

# The need for broad-spectrum multimodal markers in CNS drug development

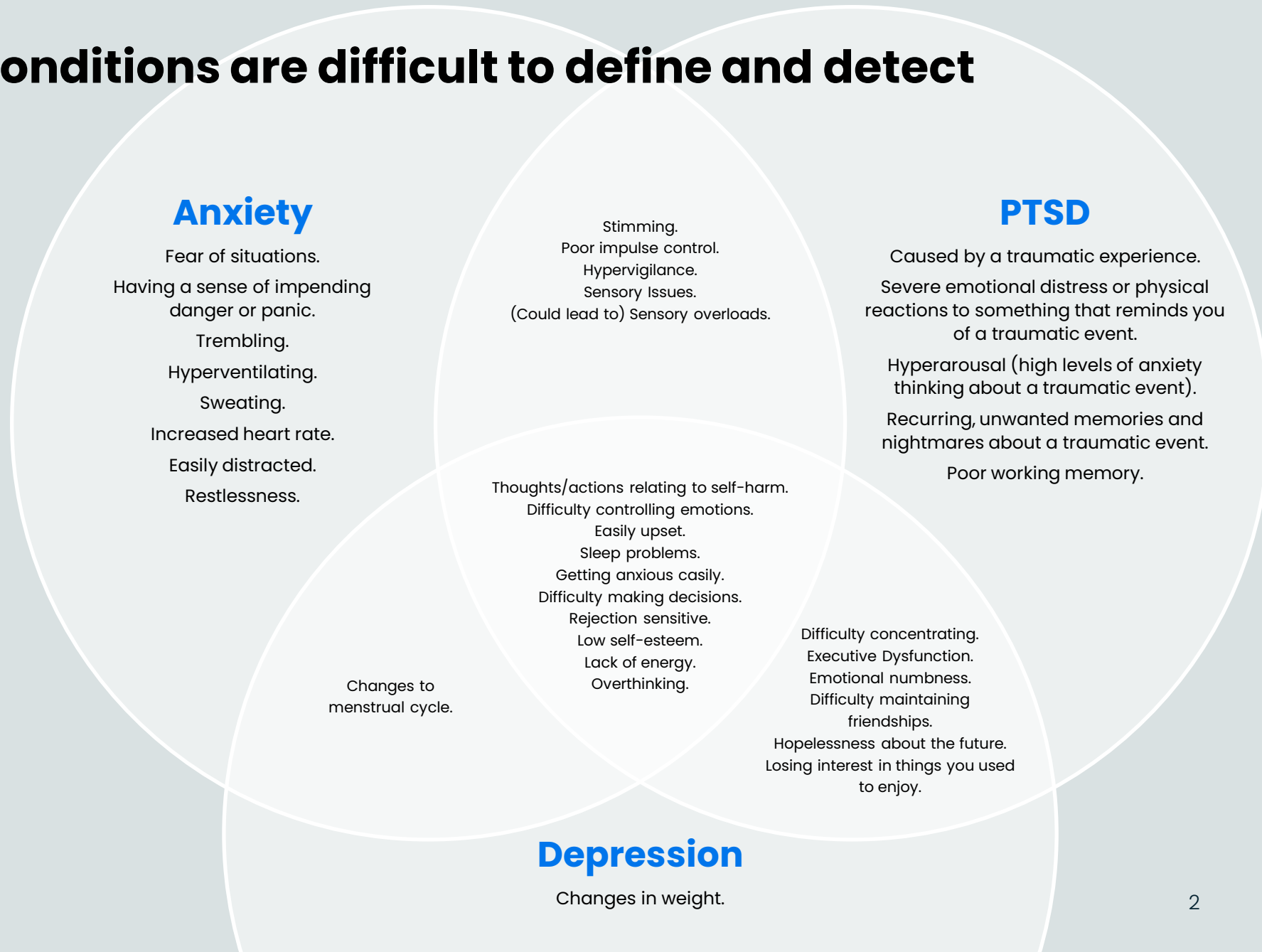
Brian Murphy PhD

**Disclosure:** I am a founder, employee and shareholder at Cumulus Neuroscience

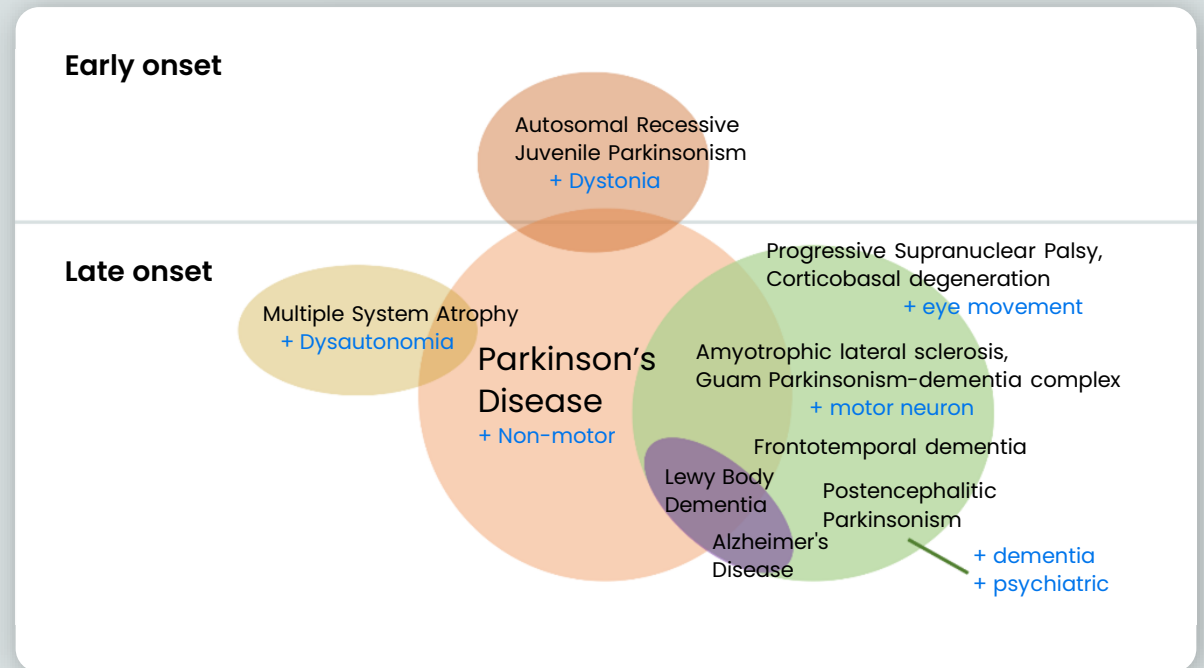
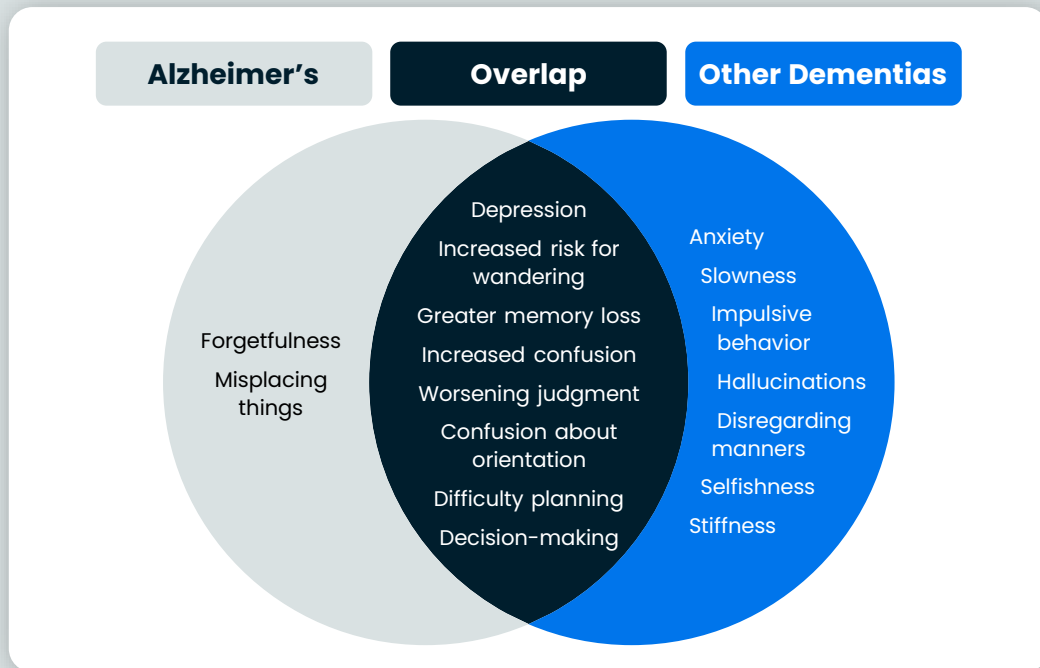
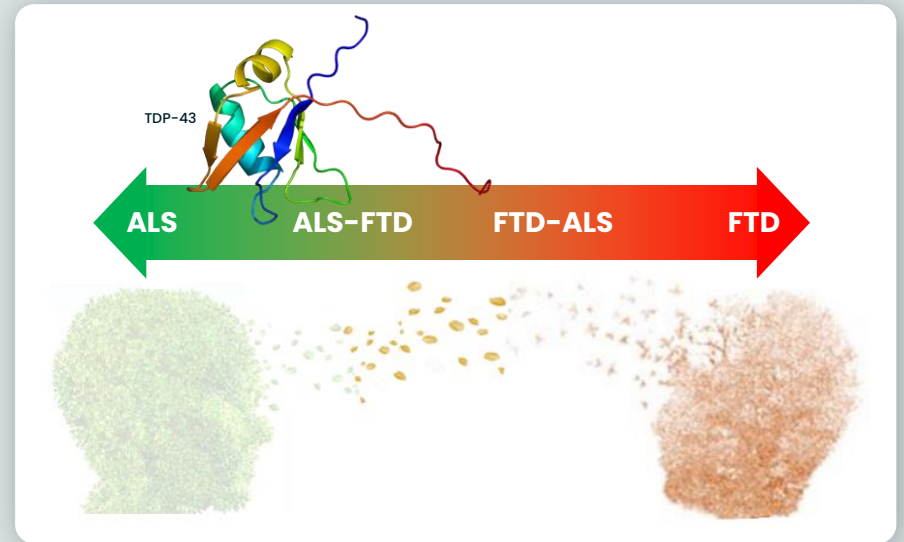
# Why psychiatric conditions are difficult to define and detect

