

Validating a novel digital cognitive platform: sensitivity to change following an alcohol challenge

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Cumulus Real-World Neurophysiology and Cognitive Testing Platform

Developed in collaboration with leading pharma companies (below) 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; audit ready including FDA 510(k), UKCA, HIPAA, GDPR, ISO13485.

Designed for and with patients and clinicians.

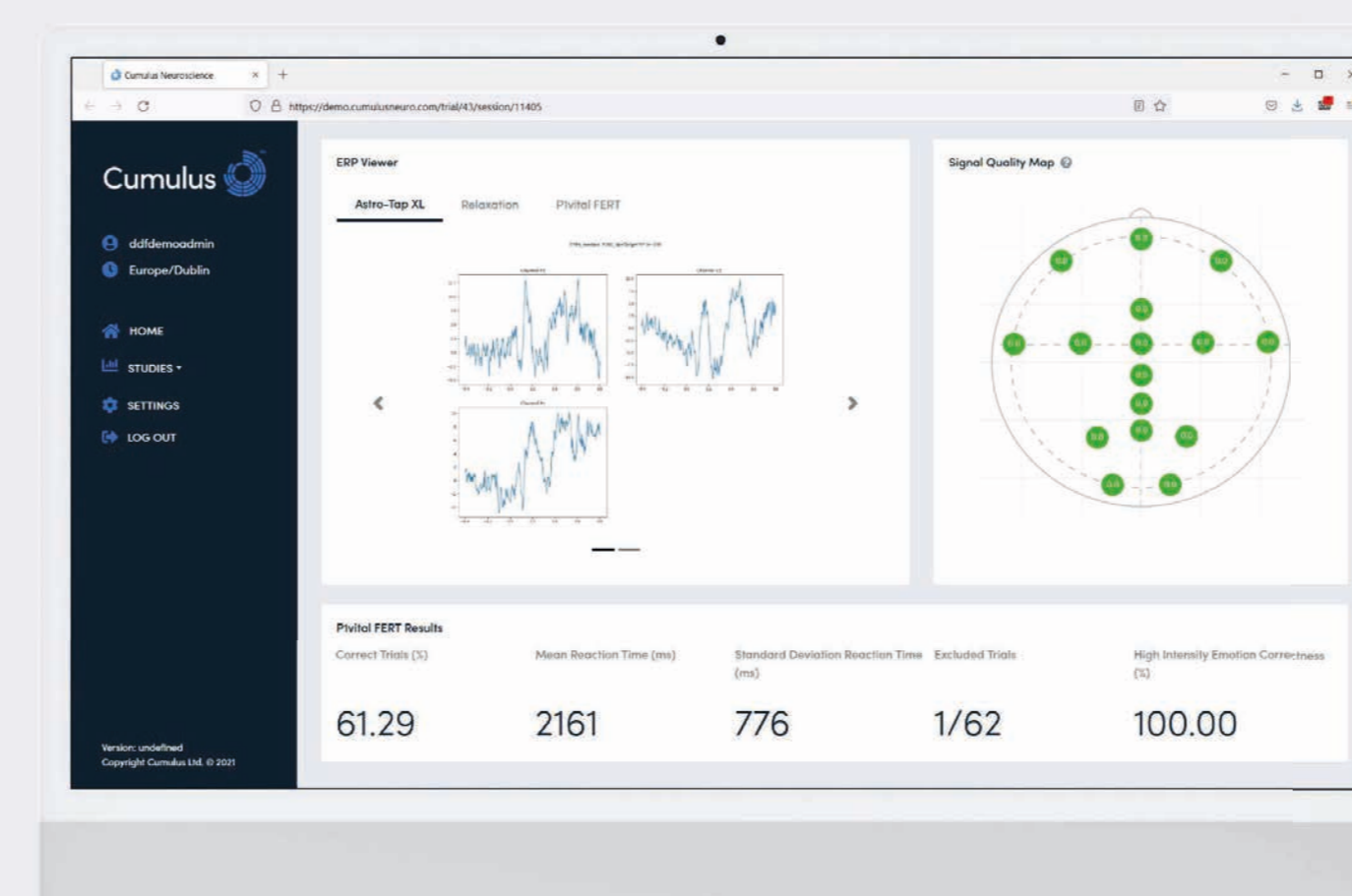
Secure automatic upload and QC.

