Enriching Participant Eligibility for Clinical Trials through Pre-Screening for Cognitive Deficit.

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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:
  - 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 quantitative 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.
- Pharmacog: 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).

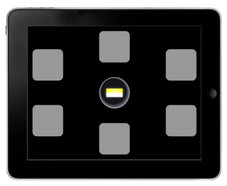

Figure 1
Visual episodic memory assessed using the CANTAB Paired Associates Learning (PAL) task

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 multidomain 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 -.859 (RBANS DMI) to -.611 (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 -.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.

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 P-tau and T-Tau (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).

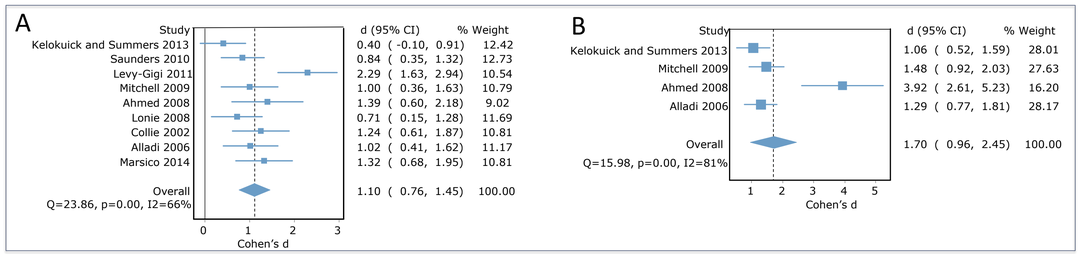

Figure 2: Forest plots showing the magnitude of case-control differences from 9 studies reporting means and standard deviations on PAL for aMCI (A) and multi-domain MCI (B) patients.

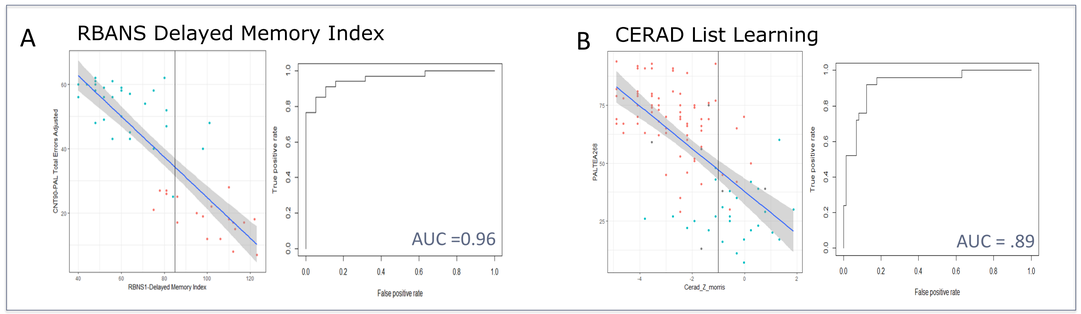

Figure 3: Scatter plots shows the relationship between performance on CANTAB PAL (y axis) and RBANS delayed memory index (A) or CERAD list learning (B) (Abbott et al 2017a,b). The vertical line indicates a 1 SD deficit in both tasks. Colours represent the predicted group membership based on logistic regression analysis. ROC curves show the overall sensitivity of PAL in predicting memory deficit derived from logistic regression. The overall AUCs are 0.96 for RBANS and and 0.89 for CERAD list learning.