For complex mental illnesses, such as depression, anxiety and PTSD, reliable and timely diagnosis has been challenging due to:

- **Complex spectrum of overlapping symptoms**
  - Heterogeneity
  - Comorbidities
  - Differences in life experiences
- **Subjective assessments**



# Like neuropsychiatry, neurodegenerative diseases exist on a spectrum



# Key measurement challenges in CNS therapies



Ruth McKernan



Hugh Marston

Translational challenges from Animal to Human

Difficulties in predicting drug effect, target engagement, and dose selection

Complex Spectrum of Symptoms

Difficult to know what to measure – limitations of SoC assessments, lack of biomarkers & overlapping symptoms complicate patient stratification

Snapshot Measurements

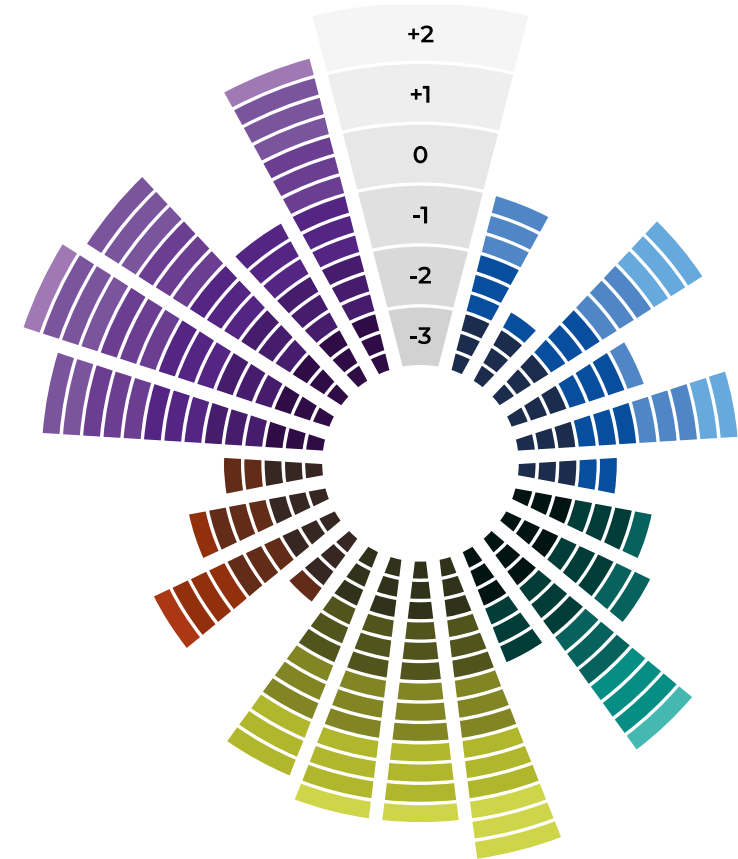
Day-to-day variation in neurocognitive function and data noise **compromise accurate measurement**

High Failure Rates

Neurological molecules have one of the **lowest rate of technical success at 5.9%**

## Consensus resulting from consultation with a group of therapy developers

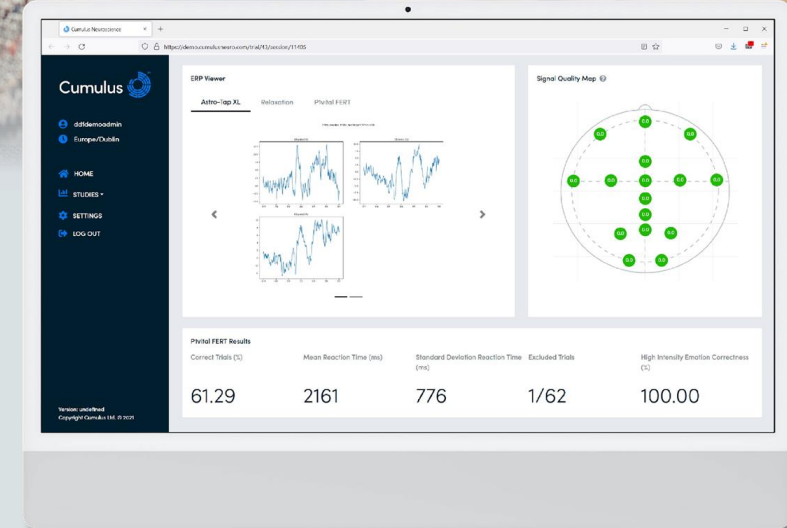
- Re-use of widely validated methods
- Objective measurement of individual functional domains and/or modalities
- Suitable for repeated assessment
- Suitable for deployment to small clinics, under-resourced settings, and patients' homes
- Usable by patients with a range of neurodegenerative, psychiatric and neurodevelopmental conditions
- Covering 5 main domains of consensus importance
- Regulatory approval, audit readiness



