Accumulation of beta amyloid (Aβ) in the brain and carriage of the apolipoprotein E (APOE) ε4 allele have both been linked independently and interactively with greater neurodegeneration, cognitive decline and incipient Alzheimer’s disease (AD) (Doraiswamy et al., 2012; Mormino et al., 2014; Lim et al., 2015a,b).

However, as most studies have observed these effects over 18–20 months or more (Doraiswamy et al., 2012; Mormino et al., 2014; Lim et al., 2015a), the effect of Aβ and ε4 on cognitive decline over 12-months remains unknown.

Detection and monitoring of subtle cognitive decline over shorter time periods is critical for diagnosis of patients at risk for dementia (i.e. MCI/prodromal AD) and monitoring the therapeutic effects of symptomatic and disease modifying treatments.

In this study, we examined the effects of Aβ and APOE ε4 on rates of cognitive change assessed using the computerised cognitive battery CANTAB over 12-months in APOE ε4 carriers (i.e. Prodromal AD).

We hypothesized that Aβ+ individuals would show a greater decline in visuospatial episodic memory and this decline would be exacerbated in APOE ε4 carriers (i.e. ε4+).

Analysis was undertaken using repeated measures mixed models with maximum likelihood estimation. CANTAB task variables were the outcome measures, CSF Abeta42 and APOE ε4 were fixed factors, as was group (i.e. cognitive factor and age and years of education as covariates). The Aβ * APOE interaction was specified in an additional set of analyses which included an Aβ * APOE * time interaction.

Introduction

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Methods

Participants (aged 50–90) were recruited from the PharmaCog (European-ADN; work package 5), multicentre study (Table 1).

Inclusion criteria: 1) subjective memory complaint, 2) 150 deficit in memory (Logical memory II subscale – delayed paragraph recall), 3) MMSE between 24 and 30, 4) CDI = 0.5 (Memory box at least 0.5); 5) diagnosis of amnestic MCI.

145 individuals underwent clinical and cognitive evaluation using the CANTAB tests, high resolution 3T MRI with MPRAGE and lumbar punctures for the assessment of cerebrospinal fluid (CSF) levels of Aβ42, tau and p-tau. Individuals were divided into Amyloid+ (CSF-POS) and Amyloid- (CSF-NEG) based on CSF Aβ42 levels (CSF-POS: <550 pg/ml; CSF-NEG: >550 pg/ml).

Results

Aβ+ and APOE ε4 individuals (relative to Aβ−) showed faster decline in paired associates learning (PAL) (p=0.02, ES=0.43) over 12 months.

Aβ+ APOE ε4 individuals who were APOE ε4 carriers (Aβ+ ε4+) had a greater decline in PAL (p=0.01, ES=0.56).

No other cognitive domain including attention and executive function were affected by Aβ positivity and/or APOE ε4 carriage.

Discussion

Aβ+ individuals with MCI (compared to Aβ−) declined at a faster rate over 12-months on the CANTAB PAL task of visuospatial episodic memory (i.e. learning of an association between object and location) (Figure 1; Table 2). The difference in decline was of moderate magnitude (i.e. effect size of 0.4). These findings are consistent with previous studies (over 18 months or more) that have similarly shown greater decline (with similar magnitude) in episodic memory (using different cognitive measures) in individuals who are Aβ+ (Doraiswamy et al., 2012; Mormino et al., 2015).

Episodic memory decline was unaffected in Aβ− individuals irrespective of APOE status consistent with previous observations (Doraiswamy et al., 2012; Lim et al., 2015b; Mormino et al., 2015).

The decline in memory in Aβ+ individuals with MCI was exacerbated by the presence of the APOE ε4 allele (Figure 1; Table 2). The difference in decline was of moderate magnitude (effect size ~ 0.6) . This finding supports previous studies that have similarly shown that APOE ε4 increases Aβ related episodic memory decline and visual learning impairments (Mormino et al., 2014; Lim et al., 2015b) in pre-clinical AD (with similar magnitudes of difference).

Other cognitive domains including psychomotor speed, sustained attention, working memory and executive function were not affected Aβ positivity and/or APOE ε4 carriage consistent with previous studies (Lim et al., 2015a,b).

These findings suggest, a memory decline in Aβ+ individuals with MCI or prodromal AD can be detected as early as 12 months using sensitive computerised tests of visuospatial episodic memory. The findings in APOE ε4 are consistent with those reported in preclinical AD.

References


Table 1: Demographic and clinical characteristics of the full sample and information and study groups

Table 2. Mean slopes (ε4) and predictive (ε4+) slopes for the CANTAB task of visuospatial episodic memory (PAL) and CANTAB task of visuospatial episodic memory (PAL) in Aβ+ and Aβ− individuals over 12 months, with and without APOE ε4 carriage.