

Technical and clinical validation of novel cognitive tests for remote sampling of memory and executive function



Cumulus neuroassessment 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-III CNS trials.

Secure automatic upload and QC.

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

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

- Objectively administered and automatically scored
- Results available in minutes, enabling remote monitoring
- Suitable for detecting change over time



Memory Match: visual episodic memory



Symbol Swap: Symbol/digit coding

Continuous engagement with patients informs task design

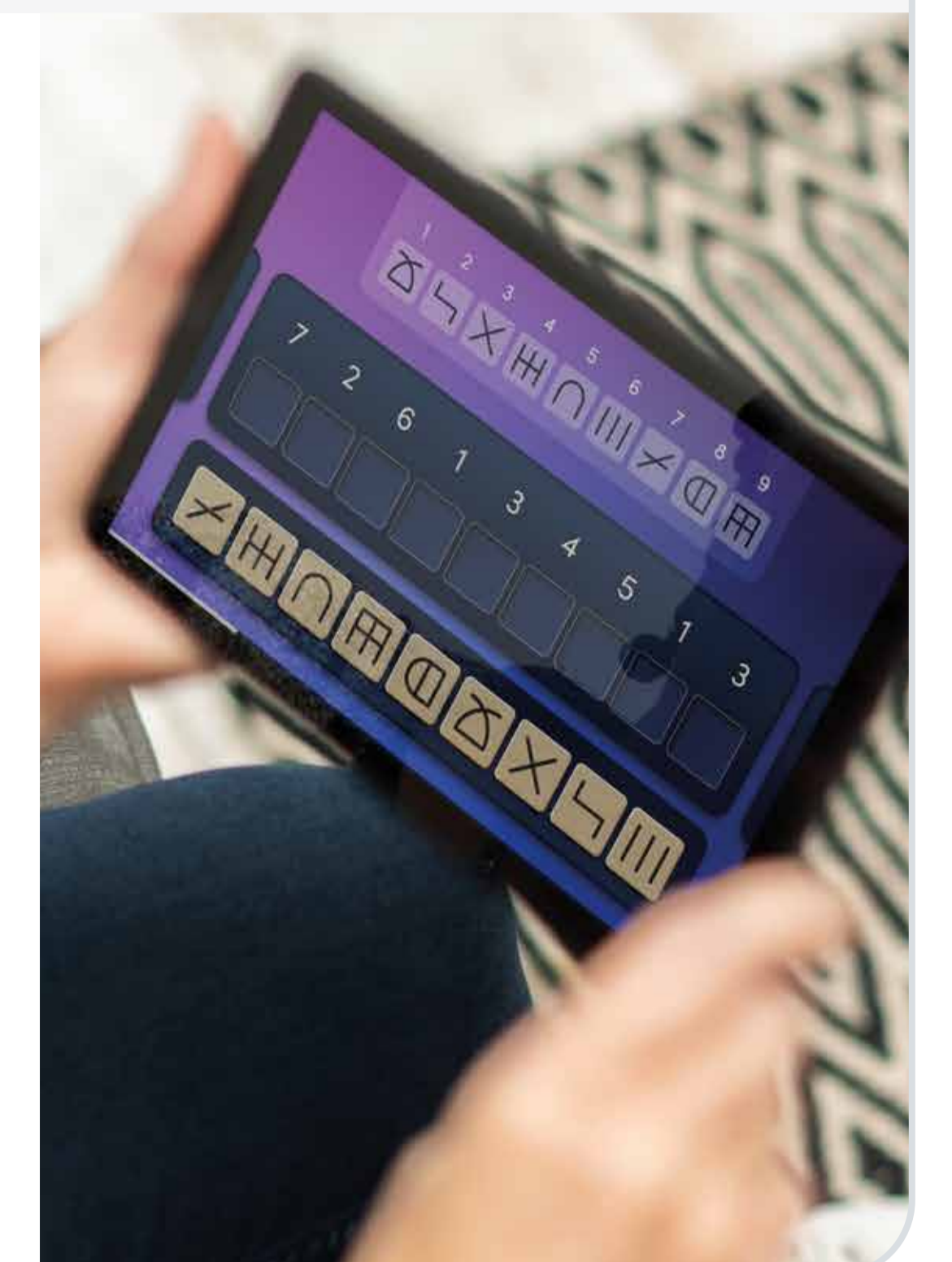
Patient Advocate User Panel members are chosen for their experience with dementia, depression, schizophrenia and other neurological conditions. Each group includes a mix of patients, family members, and healthcare professionals.