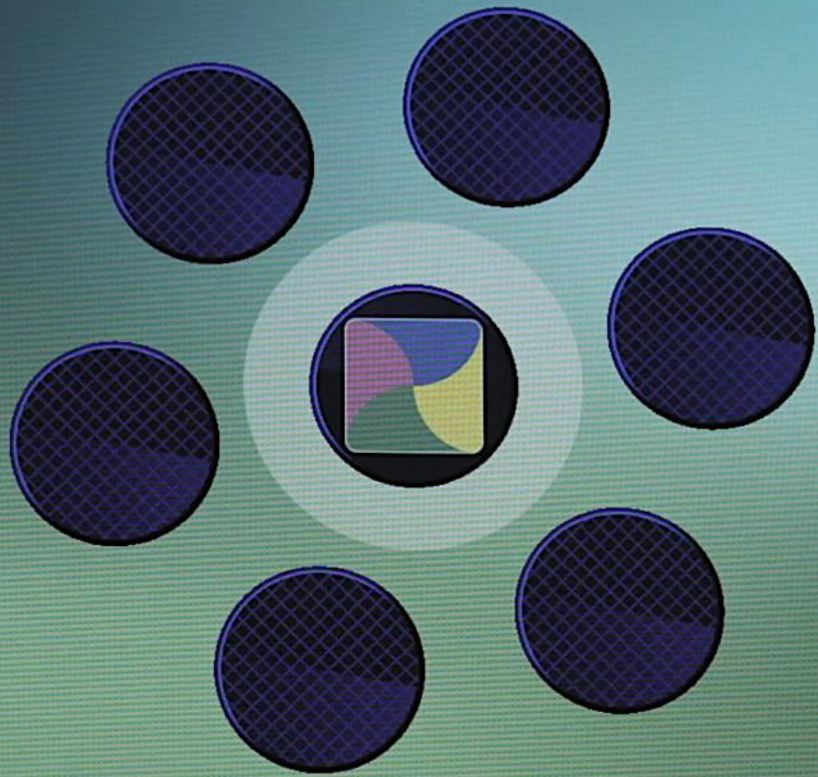
Precompetitive consortium of 10 large pharma co-designed solution, and validation studies

## Validated technologies in a patient friendly and site deployable form

- A unified patient-facing interface, including a range of tasks with broad basis in the literature
- Judicious use of gamification to encourage consistent and genuine engagement from users
- Involvement of representative patients in all stages of technology development
- Real time feedback to clinical teams on remote session compliance and data quality
- Industry standards for regulatory approval, quality assurance, data protection
- Comprehensive guidance and support for patients and clinical site teams



4 Patterns

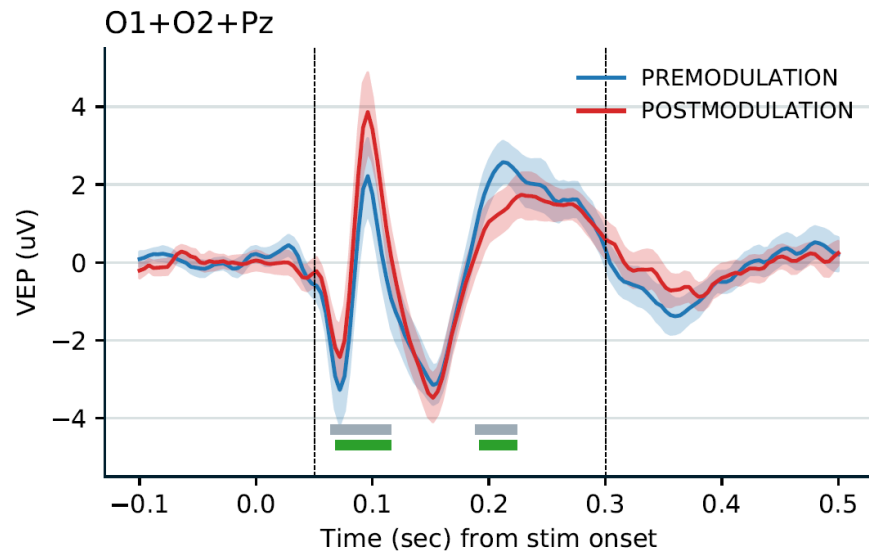




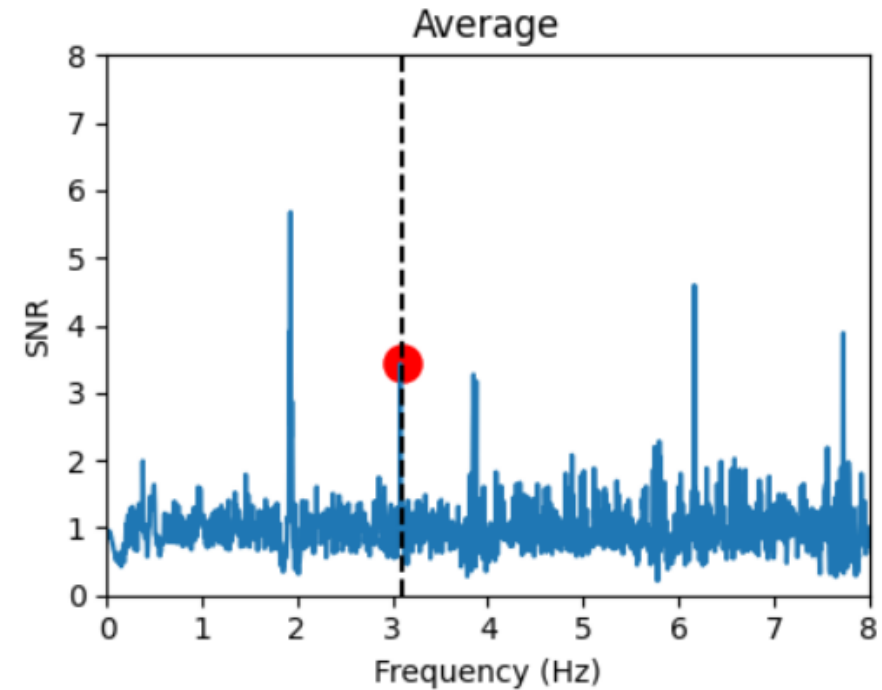


# Recruitment, Screening, Endpoints

- Short clinic-based visual tasks can elicit individual level estimates of neuroplasticity



Milanovic et al (2023), ECNP 2023



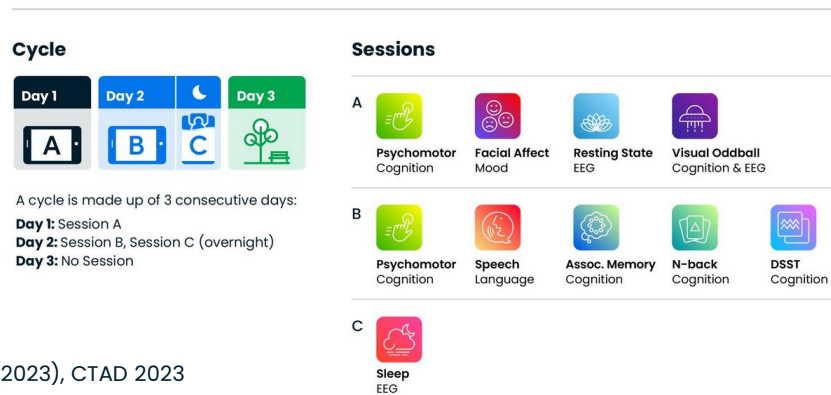
- Three-minute long passive image recognition task measures early memory impairment

Stothart et al (2021), Brain

# CNS101: Longitudinal Feasibility in AD dementia

- 59 Mild AD-type dementia and 60 controls
- In-clinic session to introduce technology
- 12-month period at-home use, total 52 sessions requested at ~30min each
- ADAS-Cog and other benchmarks at months 0, 6, 12

Diagram of the year long, staggered schedule of digital neuroassessments.