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

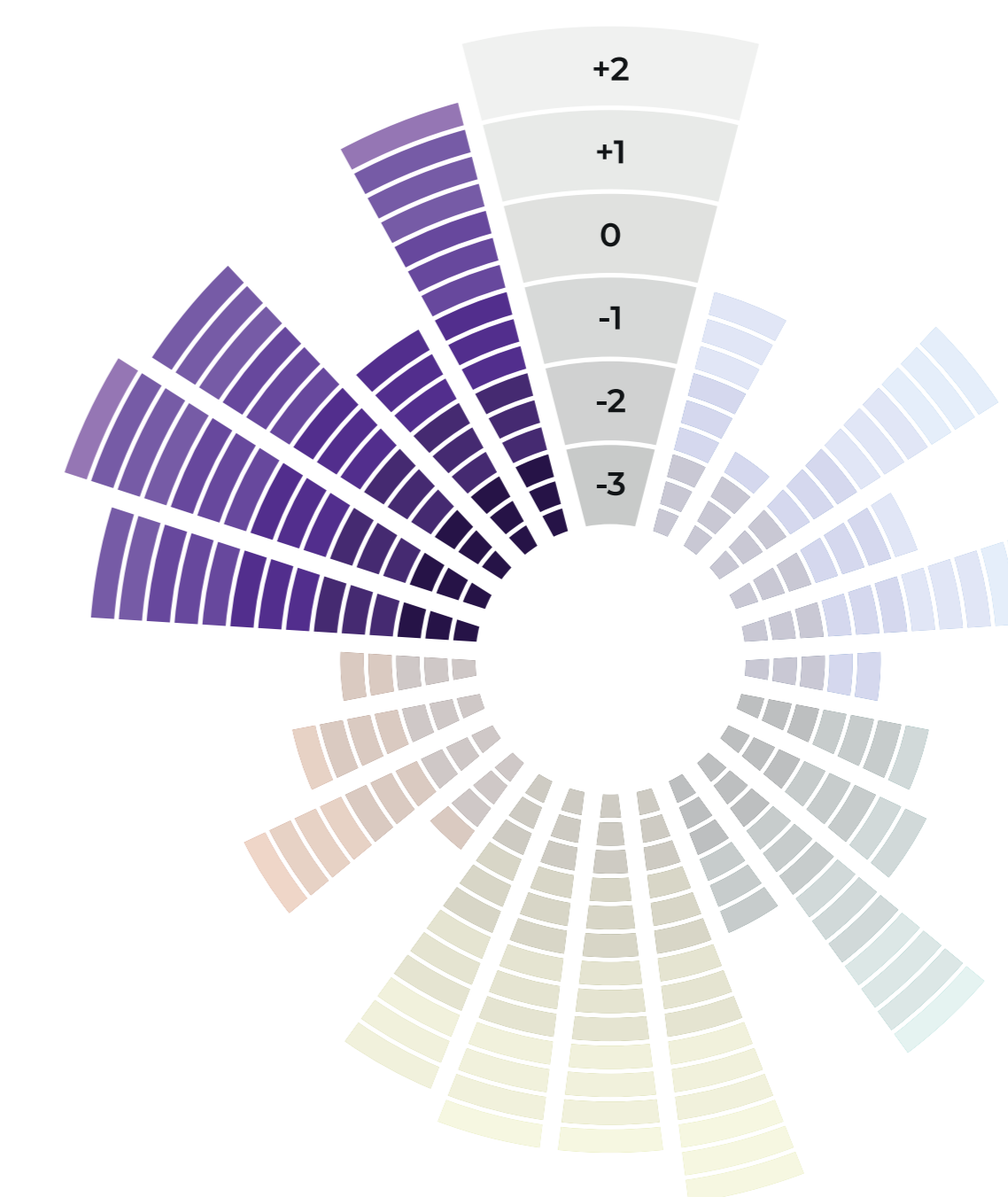


Cumulus cognitive tests are designed to be highly repeatable, with large banks of non-repeating stimuli.

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



This study focuses on novel tasks recently added to the Cognition domain of the platform.