Key Activities:

- Focus groups
- Usability testing
- User scenario simulation
- In-clinic sessions
- Remote sessions
- Study schedules

Outcomes may influence:

- Task development
- Hardware selection
- Onboarding procedures
- Session/task list features
- Study scheduling features
- Site staff training
- Participant facing materials



Introduction

- Frequently repeatable digital cognitive measures can be used to detect change over time: either due to disease progression or the therapeutic effect of an intervention.
- Current gold standard tools in clinical trials are very insensitive in early disease and require very large samples to detect any change (if such tests are even repeatable in principle) [1, 2].
- We report on the validation of two novel cognitive tests designed for sensitivity and repeatability.
- To capture the dynamics of longitudinal change, self-administration, in the home environment, may be preferred.
- This requires the creation of assessments that are acceptable and usable for patient groups.
- Automated administration and scoring improves reliability.
- Episodic memory and executive function are profoundly affected in Alzheimer's and Parkinson's disease.

Cognitive test development

Cumulus developed 2 new repeatable tasks (above)

- Memory Match, a paired episodic memory test, takes 5-15 minutes to complete, self-administered.
- Symbol Swap, a digit-symbol substitution task (DSST), takes 2 minutes to complete, self-administered.

Development was informed by engagement with our dementia patient advocate user panel, made up of patients, family members and healthcare professionals.

- Engagement included focus groups and usability testing.
- Feedback provided on task usability, instruction clarity, language, participant-facing materials and more.

Research questions – across two validation studies

Technical validation: Can tasks sensitively measure subtle induced cognitive impairment and return to normal?

We administer alcohol to achieve a BAC% equivalent to just above the UK drink-driving limit (targeting 0.08-0.1 peak BAC%).

BAC% measured via breathalyser and visual analogue scale of subjective intoxication.

Very high-frequency measurement using the tasks (up to 8 assessments within a day).

Clinical validation: Do tasks differentiate AD from control, and do scores correlate with benchmark measures of the same functions?

Effect size is compared to 45-minute, clinician administered benchmark composite (ADAS-Cog).

