The Challenge of Detecting Prodromal Alzheimer's Disease for Clinical Trials: Enriching Recruitment Through Identification of Episodic Memory Deficits at Pre-Screening

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Background

- Alzheimer's disease (AD) trials require participants with a specific biomarker and cognitive profile, targeting particular disease severity (e.g. prodromal vs MCI vs AD).
- Finding participants for clinical trials in the 'pre-clinical' or 'prodromal' stage of Alzheimer's disease prior to the onset of cognitive and functional decline can be challenging, time-consuming and expensive.
- Episodic memory tasks such as CANTAB Paired Associates Learning (PAL), are associated with AD biomarkers, hippocampal and temporal-frontal network function (de Rover 2011, Nathan 2017) and may therefore be useful for pre-screening.
- Here we assess the utility of PAL to:

A. enrich samples for amyloid positive participants, and
B. identify deficits in other commonly used cognitive tasks such as CERAD learning and delayed recall.

Methods

- Data were evaluated from EDAR, a Europe – wide prospective longitudinal study assessing the potential of biomarkers including cognitive assessments, in the early diagnosis of Alzheimer's disease.
- Participants in the EDAR study comprise a mixed population ranging from normal cognition through MCI to AD and other dementia.
- Estimates of biomarker enrichment were based on the sensitivity and specificity of the CANTAB Paired Associates Learning Task (PAL) and the age specific probability of Amyloid positivity (Aβ+) in the general population (Jansen, 2015).
- The ability of PAL to detect a deficit in the CERAD was based on logistic regression adjusted by age and gender. A one standard deviation deficit on the CERAD list learning task was calculated using age adjusted standardised norms (Morris, 1989).

Results

- The analysis sample included n=211 participants (Mean age 68.4, SD 9.3) who completed CANTAB and had available biomarker data.
- Participants were divided into Amyloid + (Aβ+) n=169, and Amyloid - (Aβ-) n=42 based on CSF Aβ42 levels (500 pg/ml) assayed using Luminex.

A.Enrichment for Amyloid Positivity

- Figure 1 illustrates the changes in sensitivity and specificity obtained at various thresholds for PAL (dashed lines A-G).
- The figure indicates the proportion correctly classified (true positives (TP), true negatives (TN)) together with misclassifications (false positives (FP) and false negatives (FN)) at each threshold of PAL.
- In this instance, false negatives equate to Aβ+ participants who by not exceeding the number of errors for the PAL cut-off would not be further screened.
- With increasing impairment on PAL, the number of participants required for screening to identify Aβ+ is reduced. The percentage reduction is dependent upon the balance between sensitivity and specificity, together with the pre-test probability. (Figures 2-3)

B.Enrichment for List Learning Tasks

- The correlation between PAL and the CERAD list learning task was -.65 and -.69 for the delayed recall task.
- Performance on PAL was highly specific for identifying a deficit in the CERAD, with an AUC of .89.
- PAL predicted a deficit in CERAD list learning (-1 SD) worse than age adjusted norms with an accuracy of 86% (Figure 4).

Conclusions

- Pre-screening on episodic memory can enrich samples for Aβ+ subjects, and identify those likely to show deficits in other cognitive tasks.
- Scoring algorithms can be tailored according to trial requirements and the protocol specific patient population.
- The CANTAB web-based platform provides a validated and highly sensitive cognitive assessment for pre-screening that can be administered on a home computer and can help reduce the rate of in-clinic screen failures (Cormack, 2016).