- Cognition**
Episodic memory, executive function, working memory
- EEG**
Neuronal integrity, network connectivity
- Sleep**
Sleep quality metrics, sleep staging
- Mood**
Emotional bias, atypical mood
- Language**
Vocabulary, language, organisation, prosody



Introduction

- Detecting cognitive change over time is a critical outcome measure for the success/failure of compounds that target Alzheimer's Disease (AD)
- Current gold-standard tools (ADAS-Cog, CDR-SB, MoCA, etc.) are very insensitive in early disease, and non-repeatable
- Very long and large-N clinical trials are required to overcome measurement noise and practice effects on existing tools [1]
- Digital cognitive biomarkers hold promise: "burst" testing at critical timepoints can potentially reduce within-subject noise [2]
- Automated administration and scoring improves reliability
- Many such digital cognitive testing tools exist, but few have been validated with respect to the ability to detect change over time (i.e., due to an intervention) [3]

Cognitive Test Battery

Cumulus developed 4 new repeatable tasks

Tasks targeted four cognitive functions affected early in the AD continuum (visuals above):

- Double-Take, an N-back working memory test
- Memory Match, a paired episodic memory test
- Rapid Response, a simple reaction time test
- Symbol Swap, a digit-symbol substitution task (DSST)

Research Questions

Q1: Can the novel tests detect the effect of a pharmacological intervention which we expect to impact cognition – and the 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.

Q2: How strong are practice effects?

Each test is administered several times in relatively quick succession, over the course of intoxication and return to sobriety.

We also administer three practice sessions of every task before the first testing day.

Methods & Results

- N = 30 healthy younger adult participants (mean 23yrs)
- Placebo (orange juice with vodka mist on the top) vs. alcohol (vodka with orange juice mixer) counterbalanced 2+ weeks apart
- Top-up dose was required on 73% of alcohol sessions due to systematic overestimates from BAC calculator used

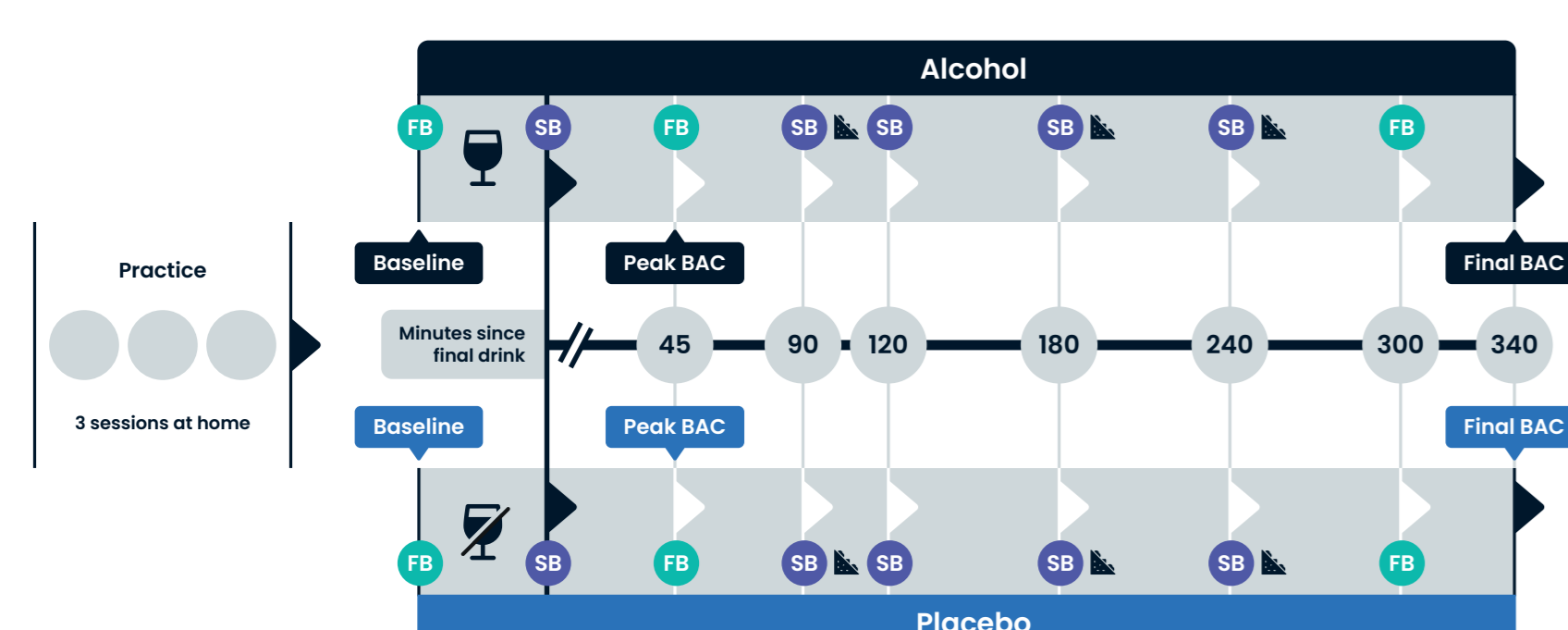
Short battery administered 8x:

