024)
- ADAS-Cog 13 clinical composite endpoint was collected at months 0, 6, 12 (Figure 1), alongside other neuropsychological benchmarks
- NeuLogiq sessions lasted ~25 minutes in any one day, with 8 assessments on a mobile tablet split across two task lists. Functional behavioural tasks (memory, executive function, affective processing and language) were overlaid with synchronous wake-EEG
- Sleep EEG was recorded overnight using the Dreem headset
- The statistical analysis plan (SAP) pre-identified 41 digital endpoints as candidate markers of disease progression
- Cohort-level progression was modelled with linear mixed-effects to estimate group-by-time interactions
- Having identified promising NeuLogiq markers, bootstrapping and Monte Carlo simulations were used to estimate the power of streamlined study designs with smaller and larger numbers of participants (Green & McLeod 2015)
- Sensitivity to plasma markers was visually examined on selected cognitive NeuLogiq markers
- Cost and time-saving projections were estimated for an illustrative 10-50% reduction in patient numbers, assuming costs to be proportional to the product of the number of participants and duration of study (DiMasi et al., 2024)

Cumulus NeuLogiq® Platform for Use in Real-World Settings

Developed in collaboration with leading pharma companies and KOLs (below).

Cumulus provides full service:

- Protocol / study / SAP design
- On-site training, off-site support
- Data reconciliation and packaging
- Reporting and custom analytics

Audit ready including FDA 510(k), UKCA, HIPAA, GDPR, ISO13485.

Designed for and with patients and clinicians, deployed in Phase 0-1b CNS trials.

Secure automatic upload and QC.

Real-time dashboard monitoring of decentralized and home-based data collection.

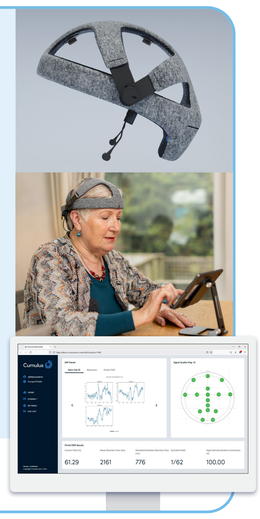
Deployed to 4 continents, multilingual support with 12 languages to date.

Cumulus cognitive and EEG / ERP tests are designed to be highly repeatable, with large banks of non-repeating stimuli.

- Objectively administered and automatically scored
- Results (including EEG metrics) available in minutes, enabling remote monitoring and QC
- Suitable for detecting change over time

Memory Match:
Visual associative memory

Symbol Swap:
Digit symbol substitution/coding task



Biogen · Boehringer Ingelheim · Bristol Myers Squibb · GSK · J&J · Lilly · MSD · Pfizer · Roche · Takeda

Study Protocol

Figure 1: CNS-101 study protocol, showing scheduled sessions (coloured squares) across the 12 month observational study, and timepoints of blood draws and benchmark assessments.

- CNS-101 patient adherence was high: 70% in Stage 2; 78-80% across Stages 3 and 4
- Study was powered for withdrawal of 33%. Attrition rates were 18.5% –27% for dementia patients, 10% for controls
- Key cognitive endpoints correlated with benchmarks: Memory Match correlated with Verbal Paired Associates I at rho = 0.75 (p = 6.2e-19); Symbol Swap correlated with DSST at rho = 0.76 (p = 5.0e-20)