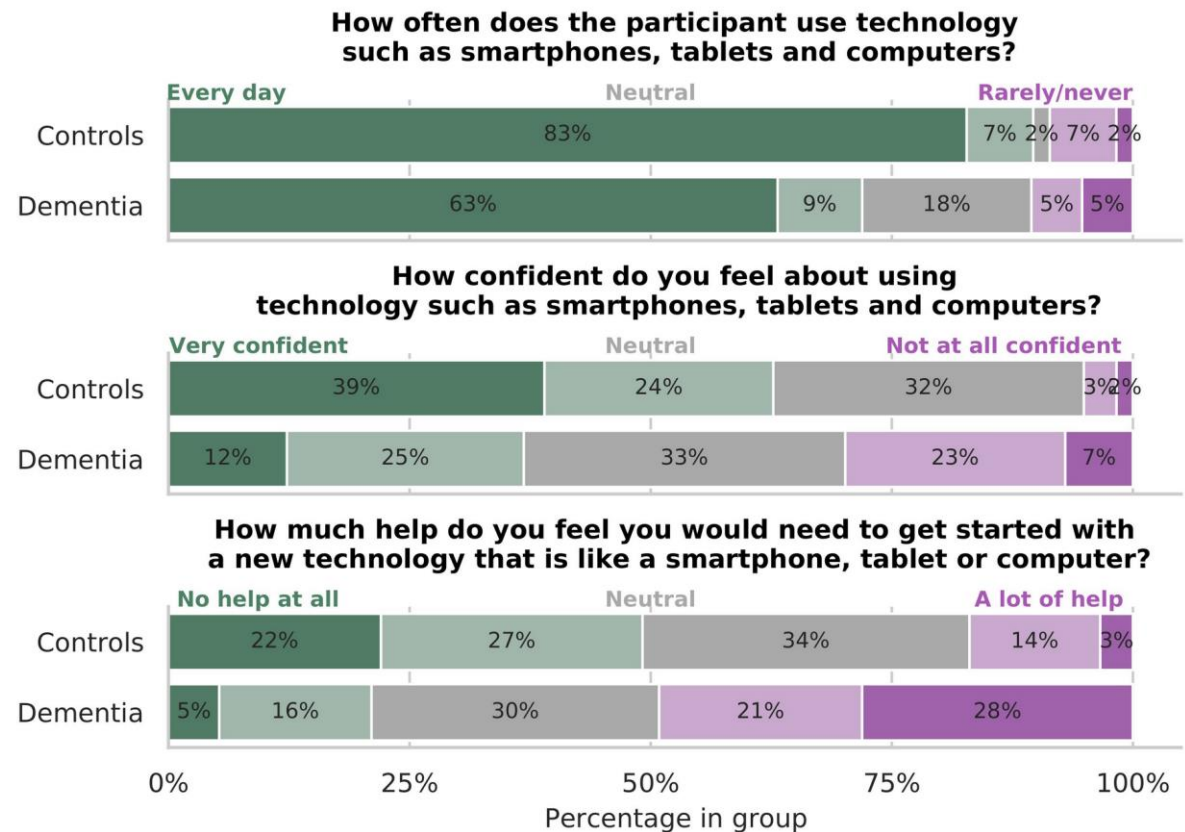
Buick et al (2023), CTAD 2023

# CNS101: Patient Views of Technology

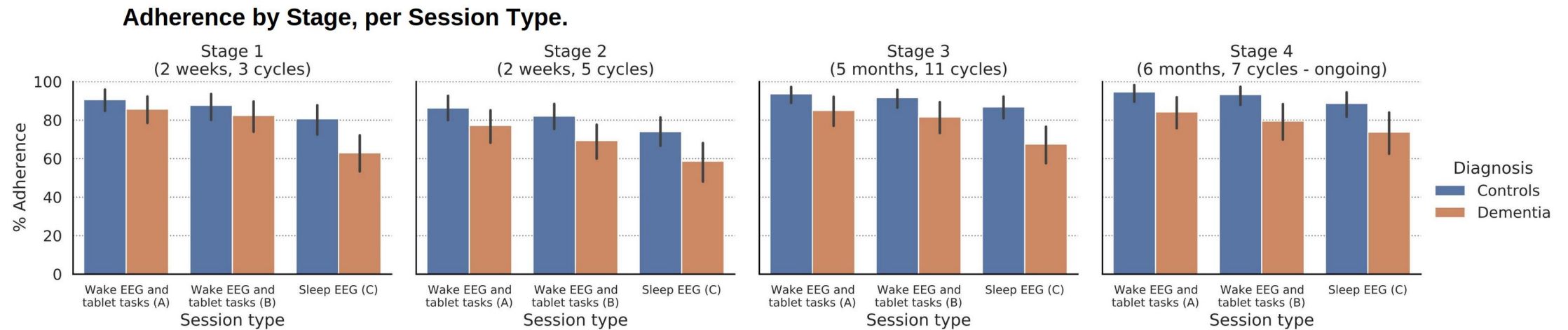
- Surveys and structured questionnaires used to understand patient views of technology before, during and after taking part in the year-long study
- All enrolled participants filled out a baseline survey on background technology usage. The number of participants completing surveys during the study (at-home and at in-clinic visits) were subject to attrition and compliance with the protocol.

	N	Mean Age	ADAS-Cog
Mild Alz. Dementia	59	73.7	25.1
Controls	60	71.1	8.9

Technology usage survey (percentage of responses per group).



# CNS101: Longitudinal Adherence to 12 months



- Withdrawal rate of 27% (16 of total 59) for dementia patients, and 10% (6 of total 60) for controls

\* interim analysis based on >99% sessions. Last patient out expected mid-March 2024

# CNS101: comparing at-home tablet tasks to cognitive benchmarks

- Aggregate data from five at-home sessions during initial “burst” sampling
- Spearman rank correlation of 0.76 for executive task
- 0.75 for associative memory task

## Executive Function

Digit Symbol Substitution

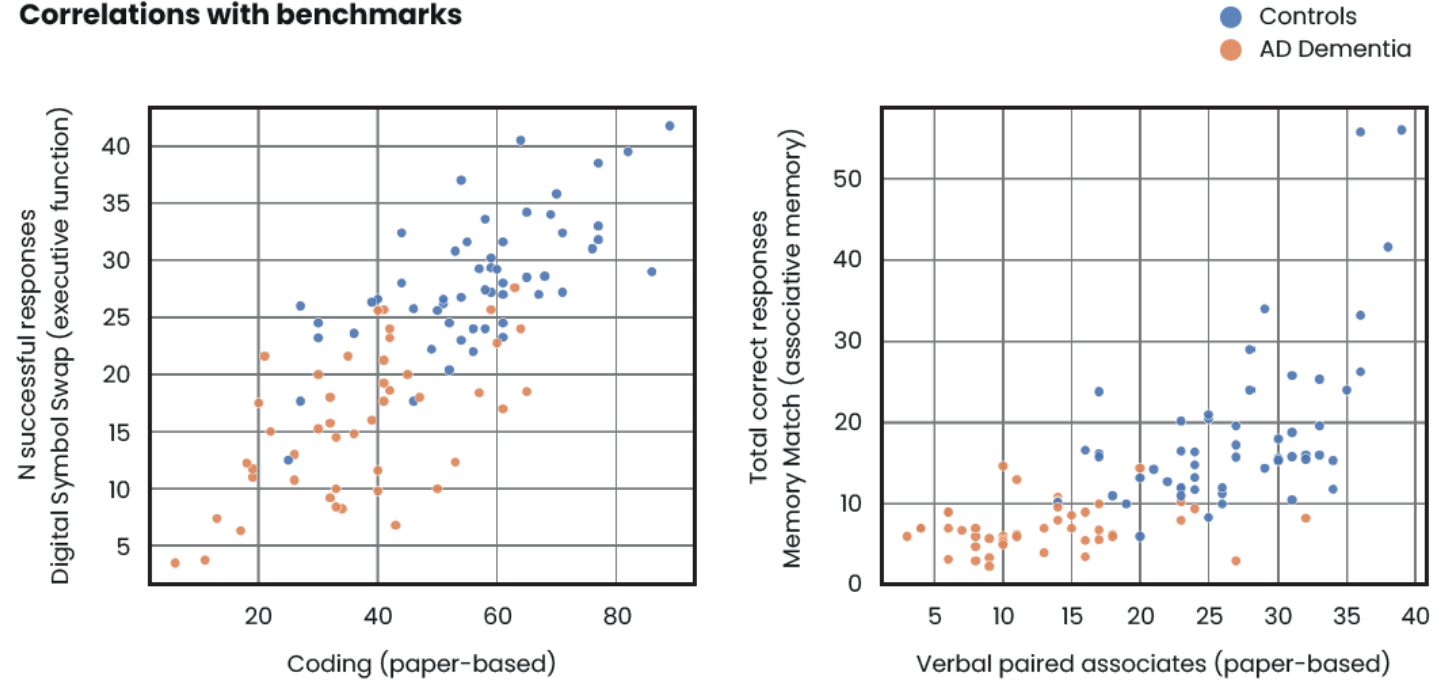


## Episodic Learning

Spatial Associative Memory



## Correlations with benchmarks

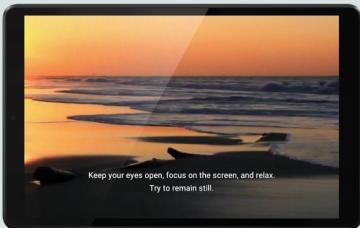


# CNS101: group effects on at-home electrophysiology

- Aggregate data from five at-home sessions during initial “burst” sampling
- Cross-sectional differences align with literature on slowing and weakening of neural activity

