Novel plasma biomarkers track cognitive performance using digital testing

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- Acetylcholinesterase (ACHE) levels were the best predictors of performance at digital testing.
- Novel markers such as PRDX6, IL-6, and VEGFD had a mild protective effect on cognition.
- Measures of long-term memory were the best predictors of ACHE and pTau217 levels.

INTRODUCTION

Plasma biomarkers can identify the presence of Alzheimer's disease (AD) in clinical populations in a rapid and cost-effective way. However, measuring cognition remains essential. Digital tests can detect early signs of cognitive impairment at scale. At present, studies looking at the relationship between plasma biomarkers and performance at digital testing have looked only at a small array of biomarkers (e.g. pTau217, GFAP, NEFL).

391 participants (subjective cognitive decline (31), mild cognitive impairment (28), AD dementia (88), Lewy body disease (18), Corticobasal syndrome (9), Frontotemporal dementia (17) and age-matched controls (201)) were recruited. They were tested on a visual short-term memory task (Oxford Memory Test (OMT)), a fully remote online cognitive assessment tool part of Oxford Cognitive Testing Portal (OCTAL: https://octalportal.com), (Figure 1).

METHODS

Three key metrics were computed: Accuracy (proportion of correctly identified items), Reaction Times and Localisation Error (distance between the original item and the response location).

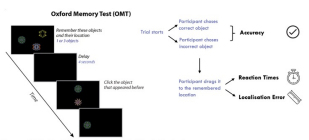


Figure 1 | Oxford Memory Test (OMT) task design

From the OCTAL platform the **Oxford Memory Test** was used in the full sample. Participants were presented with either 1 or 3 fractals randomly distributed on the screen. After a 4 second delay two fractals appeared at the centre of the screen, one of which had appeared in the memory array whereas the other one was a distractor. Firstly, they needed to identify the object they had seen previously and then drag it back to its original location. Metrics extracted from this task included: **Accuracy** (proportion of correctly identified items), **Reaction Times** (time to drag the item to its remembered location) and **Localization Error** (distance between the original item and participants' response location).

124 plasma biomarkers were measured using the Alamar platform. A subset of patient (218) completed a wider digital battery including measures of long-term memory, executive functions, visuospatial abilities and processing speed. Linear regression with age and gender as covariates was used to predict cognitive test performance and biomarkers' levels.

RESULTS

Plasma Acetylcholinesterase (ACHE) levels were the best predictors of performance at digital testing across the three short-term memory metrics studied (Figure 2).

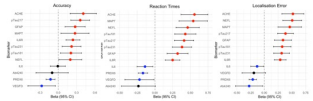


Figure 2 | Performance of key plasma biomarkers in predicting cognitive impairment at digital testing

Plasma Acetylcholinesterase (ACHE) levels were the best predictors of performance at digital testing across the three different metrics studied (Accuracy, Reaction Times, Localisation Error). For visualisation purposes accuracy represents the inverse of the proportion between correctly identified/incorrectly identified items. Positive associations are shown in red, negative in blue, non-statistically significant associations in black.

Previously described markers (e.g. pTau217, NEFL, GFAP, MAPT, pTau181, pTau231, and IL-6R) were also associated with worse performance. Novel markers such as PRDX6, IL-6, and VEGFD had a mild protective effect on cognition.

Measures of long-term memory were the best predictors of ACHE and pTau217 levels (Figure 3, panel a).

RESULTS

ACHE levels were significantly predicted by all cognitive domains (panel a), were increased in AD dementia patients compared to controls, and particularly in patients who were on Acetylcholinesterase inhibitors, unlike pTau217 (panel b).

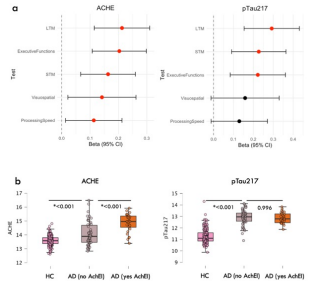


Figure 3 | Comparison between ACHE and pTau217 levels' prediction by cognitive domains, and effects of medications

Panel a: Long-term memory measures were the best predictors of ACHE and pTau217 levels. ACHE levels were predicted by all cognitive domains, unlike pTau217. For visualisation purposes all the domains have been set as higher values corresponding to worse performance. Positive associations are shown in red, non-statistically significant associations in black. A description of the tasks is available at https://octalportal.com. LTM = long-term memory, calculated from the delayed recall measure of by the Object-in-Scene Task; STM = short-term memory, corresponding to Accuracy measure of the OMT task; Visuospatial = visuospatial abilities measured by a digitized version of the Rey-Osterrieth Complex Figure Task; Processing Speed = reaction times of the Digit Symbol Substitution Test. Panel b: ACHE levels were increased in AD patients compared to controls, and particularly in patients who were on Acetylcholinesterase inhibitors (AchEI), unlike pTau217.

CONCLUSIONS

Studying a wider array of plasma biomarkers is beneficial for predicting cognitive performance.

ACHE levels seem promising in measuring cognitive outcomes at digital testing.

Further studies should unravel the best combination of plasma and digital biomarkers in patient stratification.

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