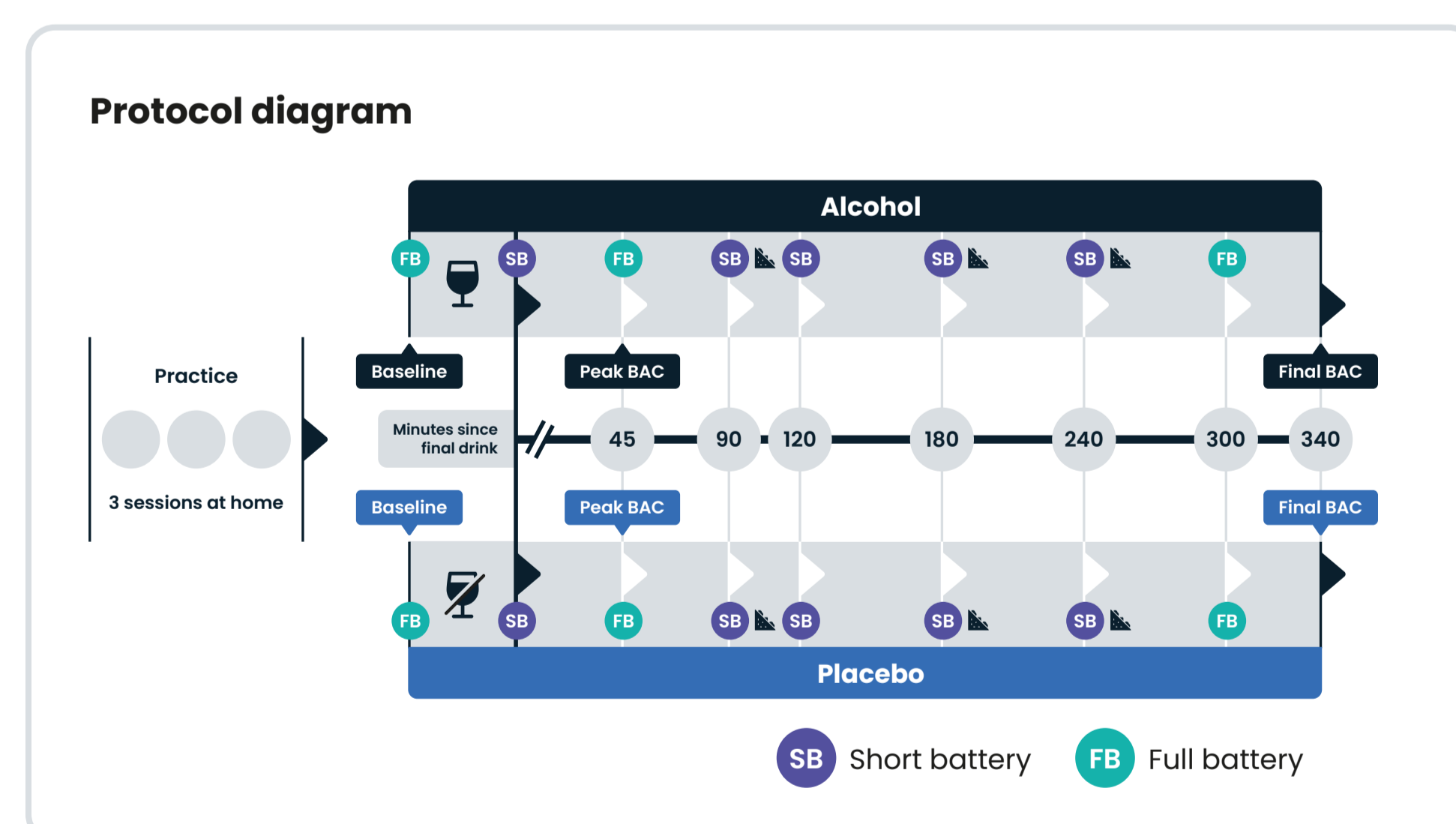
Performance is correlated against pen-and-paper equivalent tests.

Are patients able and willing to use the platform at home?