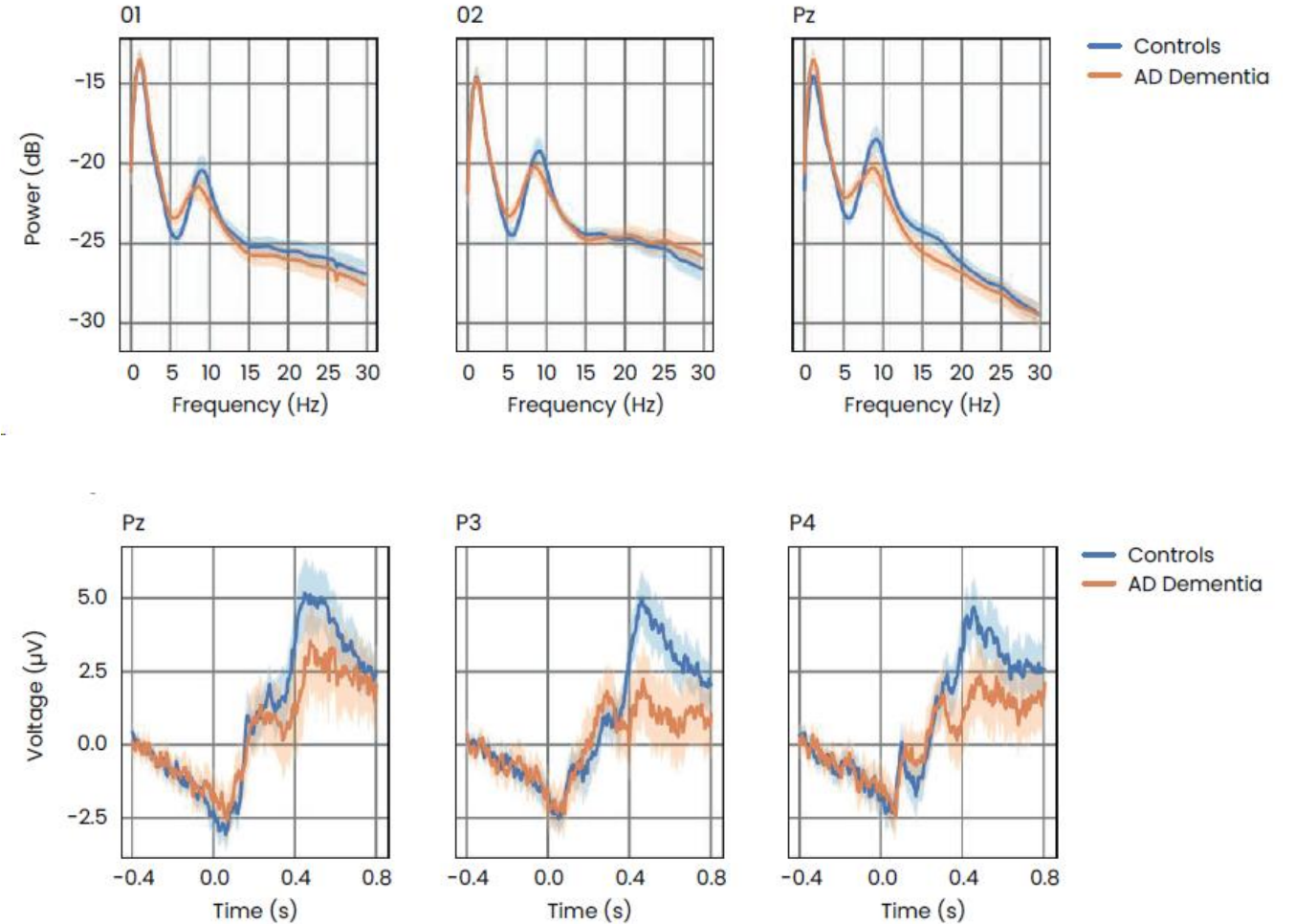
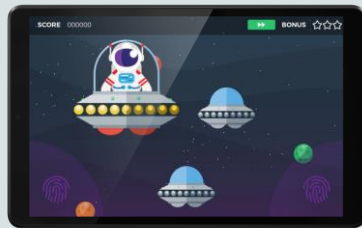
## Resting state EEG

