Neurophysiological Phenotyping of Alzheimer's Dementia at Home, Using the Cumulus NeuLoqiq® Platform with Plasma Biomarkers

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Introduction

- Current endpoint tools in Alzheimer's disease (AD) clinical trials have poor sensitivity to disease progression, necessitating very large longitudinal studies to detect effects of treatment.
- Longitudinal, repeated measurement within participants improves statistical power to detect change in principle [1].
- Digital tools such as the NeuLogiq platform may be more sensitive to disease progression than current endpoints (e.g. ADAS-Cog), when used longitudinally, at home, if feasible [2].
- Blood biomarkers are emerging as a relatively cost-effective and scalable method of stratifying dementia patients according to pathology.
- The CNS-101 study was designed by a consortium of 10 pharmaceutical companies (above) to test the feasibility and evidential power of the platform.
- In addition, we examine EEG signals associated with impairment in AD, and assess how blood biomarker status relates to NeuLogiq endpoints.

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 0-1b CNS trials.

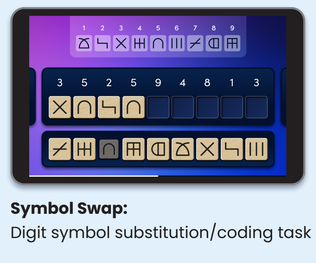
Secure automatic upload and QC.

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

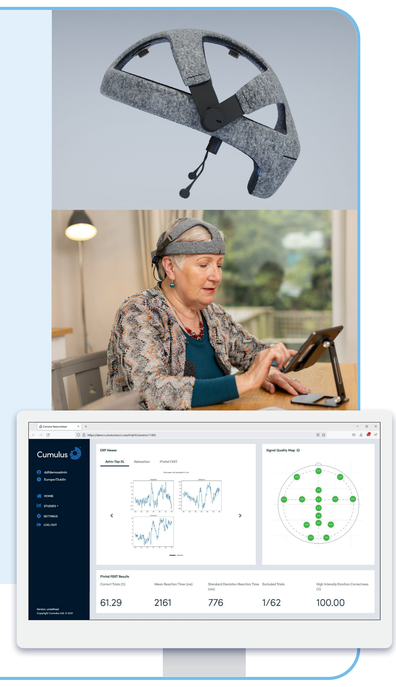
Cumulus cognitive and EEG / ERP tests are designed to be highly repeatable, with large banks of non-repeating stimuli.

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

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

Methods

Seven UK sites recruited N = 59 dementia patients (ACE-III scores >60 and ≤88) and N = 60 age-matched healthy controls (ACE-III scores >88).

Dementia patients were recruited with clinical judgment of suspected AD, with blood biomarker collection subsequently added to the study for post-hoc analysis (UK DRI Biomarker Factory: Quanterix Simoa). Ashton et al. (2024) [3] recommendation of 0.42 pg/ml was used as a single threshold for p-Tau 217 positivity.

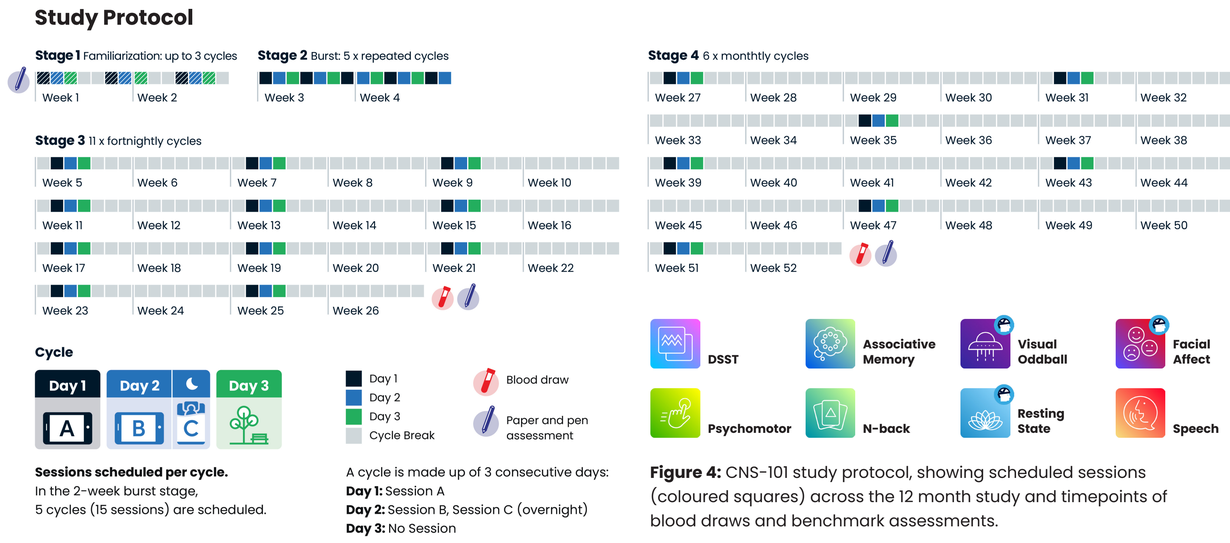
A 12 month protocol for at-home data collection was followed, consisting of an initial "burst" collection phase followed by tapering frequency of regular assessments.

