Frequent at-home multimodal measurements are more sensitive to progression than the gold-standard clinic-based ADAS-Cog composite scale

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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
- Limited sensitivity of endpoints requires long-duration, large-N trials to detect response to treatment
- Repeated longitudinal measurements can improve 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)
- A cohort of AD-type dementia patients, and matched controls, serves as model of placebo vs. efficacious treatment cohorts

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 package
- Reporting and custom analytics

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

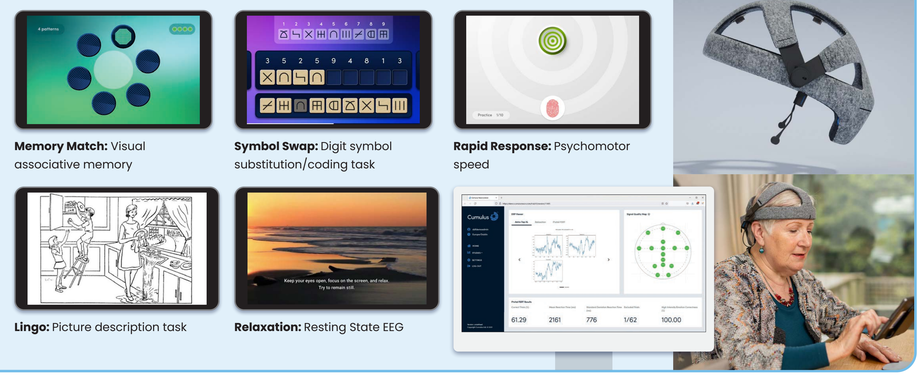
Designed for and with patients and clinicians, deployed in Phase 0-2 CNS trials.

Secure automatic upload and QC.

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

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

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



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 of p-Tau 217 plasma biomarker (Quaternix 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 neuropsych benchmarks
- NeuLogiq sessions lasted ~25 minutes in any one day, with 8 assessments on a mobile tablet split across two task lists. Functional behavioral 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
- Resting and task driven EEG yielded multiple metrics including connectivity coherence and weighted phase-lag-index (WPLI) measures
- Having identified promising NeuLogiq markers, bootstrapping and Monte Carlo simulations were used to estimate the power of streamlined study designs with small numbers of participants (Green & McLeod, 2016)

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.

NeuLogiq Platform is feasible for at-home use in multi-site AD clinical trials

- CNS-101 patient adherence was high: 70% in Stage 2; 78-80% across Stages 3 and 4
- The overall attrition rate was 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., 2024

Results

1. Conventional methods detect differential progression in the study, despite familiarity effects

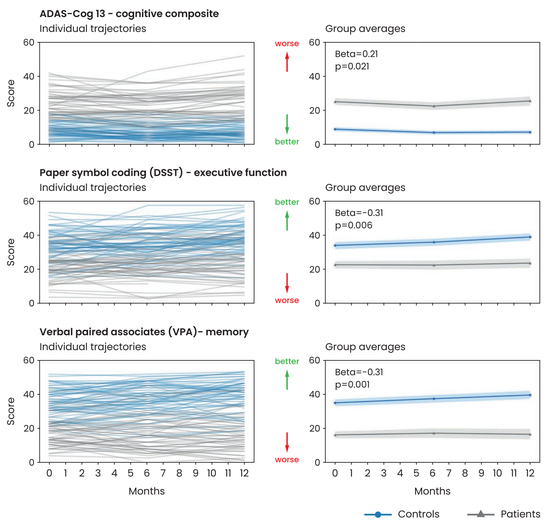


Figure 2: Twelve-month progression on benchmark measures during face-to-face visits in the clinic. On the left, individual participant trajectories are shown. On the right, dark lines indicate group mean trajectories; shaded areas indicate bootstrapped 95%CI. N=59 patients and N=60 age-matched controls at baseline. Standardized effects and p-values are linear mixed effects group-by-time interaction estimates.