Diggin et al, AAIC, 2024

Acknowledgments
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Innovate UK

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Results

1. At-home digital endpoints sensitively track progression of dementia, relative to the registered endpoint

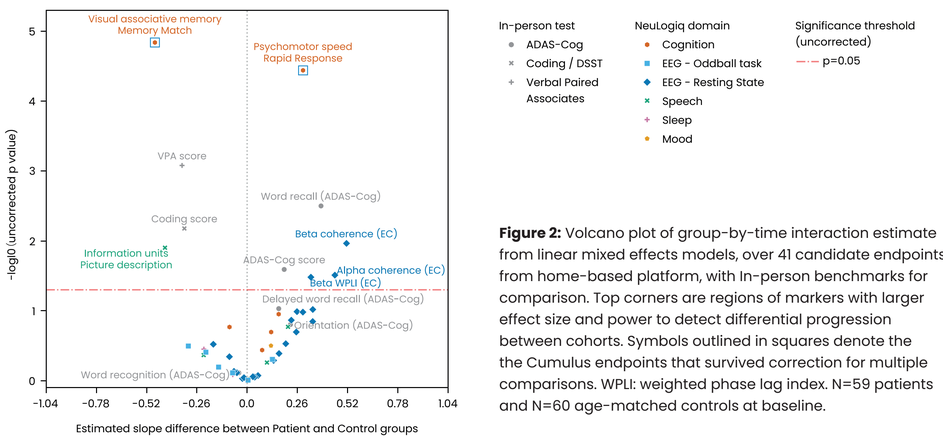

Figure 2: Volcano plot of group-by-time interaction estimate from linear mixed effects models, over 41 candidate endpoints from home-based platform, with In-person benchmarks for comparison. Top corners are regions of markers with larger effect size and power to detect differential progression between cohorts. Symbols outlined in squares denote the the Cumulus endpoints that survived correction for multiple comparisons. WPLI: weighted phase lag index. N=59 patients and N=60 age-matched controls at baseline.

2. At-home digital endpoints provide higher statistical power than ADAS-Cog, enabling leaner study designs

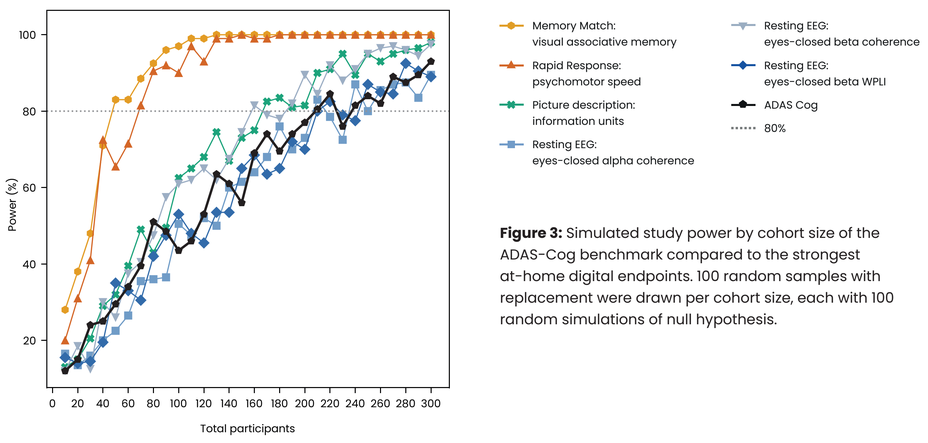

Figure 3: Simulated study power by cohort size of the ADAS-Cog benchmark compared to the strongest at-home digital endpoints. 100 random samples with replacement were drawn per cohort size, each with 100 random simulations of null hypothesis.