ADAS-Cog and other benchmark paper assessments were administered at the beginning and at 6 and 12 months. Blood was drawn at 6 and 12 months.

NeuLogiq sessions involved the completion of 8 assessments on a mobile tablet incorporating behavioural tasks (memory, executive function, affective processing and language) overlaid with EEG. Tasks were split across two session types, each of duration of ~20 minutes.

Sleep was also recorded for part of the study duration, using the Dreem headset.

The System Usability Scale (SUS) was administered at the beginning, middle and end of the study, along with a custom questionnaire on technology usage.



Sessions scheduled per cycle.
In the 2-week burst stage, 5 cycles (15 sessions) are scheduled.

A cycle is made up of 3 consecutive days:
Day 1: Session A
Day 2: Session B, Session C (overnight)
Day 3: No Session

Figure 4: CNS-101 study protocol, showing scheduled sessions (coloured squares) across the 12 month study and timepoints of blood draws and benchmark assessments.

Q1: Is the platform feasible for use by patients and clinical teams, and are the home-collected measures valid?

- Patient-judged usability of the overall system was good: mean patient SUS = 62.2.
- Patient adherence was high, at 70% of scheduled sessions completed in Stage 2 (see Figure), and 78-80% across Stages 3 and 4.
- Study was powered for withdrawal of up to 33%. Attrition rates were 18.5% overall – with 27% (16 of total 59) for dementia patients, and 10% (6 of total 60) for controls.
- Key cognitive endpoints correlated well against paper-based benchmarks: Memory Match showed a correlation with Verbal Paired Associates I of rho = 0.75 (p = 6.2e-19), while Symbol Swap correlated with the paper DSST at rho = 0.76 (p = 5.0e-20).

Q2: Are home-collected EEG/ERP measures valid?

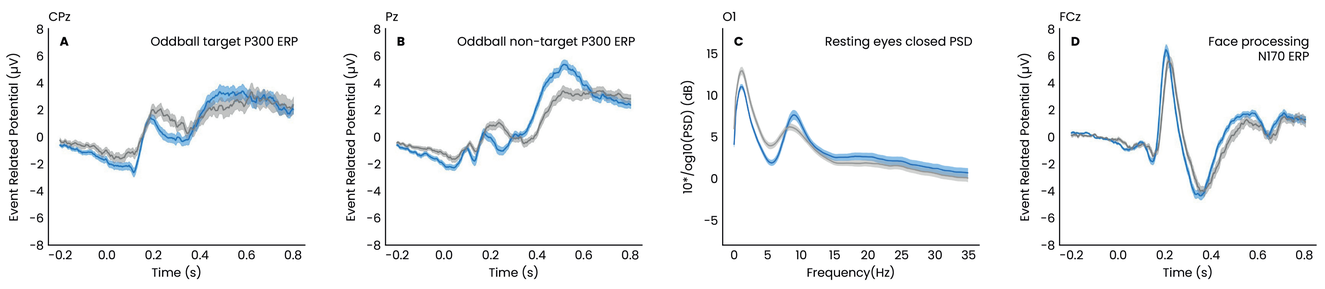


Figure 1: Study grand average ERPs by participant group (blue = control; grey = AD) from A: gamified P300 visual oddball task (target ERP); B: P300 non-target ERP; C: 2m resting state task (eyes-closed portion); D: ERP from PIvital facial emotion recognition task. All patient ERP amplitudes are reduced and peak latencies delayed. Patient PSD alpha peak is reduced in amplitude and frequency. Error bars are trimmed SEM across participants (10% outlier trim). ERPs are baselined from -0.5 to -0.25.

Q3: How do suspected AD patients and controls break down by biomarker status?

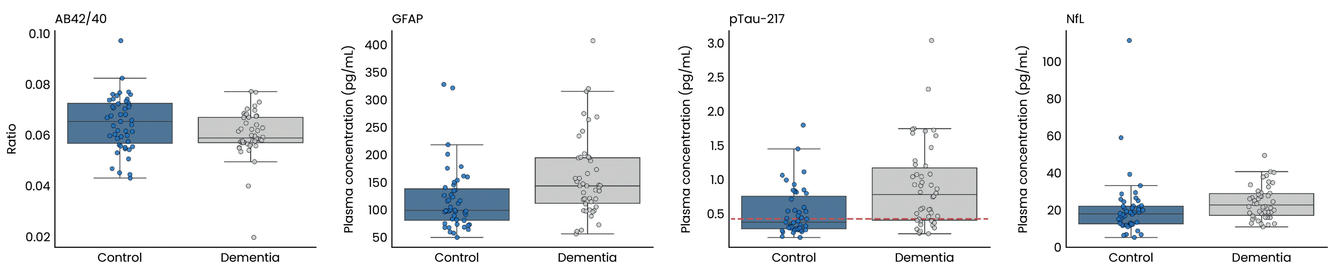


Figure 2: Biomarkers extracted from blood submitted by 93 of the ~100 participants who completed the study. Collected at the study midpoint (month 6) and end (month 12). Values shown here are an average of those collected for each participant. pTau217 was the most discriminative of participant groups. Of the patient sample, 13 were pTau217 negative (<0.42pg/ml) and 33 were pTau217 positive (≥0.42pg/ml), according to the Ashton et al. (2024) single cutoff (red dotted line).

