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:
- Differentiate patients from controls
- Enrich samples for amyloid positive participants, and
- Identify deficits in other commonly used cognitive tasks such as CERAD learning and delayed recall.

Methods

Data are synthesised from:

- Meta-analysis of published case-control studies comparing performance on PAL of patients with MCI from controls without objective cognitive impairment.

- Systematic qualitative review of published studies reporting the association between CANTAB PAL and CSF biomarkers.

- EDAR: A Europe – wide prospective longitudinal study assessing the potential of biomarkers including cognitive assessments, in the early diagnosis of Alzheimer’s disease. Participants comprise a mixed population ranging from normal cognition through MCI to AD and other dementia.

- Pharmaco: a European multicentre study (E-ADNI; work package 5) of participants aged 50-84 with amnestic MCI (subjective and objective memory complaint, MMSE 24-30). Data are presented from 145 individuals with clinical evaluation and cognitive testing with CANTAB, high resolution 3T MRI with MPRAGE and lumbar punctures for the assessment of cerebrospinal fluid (CSF) levels of Ab42, tau and p-tau. Individuals were divided into Amyloid+ (CSF-POS) and Amyloid− (CSF-NEG) based on CSF Ab42 levels (CSF-POS: >550 pg/ml; CSF-NEG: <550 pg/ml).

Results

Sensitivity to MCI

- Eight studies compared patients with a-MCI, who have a clinically isolated memory deficit, to controls. There was significant heterogeneity in estimates of effect size, but the overall level of impairment was d=1.1, indicating a substantial effect size in these patients (Figure 2).

- The study of Levy-Gigi et al. (2011) had the largest effect size. Removal of this study reduced the pooled effect size to 0.93.

- Across four of multimodal MCI studies of the pooled effect size was d=1.70. Exclusion of the study by Ahmed et al., (2008), significantly reduced the heterogeneity of the effect sizes, but resulted in a reduction of the pooled effect size to d=1.27.

Enrichment for verbal memory tests

- The correlation between PAL (total errors adjusted) and the selected cognitive measures ranged between −0.85 (RBANS DMI) to −0.61 (RBANS list learning).

- PAL was highly predictive of a deficit in the cognitive measures, with classification accuracy of 88.7 for RBANS DMI.

- Participants with a predicted deficit on RBANS (DMI) also showed a lower average MMSE score (24.8 vs 28.6) and a higher CDR-SOB score (1.85 vs 0.48).

- The correlation between PAL and the CERAD list learning task was −0.65 and −0.69 for the delayed recall task.

- Performance on PAL was highly specific for identifying a deficit in the CERAD, with an AUC of .89.

Enrichment for biomarkers

- Effect sizes for correlations between CANTAB PAL and biomarkers were summarised across three studies. There was significant heterogeneity, with mixed samples (EDAR) of dementia MCI and controls (Barnett et al., 2011) showing the lowest effect sizes for FDR- and T-Pal (Figure 4A).

- Effect sizes for between group differences between amyloid positive and negative patients were published by three studies, with a mean effect size of 0.55 (Figure 4B).

- CANTAB PAL showed good predictive properties for amyloid positivity (AUC=0.64) in a group pre-screened for memory impairment (Doherty et al., 2016, Figure 4C).

Conclusions

PAL is a brief, computerised task which can be used to pre-screen subjects and identify those with episodic memory deficits early in the recruitment process, to enrich samples for biomarker positive subjects. This task can be used at home as a web-based assessment as well as in-clinic, potentially reducing trial costs, screen failure rates, site and patient burden, by targeting subjects with a high probability of meeting screening criteria.