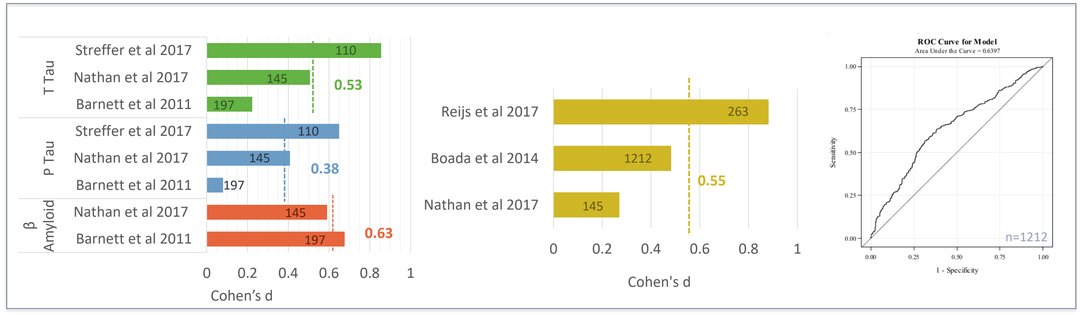

Figure 4: A Correlations between CANTAB PAL and CSF biomarkers of tau and beta amyloid from three studies, converted to Cohen's d estimates of effect size. B shows effect size differences between amyloid positive and negative subjects. The ROC curve for discriminating AB+ from AB- is taken from Doherty et al., (2016).

Conclusions

PAL is a brief, computerised test 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

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The authors report no conflict of interest for this work.

References

- Abbott et al (2017a) Pre-screening for episodic memory Deficits can enrich for eligible subjects in early AD clinical trials. Alzheimer's and Dementia 13(7):P1319-P1320
- Abbott et al (2017b) The challenge of detecting prodromal Alzheimer's disease for clinical trials: enriching recruitment through identification of episodic memory deficits at pre-screening. Presented at International Conference on Alzheimer's & Parkinson's Diseases in Vienna, Austria.
- Ahmed et al (2008) Predicting rapid clinical progression in amnestic mild cognitive impairment. Dementia and Geriatric Cognitive Disorders. 25: 170-177
- Alladi et al (2006) Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. Psychological Medicine 36(4):507-15
- Barnett et al (2011) Cognitive and CSF biomarkers in older adults, MCI, and dementia. Alzheimer's and Dementia 7(4)
- Boada et al. (2014) Using CSF Aβ42 for patient identification for a Phase 3 study of gantenerumab in patients with prodromal AD. J Prev Alz Dis. 1(3):214-296
- Collie et al (2002) Selectively Impaired Associative Learning in Older People with Cognitive Decline. Journal of Cognitive Neuroscience 14(3): 1–9
- Doherty et al (2017) The predictive utility of cognitive measures at screening for determination of CSF ABETA (1-42) status in subjects with prodromal Alzheimer's Disease: Data from the Scarlet RoAD trial. Alzheimer's & dementia: the journal of the Alzheimer's Association 12(7):P821-P822
- Kelekociuk & Summers (2014) Lowered performance in working memory and attentional sub-processes are most prominent in multi-domain amnestic mild cognitive impairment subtypes. Psychogeriatrics 14: 63–71
- Levy-Gigi et al (2011) Impaired context reversal learning, but not cue reversal learning, in patients with amnestic mild cognitive impairment. Neuropsychologia. 49: 3320-3326
- Lonie et al (2008) Clinical referral patterns and cognitive profile in mild cognitive impairment. BJPsych 192:59-64
- Marsico et al (2014) Cognitive and Functional Profiles in Mild-to-Moderate Alzheimer 's disease and Mild Cognitive Impairment Compared to Healthy Elderly. Advances in Alzheimer's Disease. 3: 168-186
- Mitchell et al (2009) Outcome in subgroups of mild cognitive impairment (MCI) is highly predictable using a simple algorithm. J Neurol 256:1500–1509
- Nathan et al (2017) Association between CSF Biomarkers, Hippocampal Volume and Cognitive Function in Patients with Amnestic Mild Cognitive Impairment (MCI). Neurobiology of ageing 53: 1-10
- Reijs et al (2017) Memory Correlates of Alzheimer's Disease Cerebrospinal Fluid Markers: A Longitudinal Cohort Study Journal of Alzheimer's Disease 60: 1119–1128
- Saunders et al (2010) Attention and working memory deficits in mild cognitive impairment. Neuropsychology. 32(4): 350-357
- Streffer et al (2017) Interaction of Tau and Amyloid Pathology is Relevant for Cognitive Changes. Moving the Amyloid Cascade Hypothesis to an Interaction Model. Presented at International Conference on Alzheimer's & Parkinson's Diseases in Vienna, Austria.

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