- Rapid Response (simple reaction time), Symbol Swap (DSST)

Full battery administered 3x: at baseline, +45min (peak BAC), and +300min

- Memory Match (paired episodic memory), Double Take (N-back), Rapid Response (simple reaction time), Symbol Swap (DSST)

Study protocol

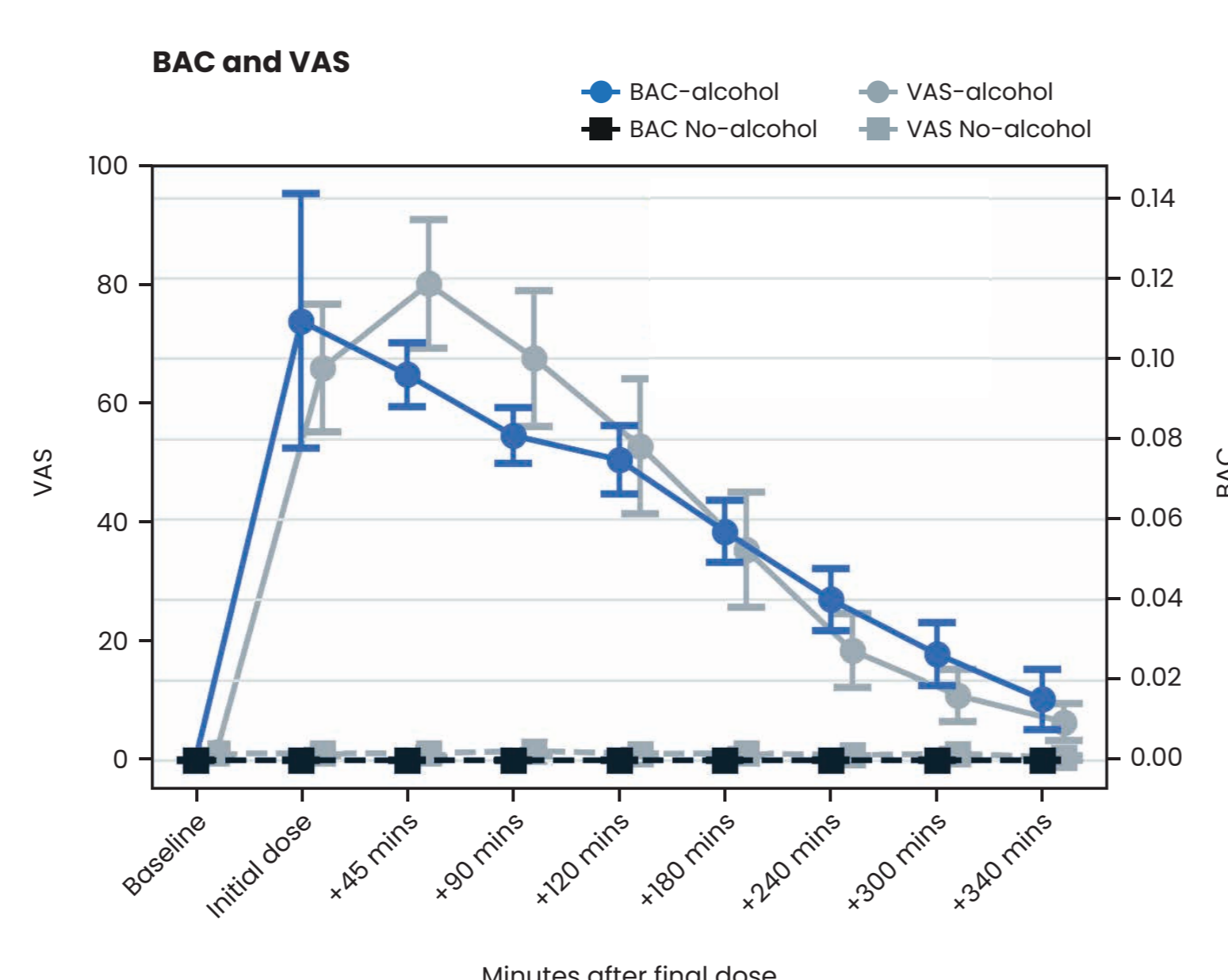


SB Short battery FB Full battery

BAC = Blood alcohol concentration % assessed by breathalyser

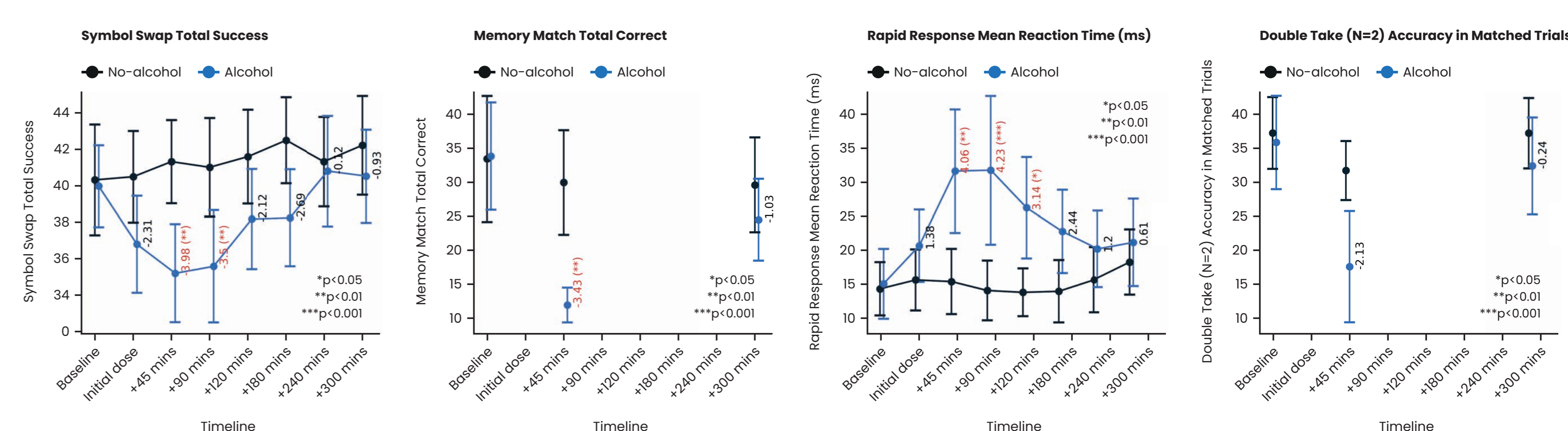
Q1: Can the novel tests detect the effect of a pharmacological intervention which we expect to impact cognition – and the return to normal?

Perceived and measured intoxication



BAC% measures confirm that the target dose was reached, on average. Note that the BAC% measurement after the initial dose is invalid due to proximity to alcohol ingestion.

Task performance over time, on alcohol and placebo days



Modelling the effect of alcohol on performance: 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). On Double-Take, the accuracy measure on "match" trials at 2-back difficulty was not significantly affected by alcohol, though overall accuracy at 2-back was (t = -2.947; p = 0.026).

Q2: How strong are practice effects?

Three sessions of every task performed at home:

Assessed using Wilcoxon signed-rank test between each sequential session.

- For Symbol Swap (DSST), there was a significant improvement between practice 1 and practice 2
- No other practice effects were observed during this phase
- The linear mixed model used on testing day data detected an effect of Day (i.e., a long term practice effect) on Symbol Swap (DSST)

Conclusions

- Subtle changes in cognition can be difficult to measure in dementia clinical trials, using existing tools
- The novel digital cognitive tests can sensitively measure change in dementia-relevant cognitive functions over the timescale of acute alcohol intoxication and return to sobriety
- Numerous repetition of tests is possible with minimal practice effects
- This approach can be scaled up to support clinical trials, with "burst measurement" used to reduce within-subject error and trials size
- Double Take (N-back task) may require additional trials to achieve sensitivity to change

References

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3. Falletti, M. G., Maruff, P., Collie, A., Darby, D. G., & McStephen, M. (2003). Qualitative similarities in cognitive impairment associated with 24 h of sustained wakefulness and a blood alcohol concentration of 0.05%. *Journal of Sleep Research*, 12(4), 265-274. <https://doi.org/10.1111/j.1365-2869.2003.00363.x>



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