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 ‘clinical’ 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 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 are 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

- PAL results were compared with CSF samples assayed using the Luminex platform.

- 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.

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).

References


Figure 4 - Graph shows the relationship between performance on PAL and CERAD list learning (SD). The curve reflects the rate of PAL cut-off at which the proportion of PAL positives (FP) equates to the proportion of Aβ+ (blue). The optimal threshold is indicated (blue dot) at which PAL positivity equates to Aβ+ positivity. The analysis sample included n=211 participants (Mean age 68.4, SD 9.3) who completed CANTAB and had available biomarker data.