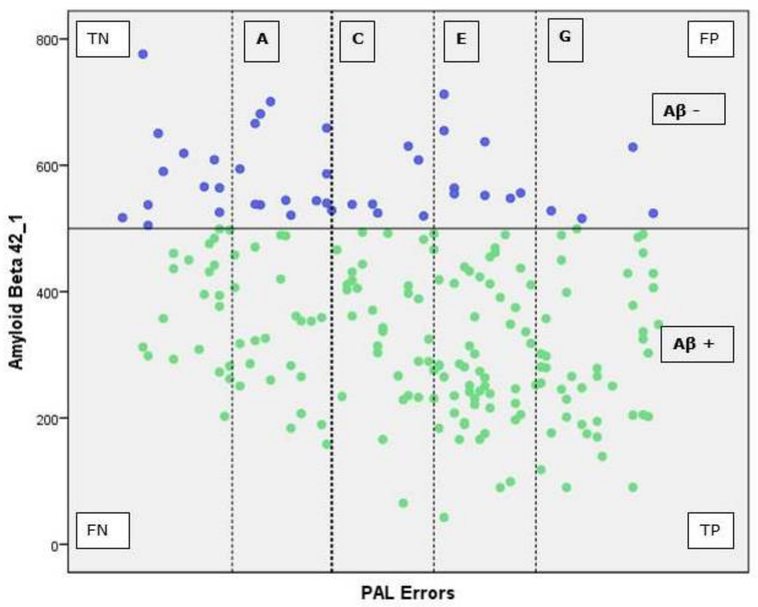


Figure 1 - Relationship between AB_42 (y axis) and CANTAB PAL (x axis). A-G relate to thresholds for PAL with increasing impairment from left to right. TN=True Negative, FN=False Negative, FP=False Positive, TP=True Positive.

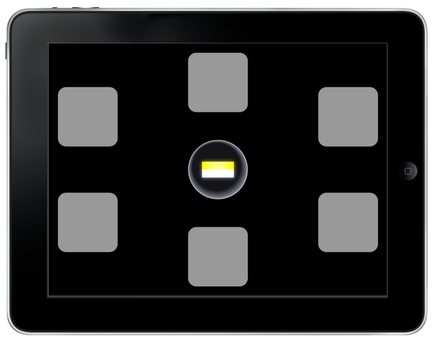


Illustration (left)
Visual episodic memory assessed using the CANTAB Paired Associates Learning (PAL) task

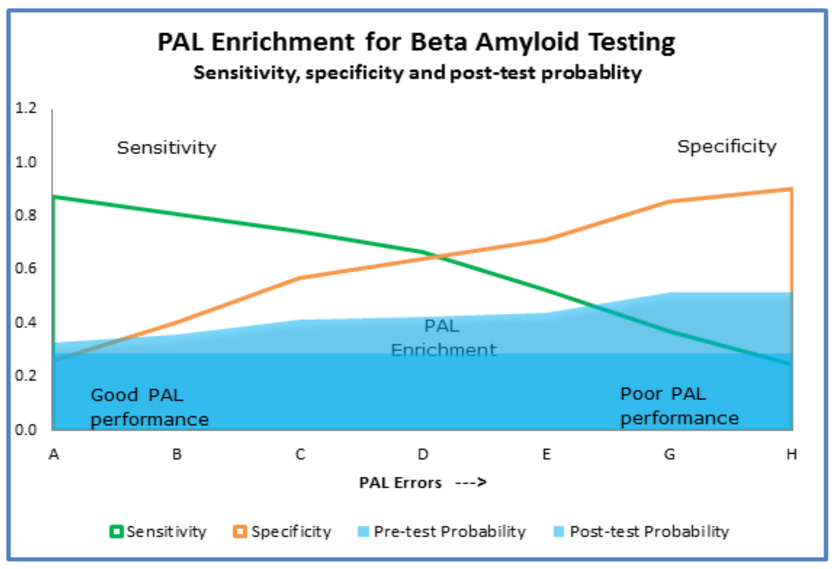


Figure 2 – Sample Enrichment by PAL . Post –test probability (i.e. enrichment) is calculated from the test sensitivity and specificity together with the pre-test probability (i.e. general population prevalence).