Technical validation: Sensitivity to change within individuals

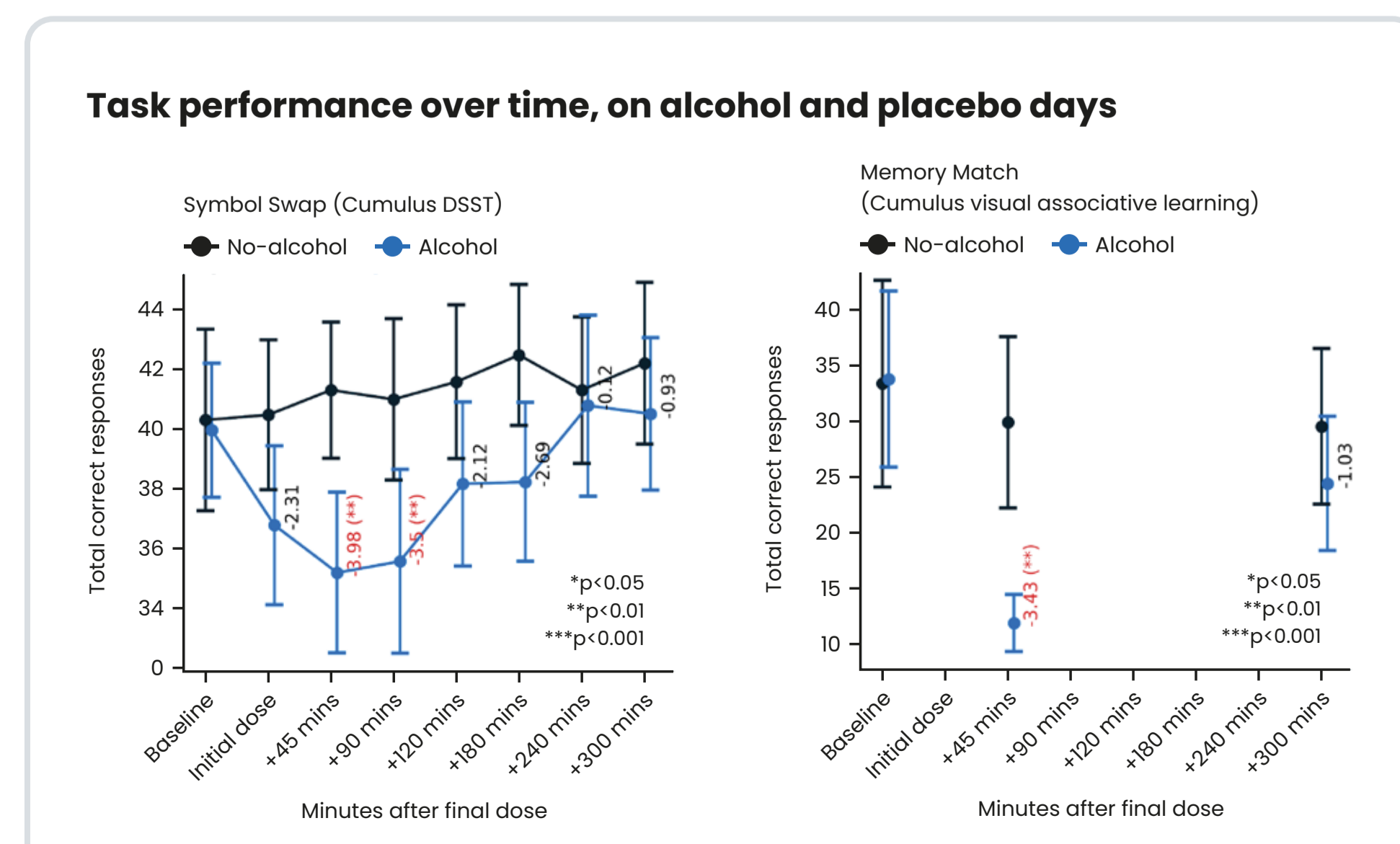
Alcohol challenge pre-validation study (in-lab technical validation)

- N = 30 healthy younger adult participants (mean 23yrs) tested twice, in a blinded crossover design.
- Very high-frequency measurement of memory and executive function to detect change over time.