Mixed models of PSDs during eyes closed



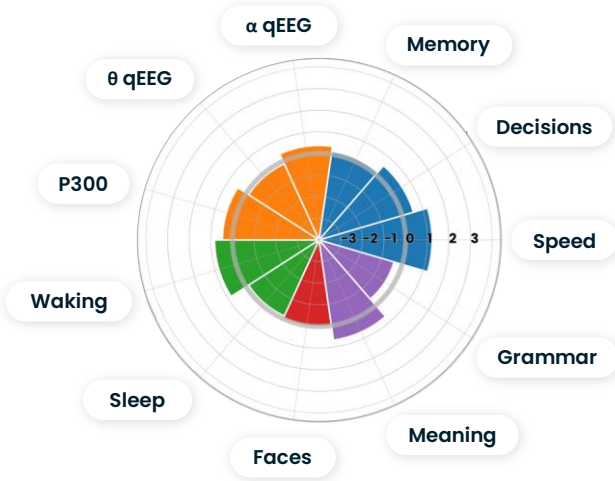
## Visual Oddball

Mixed models of Target condition P300

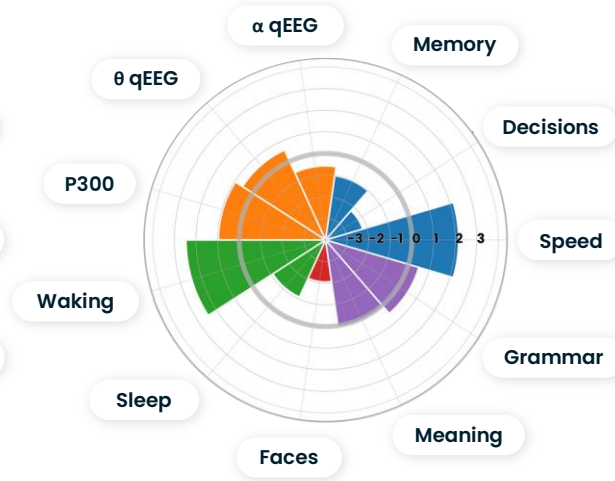


# CNS101: Individual digital “fingerprints” of disease

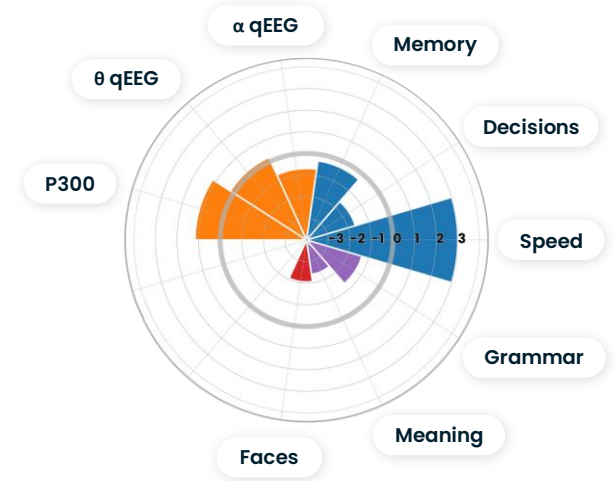
Older Healthy



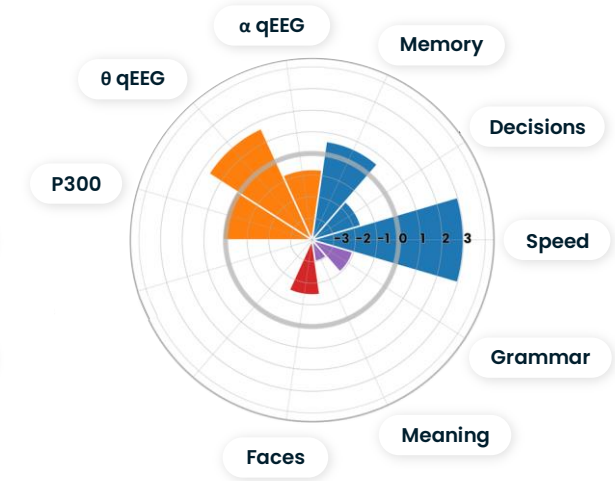
Moderate AD



Moderate ALS



Moderate FTD



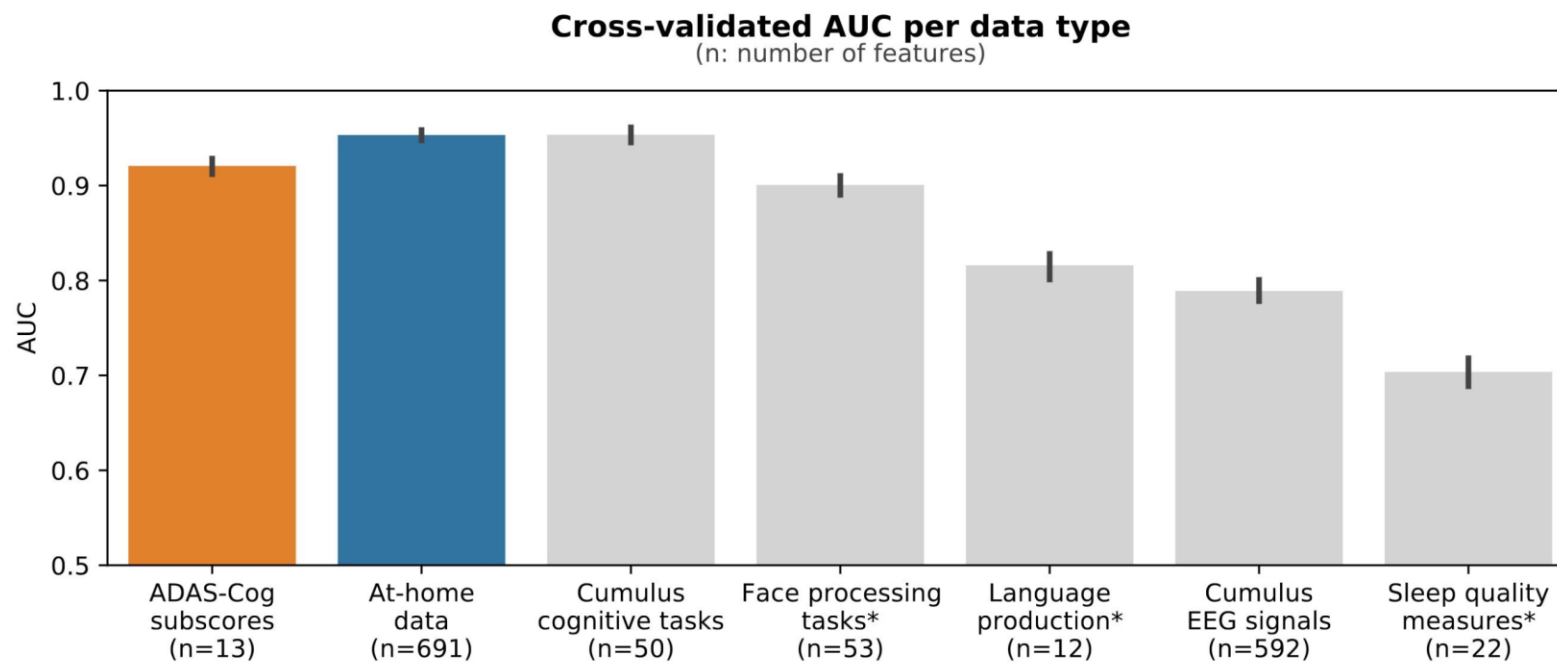
■ Cognition ■ EEG ■ Sleep ■ Mood ■ Language

Buick et al (2023), CTAD 2023

# CNS101: Multimodal Composite Discrimination

- Bagging of decision trees chosen as algorithm that performs well across heterogenous input data types
- Cross-sectional analysis from early “burst” sampling at-home
- Total 1111 sessions from n=47 patients and n=54 controls
- Ten-fold cross-validation under 10 random repartitions of the user-group
- Top performing model of AUC 0.953 yielded sensitivity of 87.1% and specificity of 89.8%

Comparison of detection performance of ADAS-Cog versus Cumulus at-home data modalities (\*3rd party assessments).







International Society for CNS Clinical Trials and Methodology

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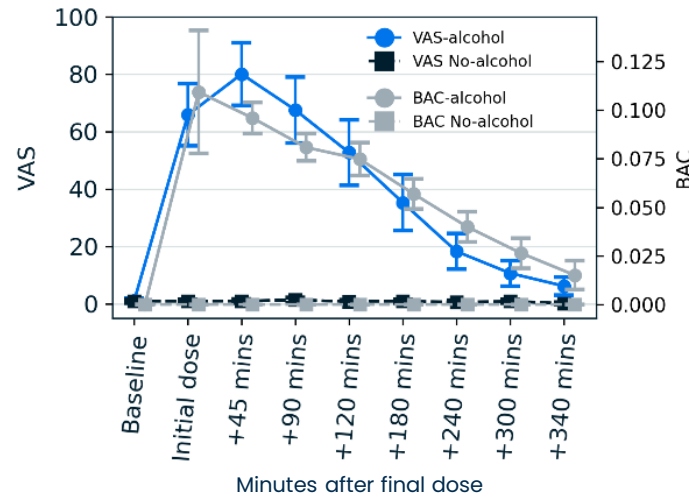
# Questions?



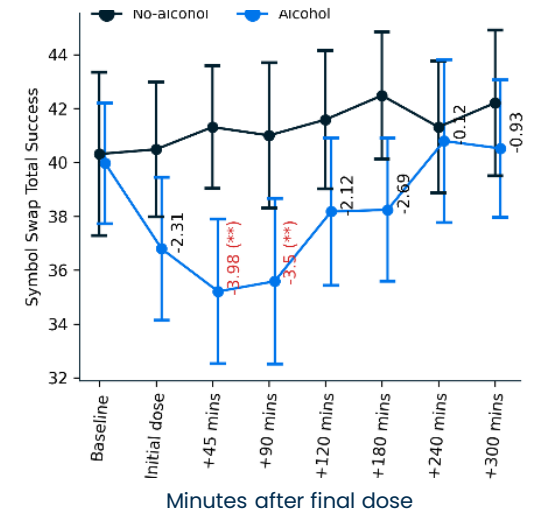
# Cognition tasks show subtle sedative effects

- Memory and executive functions are modulated directly by levels of alcohol
- Many drugs have sedative effects, and subtle impairments are seen in many neurodegenerative and psychiatric conditions.
- 30 young healthy participants brought just above drink driving limit
- **Similar effects to conventional benchmarks for memory and executive function at peak intoxication.**

