Feasibility of the Cumulus electrophysiological neurocognitive platform to enable de-centralised trials in Alzheimer's Disease

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Cumulus Real-World Neurophysiology Platform

Developed in collaboration with leading pharma companies and KOLs

Cumulus provides full service:

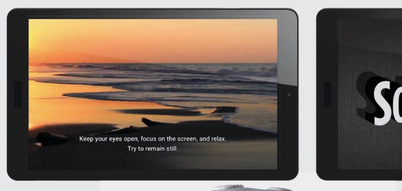
- Protocol/study/SAP design
- On-site training, off-site support
- Full data package
- Reporting and custom analytics

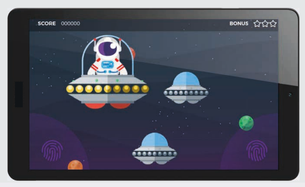
Certified Medical Device

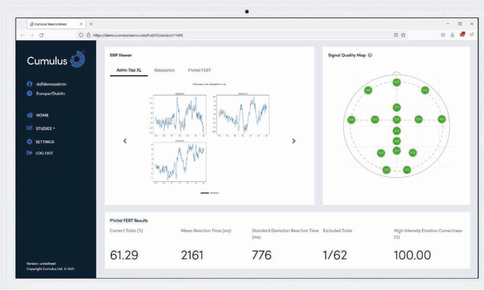
Designed for and with patients and clinicians

Secure automatic upload and QC

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







Introduction

- Neurofunctional biomarkers (e.g., haemodynamic or electrophysiological) requires travel to a clinical trial centre equipped for specialised imaging, but such visits became harder to justify during the pandemic
- Digital endpoints can be deployed easily, to broader populations, at lower risk and inconvenience to patients
- We report on a Covid-era deployment of a patient-friendly at-home neurophysiological biomarker tool, as an adaptive addition to a phase 1b trial of an experimental Alzheimer's therapy
- The P300 and Mismatch Negativity (MMN) are among the most extensively studied EEG markers in the context of dementia and aging research and have been linked to episodic memory, executive function and context updating processes. Decrease in alpha power is also a well-characterized marker of AD (Horvath, 2018; Babiloni et al., 2020)

Research Questions

Q1: Is unsupervised at-home use of functional neurophysiology feasible?

We evaluate adherence to the study protocol with regards to functional impairments.

Q2: Can we capture EEG data from the home?

The construct validity of the EEG endpoints captured in the home was evaluated across all participants.

Methods

- Patients visited the clinic for weekly XPro1595 injections, over 12 weeks
- Recordings were captured in-clinic around the time of weekly injections aimed at capturing acute drug effects, together with regular burst sampling in the home
- The tasklist included a 15-min MMN task, a 15-min P300 task, and a 7-min resting state
- Patients had the option to complete passive tasks only (e.g., the MMN and resting state) if the P300 active task proved to be too difficult based on their impairment level

Results

Q1: Is unsupervised at-home use of functional neurophysiology feasible?

	Participant #1	Participant #2	Participant #3
MMSE score	13	15	25
Scheduled sessions	42 sessions	37 sessions	37 sessions
% sessions adhered to per-protocol	100%	91.9%	97.3%
% of technically successful sessions	97.6 % (1 session failed)	100%	100%

- Three mild to moderate AD patients with MMSE scores of 13, 15 and 25 (one male, two female) completed 14 weeks of at-home recordings, with the assistance of a study partner
- A total of 111 sessions were collected out of 116 requested across all participants
- The two patients with a higher level of impairment chose to only conduct passive tasks in the home

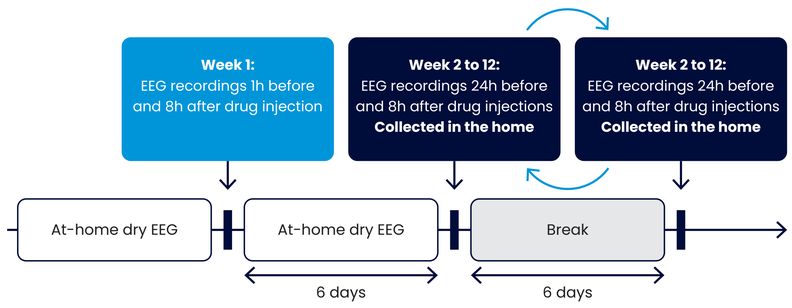


Fig 1. Study Protocol Diagram

Q2: Can we capture EEG data from the home?

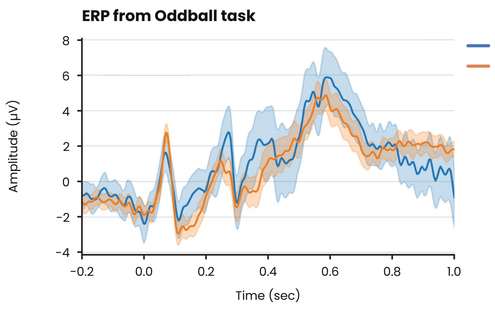


Fig 2. Grand average of the P300 ERPs extracted from the gamified visual oddball task at channels Pz, P3, and P4 across all sessions for participant #3.

