Paired associate learning deficits associated with elevated beta-amyloid in cognitively normal older adults

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Introduction

Previous studies have shown that paired associate learning (PAL), a type of episodic memory, is often impaired in early stages of Alzheimer's disease. Such tasks require that a set of associations (e.g., pattern-location) be learned over several trials, where the objective is to reduce errors at each trial. Information regarding the type of errors made is collected, allowing analysis of the specific processes underlying each error type to be examined. Currently, the sensitivity of PAL errors to impairment and decline in cognitively normal (CN) older adults with elevated levels of beta-amyloid (Aβ+) is unknown. This study examined PAL performance associated with Aβ+ in CN older adults, both within a single assessment, and over time.

Methods

Cognitively normal older adults (n=356) enrolled in the study underwent Aβ neuroimaging and serial cognitive assessment. Participants were classified based on dichotomized Aβ imaging results, resulting in 210 Aβ- CN and 146 Aβ+ CN individuals. The Continuous Paired Associate Learning (CPAL) task was administered every 18-months over a period of 54 months. Outcomes include total number of errors made across trials, as well as exploratory errors. Exploratory errors result when an incorrect location that has not been searched is selected. Lower errors equal better performance. Due to distribution bias within CPAL outcome measures values were log(10) transformed. All analyses were adjusted for age and APOE e4 carriage.

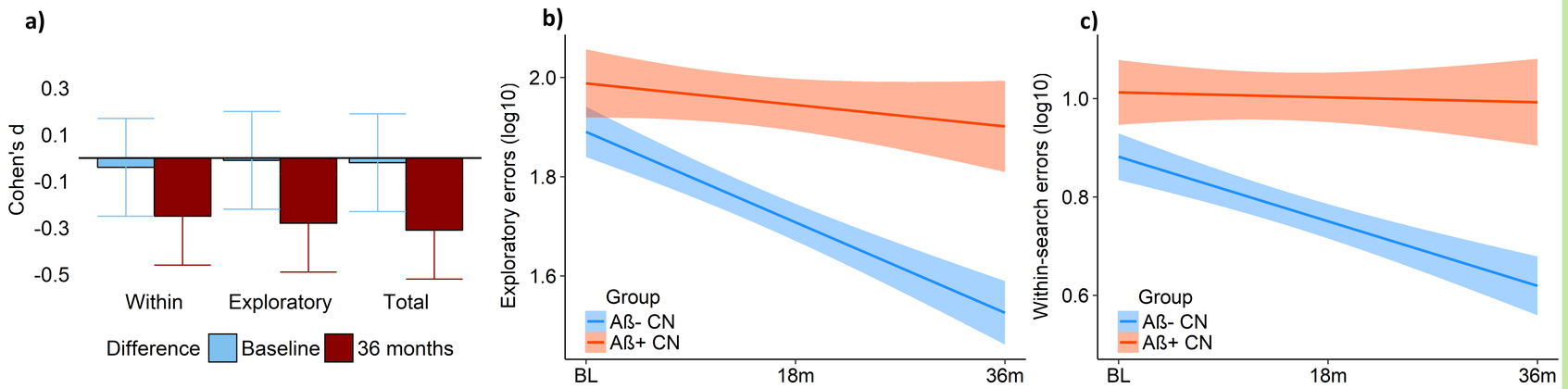
Results

Group differences at baseline on demographic, clinical, memory scores and CPAL outcomes were assessed via one-way ANOVAs (Table 1). Differences in rate of change over 36 months in CPAL outcomes were assessed via linear mixed modelling. Figure 1a displays the magnitude of the group differences at baseline and at 36 months. Negative effects equal worse performance in Aβ+ CN compared to Aβ- CNs. No group differences in verbal list learning or PAL were evident at baseline, with effects trivial in magnitude (Cohen's *d*'s < .20). Significant performance reductions in exploratory, within-search, and total errors were evident in the Aβ- CNs over 36 months (Figure 1a,b,c). Rate of change in Aβ+ CNs was significantly different, equivalent to a moderate effect (Figure 1a).

Table 1: Biomarker-classified group characteristics

	Aβ- CN	Aβ+ CN	Cohen's d [95% CI]
N	210	146	
% Female	59%	53%	
% APOE e4	15%	45%***	
Age	69.39 (5.63)	72.86 (6.23)***	
Premorbid IQ	108.77 (6.35)	108.44 (7.42)	
MMSE	29.14 (0.82)	28.58 (1.33)***	
CDR	0 – 0.5	0 – 0.5	
HADS Depression	2.65 (2.31)	2.74 (2.42)	
HADS Anxiety	4.54 (2.89)	4.34 (3.16)	
CVLT total	52.58 (12.03)	50.88 (10.03)	-0.15 [-0.36, 0.10]
CVLT Delay recall	12.13 (3.62)	11.73 (3.14)	-0.12 [-0.33, 0.10]

Figure 1: a) Magnitude of impairment and decline compared to Aβ- CN; b) exploratory and c) within-search errors



Summary

Results suggest that the CPAL error subtypes and total score are sensitive to detecting reductions in PAL over time, but not at baseline, in Aβ+ CN older adults. Moreover, Aβ- CN older adults significantly improved their performance over time, indicative of practice effects, and therefore benefit gained from repeated exposure. Importantly, this effect was lacking in Aβ+ CN older adults, suggesting that memory dysfunction associated with Aβ+ may be best understood as dysfunctional learning. Significant differences in exploratory errors lend support for this, as greater exploratory errors represent ineffective consolidation of acquired information. Further, results demonstrate that assessing change in Aβ+ related cognition over time, rather than at a single assessment, provides greater understanding of dysfunction in this early stage of disease.

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