Q4: What is the relationship between biomarker status and study endpoints?

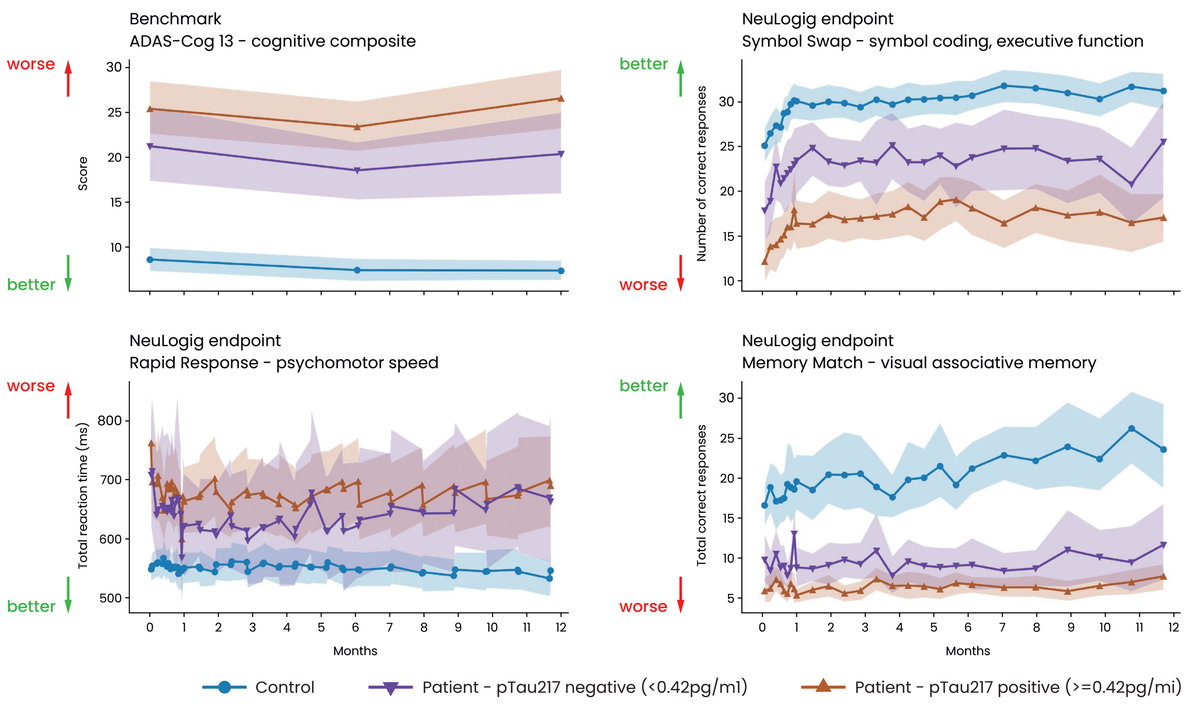


Figure 3: Benchmark (ADAS-Cog) and NeuLogiq (executive function, reaction speed and memory) primary metrics over time, with patients split by pTau217 status (controls not split). Each dot represents a measurement timepoint. All NeuLogiq measurements were taken at home, without researcher supervision. Error bars are 95% confidence intervals.

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Conclusions

- Patients are willing and able to perform repeated cognitive and EEG testing at home.
- Cumulus endpoints show greater separation with AD pathology (pTau217) than the benchmark endpoint (ADAS-Cog) over the study timecourse.
- Endpoints accord with standard benchmarks and demonstrate patterns of patient impairment consistent with the literature.
- EEG biomarkers, including passive and task-based components, demonstrate morphology and group differences as expected based on the literature.

References

1. Öhman F, Hassenstab J, Berron D, Schöll M, Papp K V. Current advances in digital cognitive assessment for preclinical Alzheimer's disease. Alzheimer's Dement Diagnosis, Assess Dis Monit. 2021;13(1):1–19.
2. McWilliams EC, Barbey F, Dyer JF, Islam MN, McGuinness B, Murphy B, et al. Feasibility of Repeated Assessment of Cognitive Function in Older Adults Using a Wireless, Mobile, Dry-EEG Headset and Tablet-Based Games. Front Psychiatry. 2021;12(June):1–17.
3. Ashton NJ, Brum WS, Molfetta G Di, Benedet AL, Arslan B, Jonaitis E, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurol. 2024;81(3):255–263. PMID: 38252443