2. Digital endpoints reflect Alzheimer's Disease biomarker status

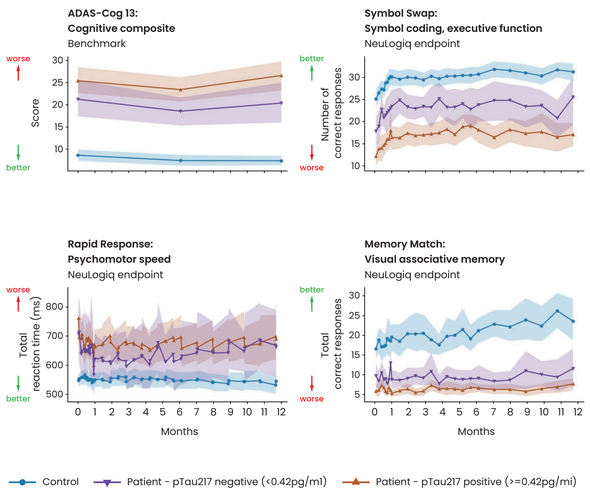


Figure 3: Benchmark (ADAS-Cog) over time versus NeuLogiq digital endpoints (executive function, reaction speed and memory), with patients split by p-Tau 217 status (N=33 AD-positive patients, N=13 negative), controls not split (N=47). Each dot represents a measurement timepoint. All NeuLogiq measurements were taken at home, without researcher supervision. Shaded areas indicate bootstrapped 95% CI.

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

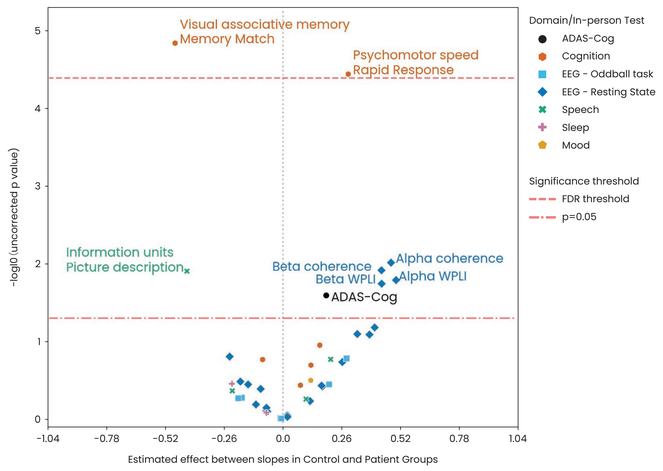


Figure 4: Volcano plot of group-by-time interaction estimate from linear mixed effects models, over 41 candidate endpoints from home-based platform, with ADAS-Cog 13 for comparison. Top corners are regions of markers with larger effect size and power to detect differential progression between cohorts. FDR: false discovery rate correction for multiple comparisons; WPLI: weighted phase lag index. N=59 patients and N=60 age-matched controls at baseline.

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

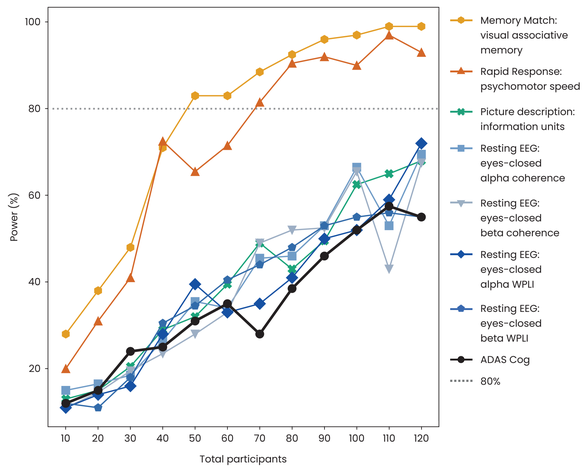


Figure 5: Simulated power by cohort size of the ADAS-Cog 13 benchmark compared to the strongest at-home digital endpoints. 100 random samples with replacement were drawn per cohort size, each with 100 random simulations of null hypothesis. The two groups were resampled from the N=59 patients and N=60 age-matched controls who had ADAS-Cog assessments taken.

Conclusions

- 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
- Benchmark endpoints differentiate the model cohorts, despite learning/familiarity effects
- Brief but repeated home-based digital cognitive endpoints are more sensitive to change than the ADAS-Cog 13 composite benchmark
- Passive EEG markers and naturalistic language based markers are similarly powerful to ADAS-Cog 13 (which takes ~45 minutes of clinician time to administer)
- Individual digital endpoints can enable streamlined study designs which may reduce overall costs, accelerate results leading to earlier go/no go decisions. A digital composite measure may provide additional study power

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