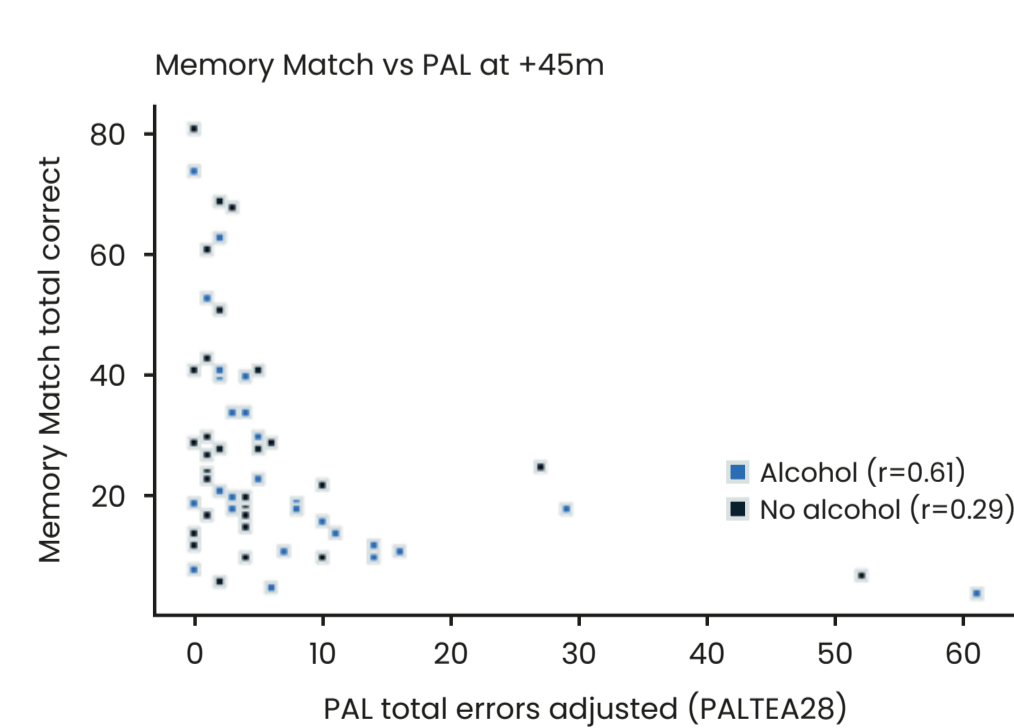
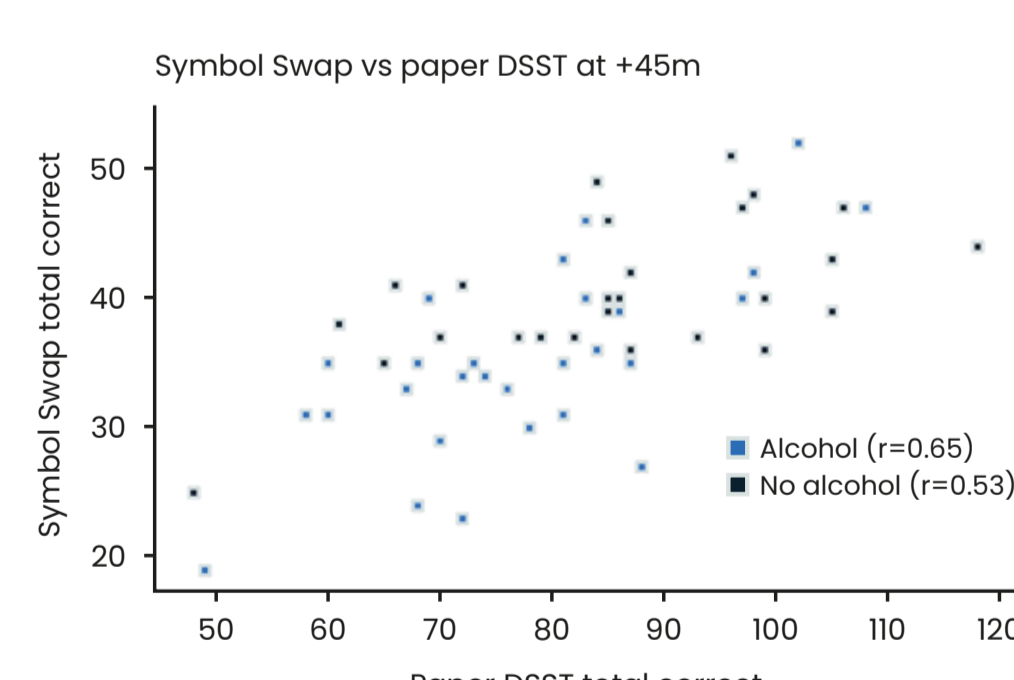
Are the tasks sensitive to subtle impairment due to alcohol?

We used a linear mixed model with fixed effects of Age, Sex and Day (i.e., chronological session order – to test for longer term practice effects) and a random effect of Participant. Performance plots above show t values for significant effects of alcohol by timepoint (p values Holm-Bonferroni corrected). Note that due to length, Memory Match was performed only three times during the session. Significant effects of alcohol were observed around peak intoxication.



Does alcohol-induced impairment correlate across Cumulus and benchmark measures?

Spearman correlations are taken at +45m post-dose, separately for the alcohol and no-alcohol sessions, to obtain meaningful spread in performance. Symbol Swap is correlated with the paper DSST, and Memory Match with CANTAB PAL (PALTEA28).

