Learning in preclinical Alzheimer's disease: Repeated administration of the International Shopping List Test

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Introduction

Decline in episodic memory is a hallmark clinical feature of Alzheimer's disease (AD) that is evident in early stages of disease. High levels of amyloid-beta (Aβ+) indicates that the AD pathological process has begun, although for many, it may be up to 30 years before clinical symptoms of dementia become evident. Mild Cognitive Impairment (MCI) precedes dementia, but AD pathology is not always present in these individuals, and could be due to other pathological processes. Previous research shows that episodic memory is one of the first cognitive functions that decline during the long presymptomatic period. This study aimed to characterise the nature and magnitude of episodic memory decline, associated with Aβ+ in individuals clinically classified as CN and MCI.

Methods

Non-demented older adults (n=109) enrolled in the AIBL-ROCS sub-study underwent Aβ neuroimaging and serial cognitive assessment. The International Shopping List Test (ISLT) was administered 9 times in 18-months, with word lists varying randomly between assessments. Aβ PET neuroimaging was combined with clinical assessments to classify participants as Aβ- or Aβ+ CN and MCI.

Group differences at baseline on demographic, clinical, and neuropsychological measures were assessed via one-way ANOVAs or chi-square analyses (Table 1). Analyses were adjusted for APOE e4 carriage, age and mood variables. The prospective analysis was conducted via linear mixed modelling (LMM)

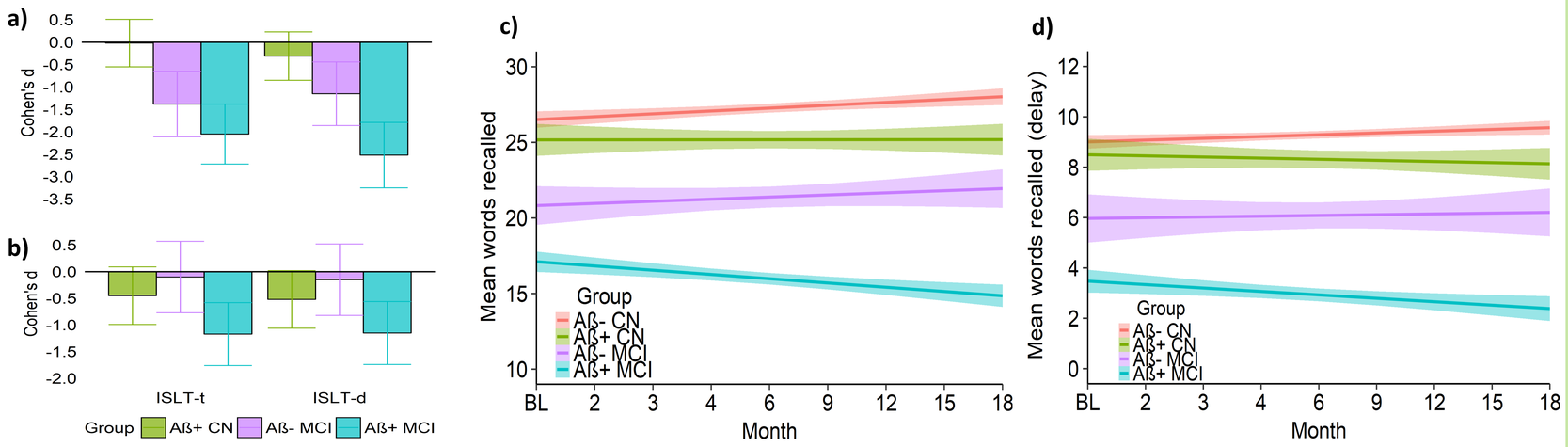
Results

Groups significantly differed at baseline on ISLT total and delayed recall (Figure 1a). The zero line represents the Aβ- CN group performance, with no difference between the CN groups at baseline, and both Aβ- and Aβ+ MCI groups performing significantly worse than Aβ- CN. Impairment was larger in magnitude for the Aβ+ MCI than the Aβ- MCI group. Significant improvement over the 18 months was evident in the Aβ- CN group on both total and delayed recall, with stable performance in the Aβ+ CN and the Aβ- MCI groups (Figure 1c and d), and significant decline in the Aβ+ MCI group. Only Aβ+ groups rates of change significantly differed compared to Aβ- CNs over time (Figure 1b), equivalent to a moderate (Aβ+ CN Cohen's $d > 0.40$) and large effect (Aβ+ MCI Cohen's $d > 1$).

Table 1: Biomarker-classified group characteristics

	Aβ- CN	Aβ+ CN	Aβ- MCI	Aβ+ MCI
N	50	25	12	22
% Female	60%	52%	42%	64%
% APOE e4	10%	24%	17%*	55%
Age	70.72 (5.81)	75.24 (9.47)*	76.17 (8.57)*	79.45 (6.13)***
Premorbid IQ	109.48 (5.02)	109.04 (7.50)	109.17 (6.35)	109.41 (5.84)
MMSE	29.44 (0.73)	28.96 (1.31)	28.25 (0.97)**	27.36 (1.59)***
CDR-SB	0 (0.5)	0 (0)	0.25 (1.5)***	0.5 (3)***
HADS-D	2.44 (2.43)	1.55 (1.34)*	3.36 (2.25)	3.95 (2.95)
HADS-A	4.38 (2.42)	3 (2.56)*	2.64 (2.16)*	4.05 (2.28)

Figure 1: a) Impairment and b) decline compared to Aβ- CN; c) total and d) delay recall scores over 18-months



Summary

Although the ISLT word lists vary randomly, performance significantly improved over time in the Aβ- CN group, with increases also observed for the Aβ- MCI group , indicating the presence of practice effects in the absence of Aβ+. Indeed, the Aβ+ groups displayed significantly different trajectories over the 18 month period. This suggests that the presence of Aβ+, regardless of clinical diagnosis, impacts cognition and reduces learning from repeated assessments. Our findings highlight that individuals with AD pathology display deficits in learning from repeated assessment, even when cognitively normal. Furthermore, once MCI is reached, the presence of Aβ+ results in significant deficits both cross-sectionally, and longitudinally. Lastly, MCI alone is not sufficient for decline in memory over time.

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