3. Digital endpoints reflect Alzheimer's Disease biomarker status

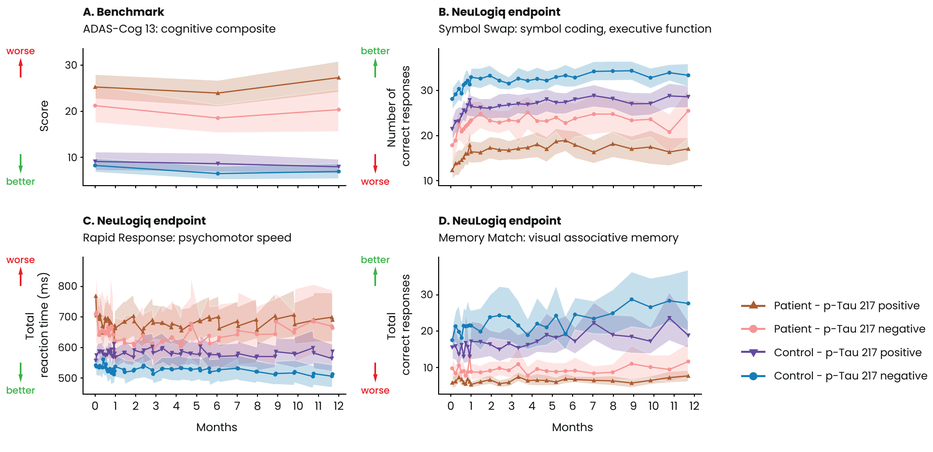

Figure 4: Benchmark (ADAS-Cog) over time (A) versus NeuLogiq digital endpoints ((B) executive function, (C) psychomotor speed and (D) visual associative memory), with patients and controls split by p-Tau 217 status: 34 positive patients, 13 negative patients, 21 positive controls and 26 negative controls. Each point represents a measurement timepoint. All NeuLogiq measurements were taken at home, without researcher supervision. Shaded areas correspond to 95% bootstrapped confidence intervals.

4. Smaller cohorts shorten trials and save up-front costs

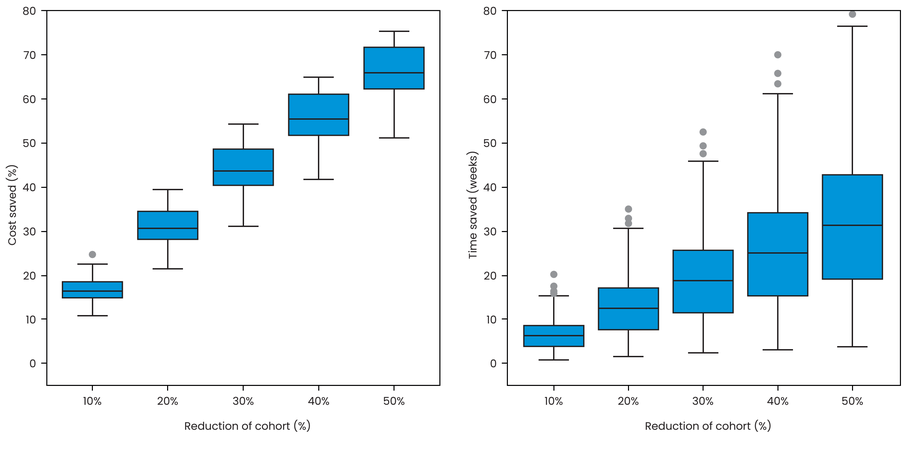

Figure 5: Percentage costs saved (left) and time saved (right) given a reduction in the cohort size. Reducing the cohort size by 50% yields median cost savings of 65.9% and median time savings of 35.2 weeks (8.1 months). Cost and time-saving projections were estimated using clinical trial information from 77 industry-led interventional phase 2 studies, July 2020 to July 2025, in Alzheimer's Disease from clinicaltrials.gov, and following cost estimation methods in DiMasi et al., (2024). Line in box shows the median, box shows interquartile range (IQR), whiskers show the point at 1.5x IQR, outliers are those past the whiskers.

Conclusion

- Brief but repeated home-based digital cognitive endpoints (~5 minutes) are more sensitive to change than the registered ADAS-Cog 13 composite
- Brief passive EEG markers and naturalistic language-based markers are similarly powerful to ADAS-Cog 13 (which takes ~45 minutes of clinician time to administer)
- NeuLogiq at-home endpoints showed greater separation with AD pathology (p-Tau 217) than the benchmark endpoint (ADAS-Cog 13) over the study time-course
- More sensitive endpoints could enable trial designs with smaller cohorts, which save on up-front costs, and reduce burden on clinicians and patients
- Today sponsors can use these measures to corroborate registered endpoints, and to inform adaptive study design decisions (e.g. a ph1b study that rolls-over to a ph2)

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