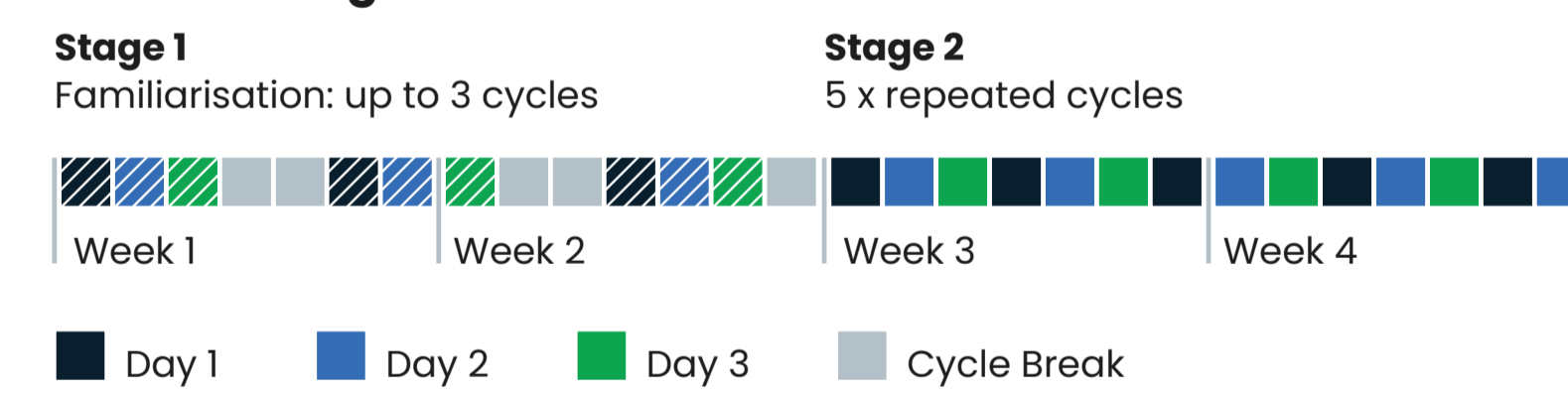


Clinical validation: Sensitivity to AD-related cognitive impairment

At-home feasibility study: AD dementia and matched healthy controls

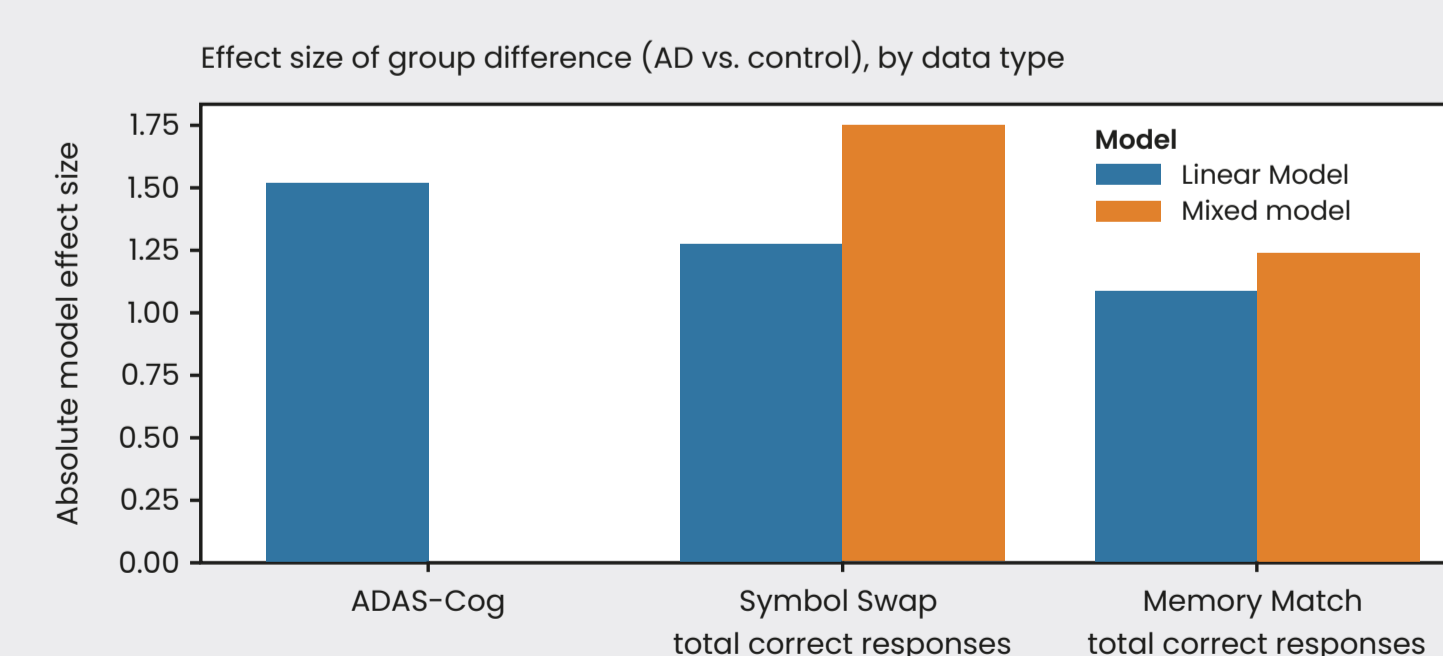
- N = 59 mild dementia patients (ADAS-Cog 25.1) and N = 60 age-matched controls (ADAS-Cog 8.9).
- Analysis focuses on the initial "burst measurement" phase, 2 weeks out of a 1-year at-home study.