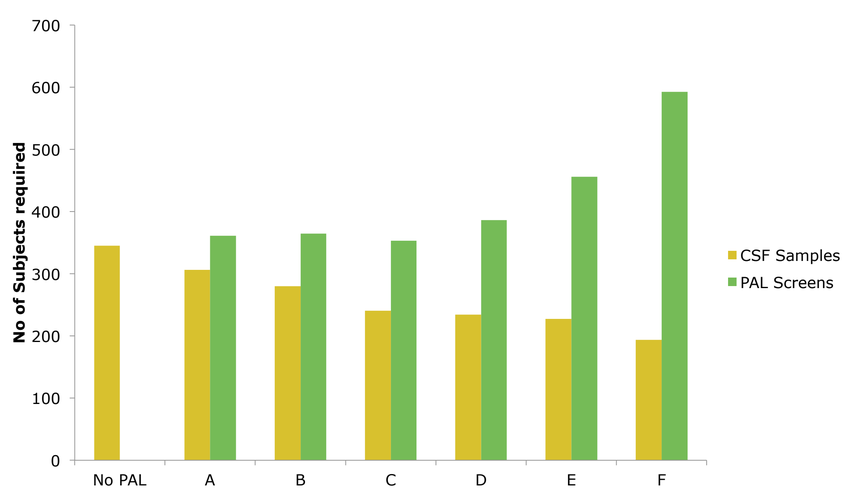


Figure 3 – Illustration of potential reduction in CSF samples required with increasing impairment on PAL. Based on pre-test probability of 29% (Jansen 2015) 345 subjects would be required to obtain 100 positive screens.

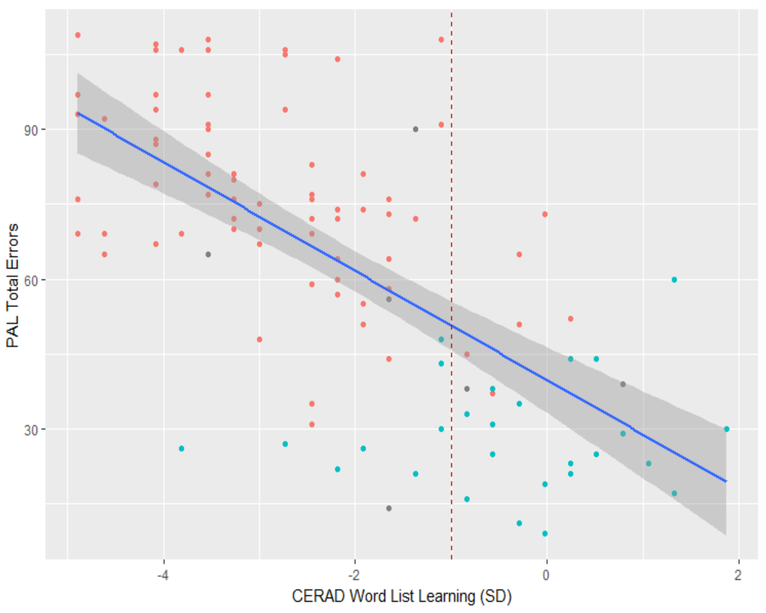
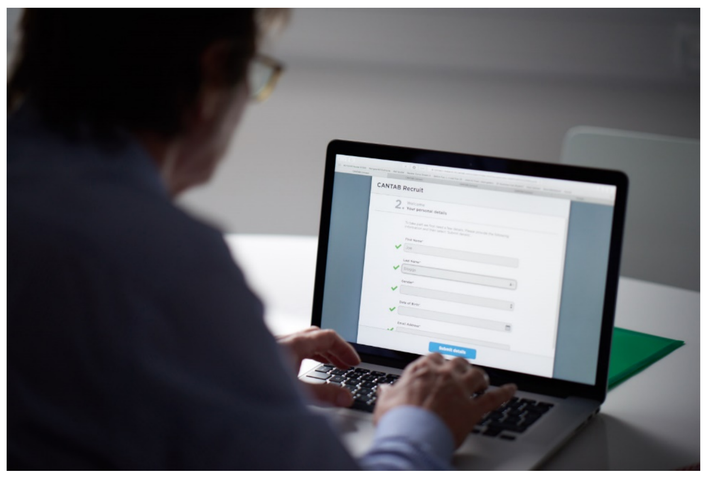


Figure 4 - Graph shows the relationship between performance on PAL (y axis) and CERAD list learning (x axis). The vertical line indicates the 1SD cut-off . Coloured dots=predicted group membership logistic regression (red =predicted deficit, blue no deficit) Overall accuracy = 86% Correct, 14% Misclassifications.



Above - Completing CANTAB's Web-based software

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