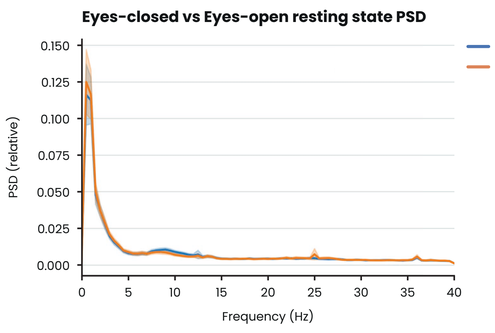


Fig 3. Power Spectral Density extracted from the resting state task at channel O1, O2, Pz, P3, P4, CPz across all participants.

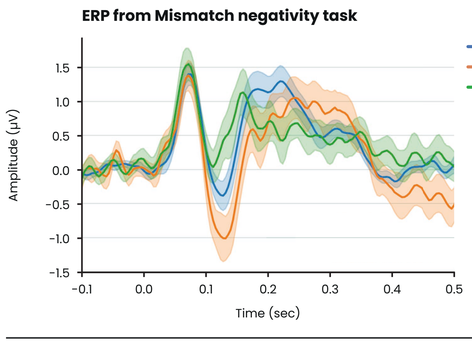


Fig 4. Grand study average of the MMN ERPs extracted from the gamified passive auditory oddball task at channels Fz, FCz, FCC3, and FCC4 across all participants.

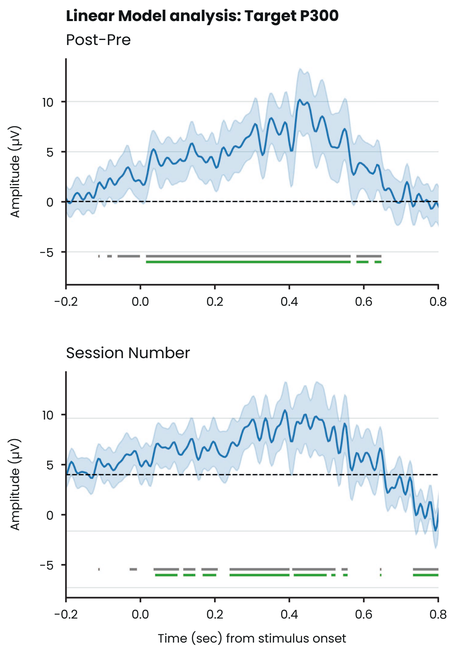


Fig 5. Modulation of the Target P300 ERP.
Top Panel: 8hr after the injections of Xpro1595.
Bottom Panel: after 12 weekly injections of XPro1595.
The green lines indicate where the modulations in amplitude reach significance after multiple comparisons corrections. The grey lines correspond to uncorrected significant differences.

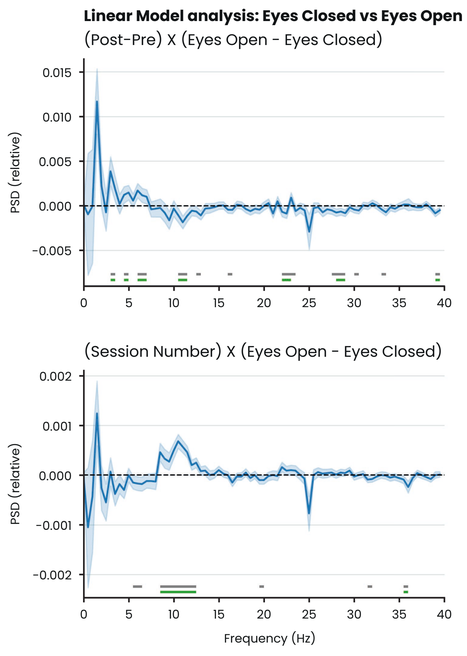


Fig 6. Modulation of the Spectral Band Power.
Top Panel: 8hr after the injections of Xpro1595.
Bottom Panel: after 12 weekly injections of XPro1595.
The green lines indicate where the modulations in amplitude reach significance after multiple comparisons corrections. The grey lines correspond to uncorrected significant differences.

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References

1. Horvath, Andras, et al. "EEG and ERP biomarkers of Alzheimer's disease: a critical review." *Frontiers in bioscience (Landmark edition)* 23 (2018): 183-220.
2. Babiloni, Claudio, et al. "What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons." *Neurobiology of aging* 85 (2020): 58-73.

Discussion

- The core feature expected in human EEG Power Spectral Density (spectral power decay) is observable in all patients
- The morphology, and scalp topography of the EEG signals extracted from the MMN and P300 tasks are canonical
- Early part and peak of the P300 are boosted acutely and longitudinally across the 12 weeks of treatment
- On resting state, PSD of EC showed increase in alpha and decrease in theta acutely, and alpha decreased across the 12 weeks of treatment
- No clear drug effects could be observed on the MMN

Conclusions

- The Cumulus platform can be frequently and correctly used by mild to moderate AD patients in the home over long periods of time (e.g., >3 months) including 'burst' measurement periods in-lab or at-home
- The capture of electrophysiological correlates characteristic of AD pathology in patients in decentrialised trials hold many promises to accelerate AD clinical research
- Digital technology grounded in the brain has the potential to provide objective, frequent and patient centred tracking of biomarkers of AD-relevant functional neurophysiology