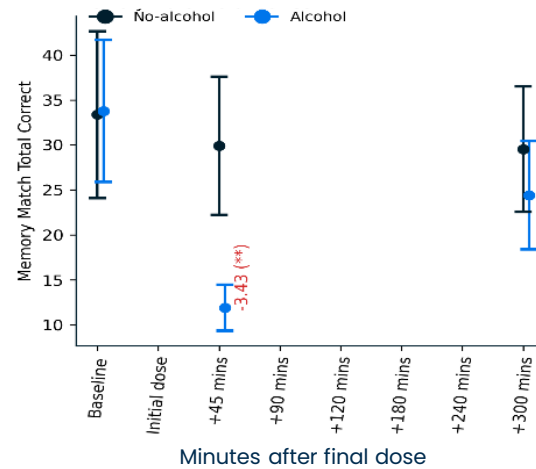
BAC vs self-reported (VAS) intoxication



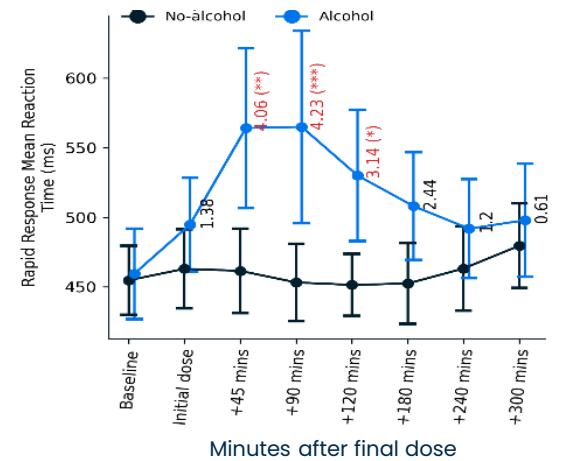
Symbol Swap (Cumulus DSST) score



Episodic memory score

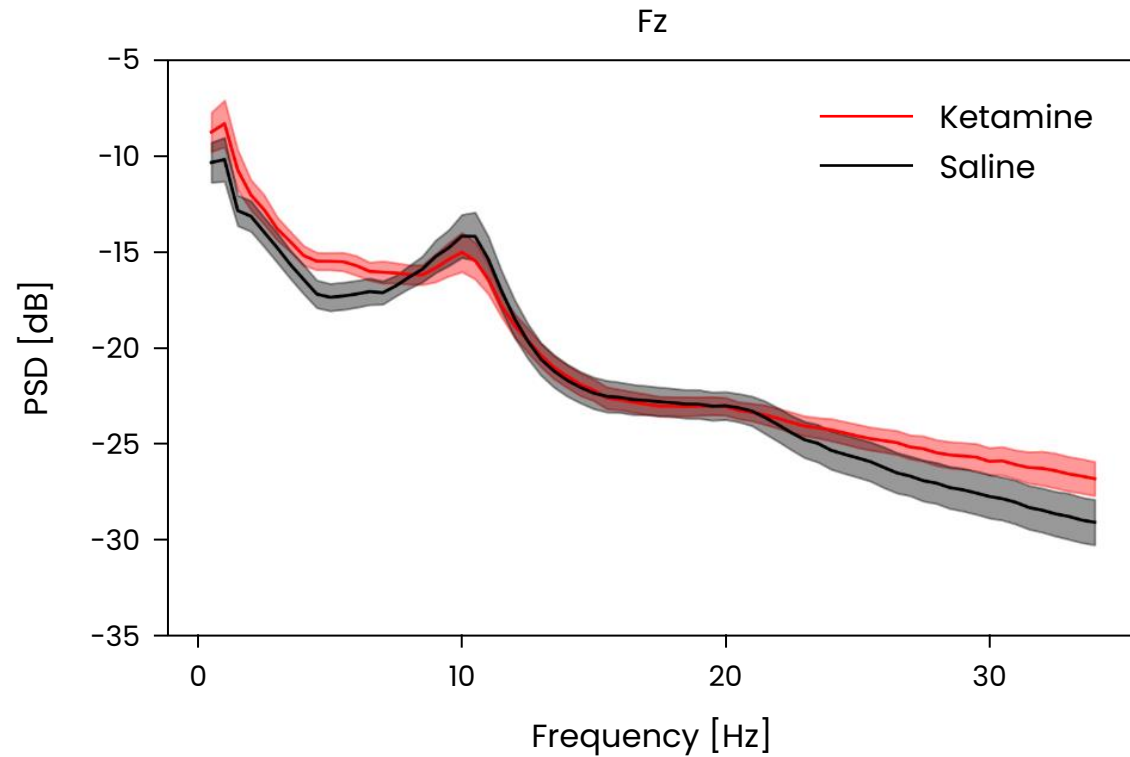
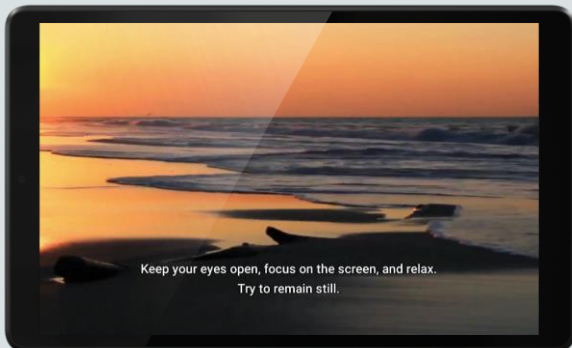


Simple Reaction Time



# Resting EEG gives direct immediate insight into drug engagement

- 30 person cross-over placebo-controlled study with intravenous racemic ketamine.
- **Predicted eyes-closed qEEG changes seen within minutes:** disruption of alpha/beta activity, and enhancement of gamma activity.

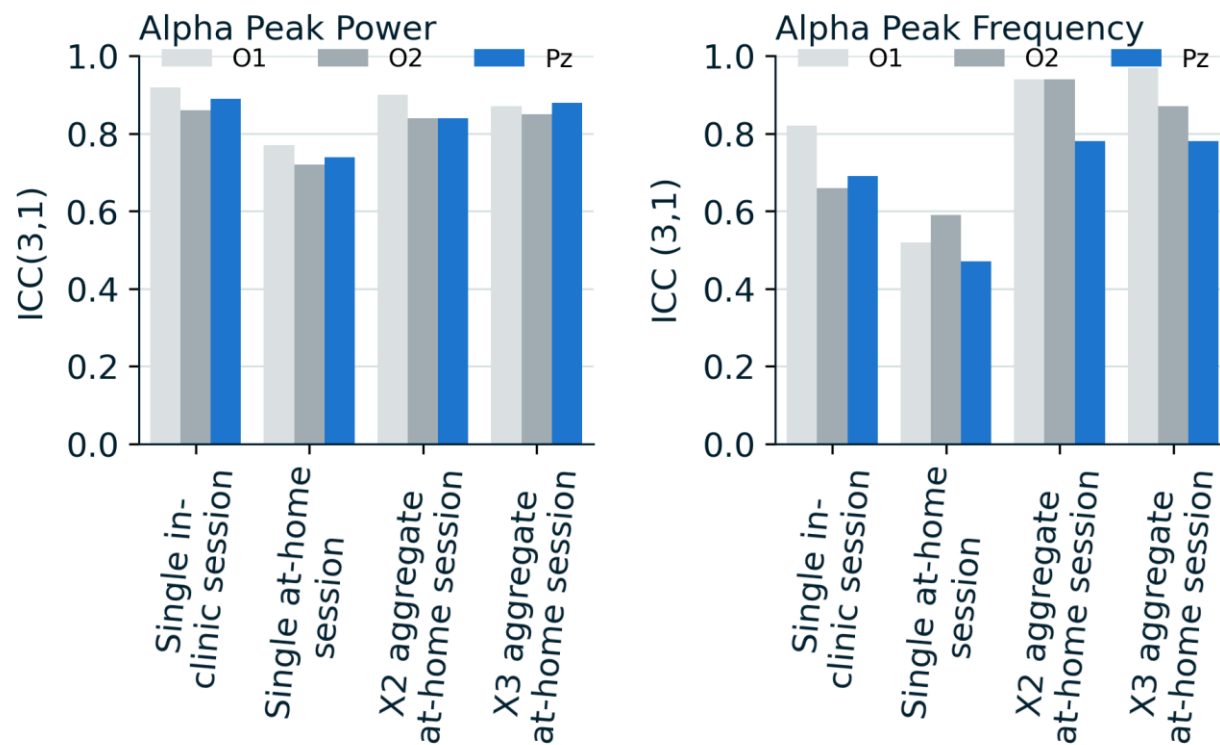
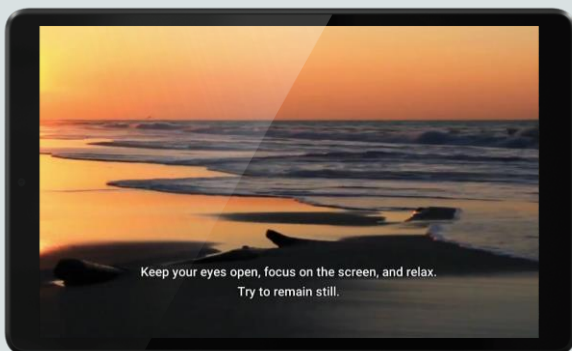


**Murphy, B.**, Barbey, F., Bianchi, M., Buhl, D. L., Buick, A. R., Danyeli, L., Dyer, J. F., Götting, F., Izyurov, I., Javaheripour, N., Krylova, M., Nolan, H., O'Donnell, P., & Walter, M. (2020). Demonstration of a novel wireless EEG platform to detect the acute and long-term effects of ketamine, in the lab and in the home. *FENS, Glasgow*.