Protocol diagram



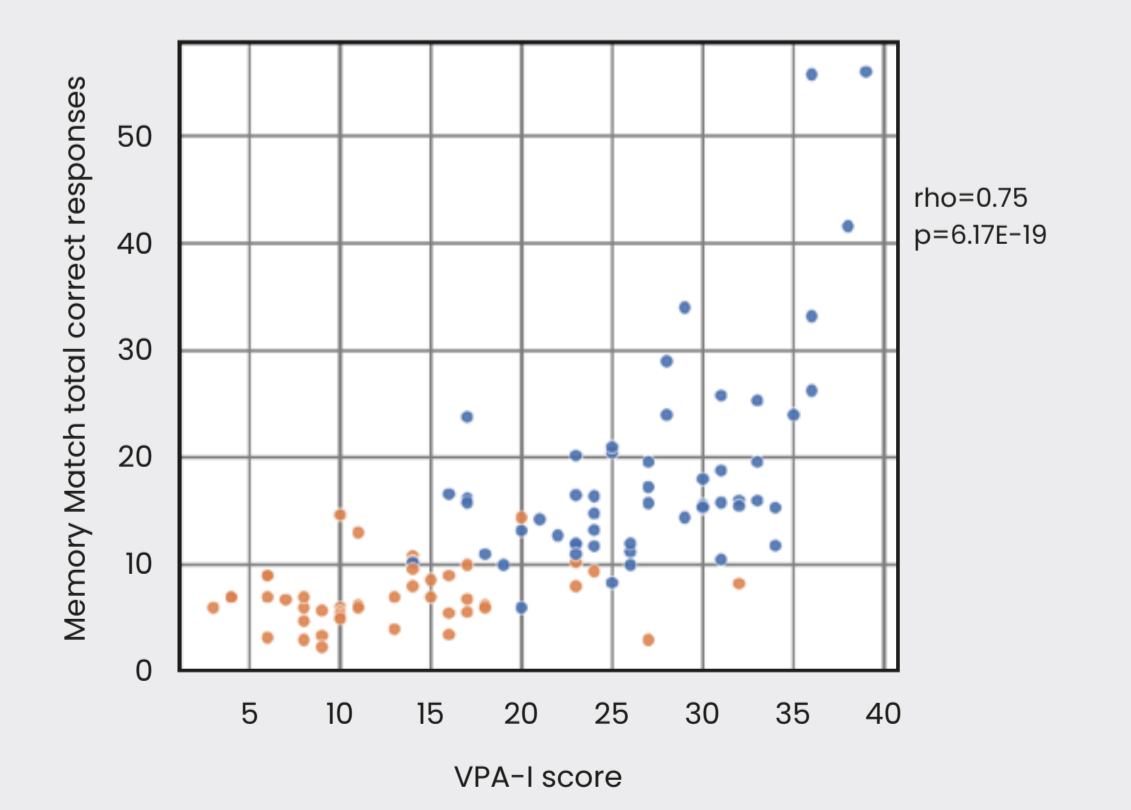
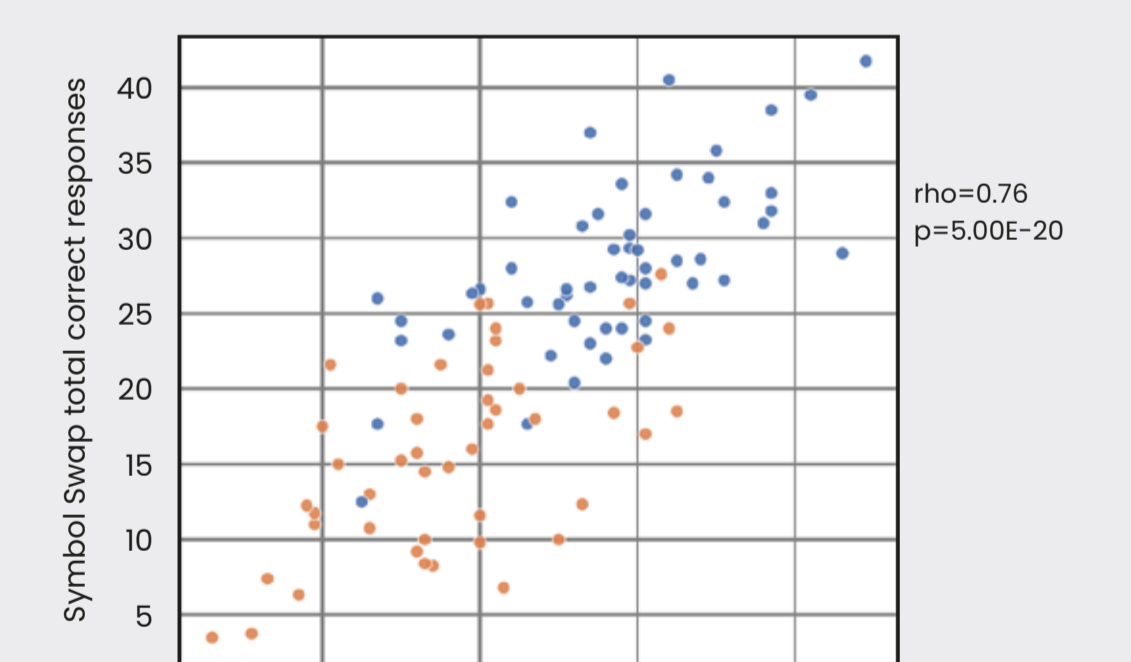
Can tasks differentiate AD from controls as well as ADAS-Cog?

Group effect size of selected Cumulus variables (from a 2m and ~10m minute digital task, self-administered at home) and the ADAS-Cog 13 (45m clinician-administered battery). Using a simple linear model, the average of Cumulus results in a lower effect size than that obtained from ADAS-Cog, but with mixed models, we exploit within-user variability to obtain a greater effect size.



Does performance on Cumulus tasks correlate with benchmark measures?

Strong correlations were observed between Cumulus tasks and paper-based benchmarks (DSST and Verbal Paired Associates I).



Conclusion

- Engagement with patients and their representatives via Cumulus user panels produces short, repeatable tasks that patients are willing and able to use at home.
- The novel digital cognitive tests can sensitively measure short term changes in dementia-relevant cognitive functions, over the timescale of acute alcohol intoxication and return to sobriety.
- "Burst measurement" in the context of clinical trials can boost the sensitivity of 2 minute long, home administered digital measures of AD-related cognitive impairment beyond that of gold-standard clinician administered tools.
- Both new tasks correlate strongly with existing paper and digital tools that purport to measure the same cognitive functions, in the context of intoxication, aging and dementia.



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References

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