O'Donnell, P., Johannesen, J., (2022) Scalable ERPs for clinical trials: At home assessments with remote devices. *IPEG, NYC*  
(Presented by Sage)

# Resting EEG is reliable in lab, and in-home after aggregation

- 30 person cross-over study, off-drug data.
- **qEEG endpoints are reliable when collected in clinic, and reliability is matched or exceeded with as few as 2 or 3 at-home sessions in aggregate.**

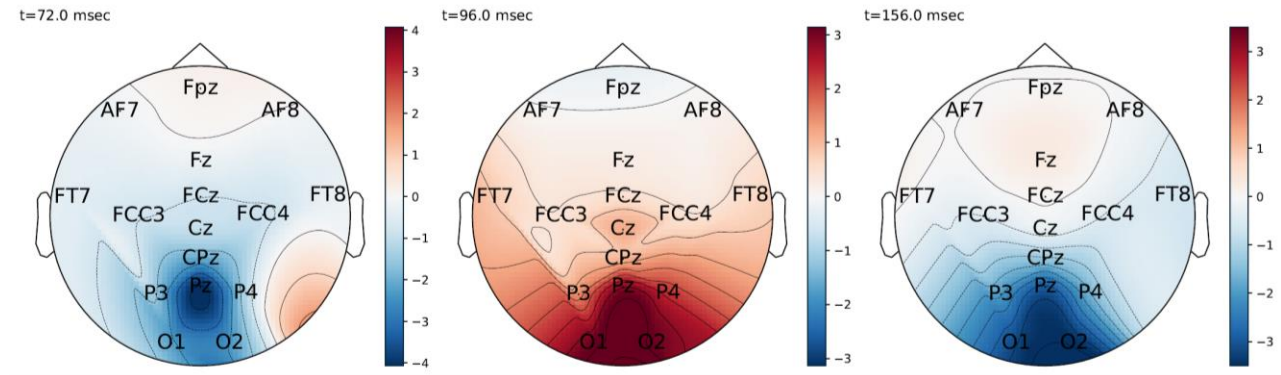
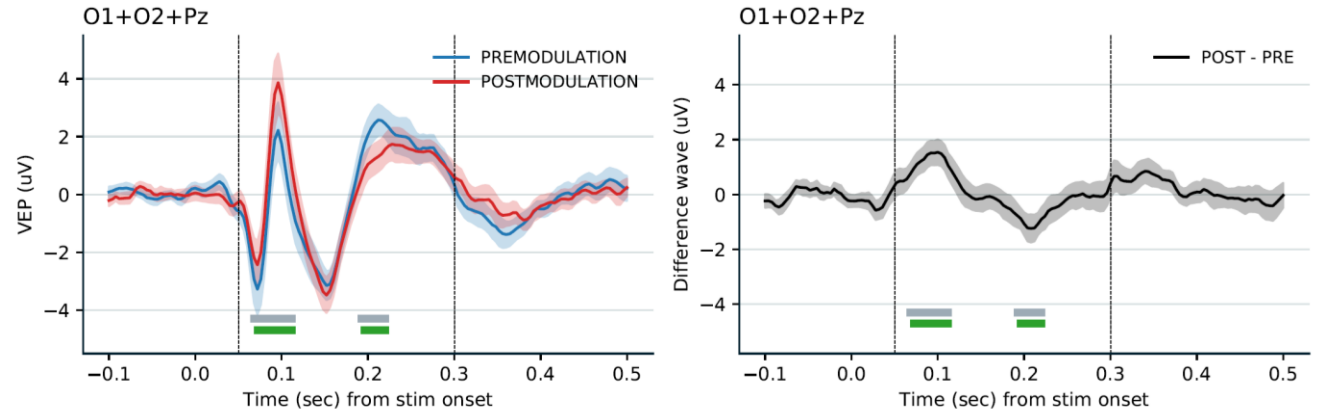


**Islam, N.,** Barbey, F., Buick, A., Nolan, H., Rueda-Delgado, L., Murphy, B. (2022) Feasibility and reliability of real-world functional neurophysiology with at-home use of Cumulus' wireless EEG. *IPEG, NYC*

**Barbey, F.,** Farina, F. R., Buick, A. R., Danyeli, L., Dyer, J. F., Islam, N., Krylova, M., Murphy, B., Nolan, H., Rueda-delgado, L. M., Walter, M., & Whelan, R. (2022). Neuroscience from the comfort of your home: Repeated, self-administered wireless dry EEG measures brain function with high fidelity. *Frontiers in Digital Health*, 4(944753). <https://doi.org/10.3389/fdgth.2022.944753>

# Neuroplasticity can be measured non-invasively

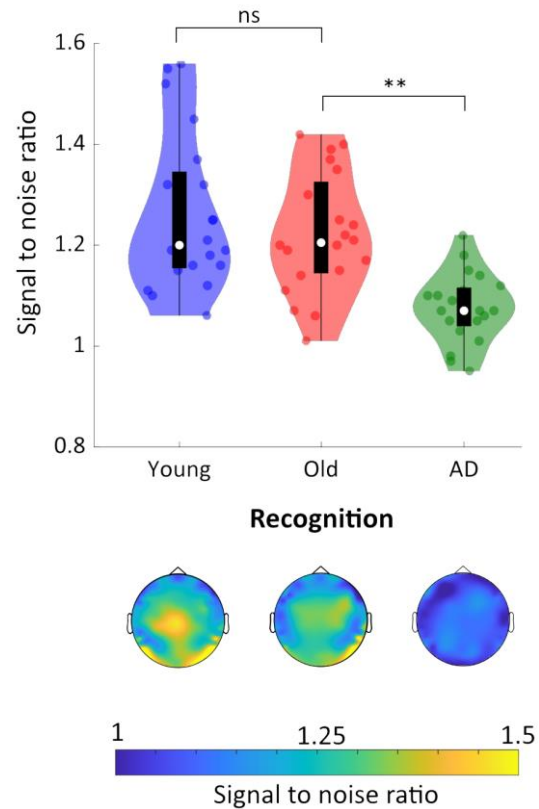
- Data from 11-minute in-clinic VEP-LTP task in off-drug baseline of 24-person phase 1a clinical trial for psychiatric indication.
- **Very robust group level neuroplasticity observed.** Topography and morphology of signals consistent with high-burden conventional task.



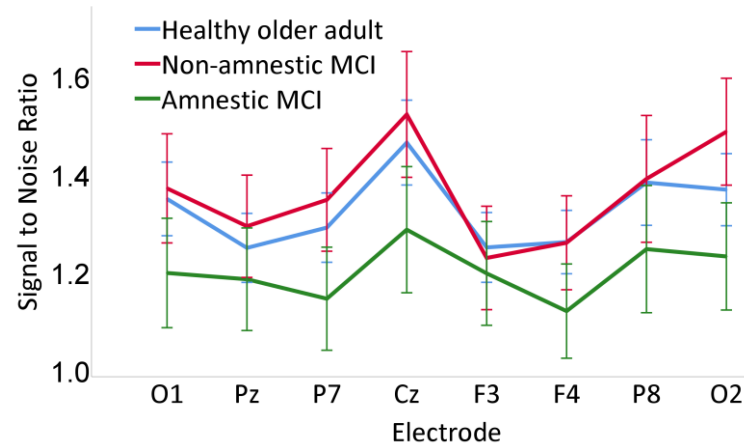
McWilliams et al. (2023) *ECNP*  
Milanovic et al. (2023) *ECNP*

# Fastball: mechanistic assessment of memory

Specific to AD, not age



Specific to aMCI, not naMCI



Translates to Mobile Dry EEG

