Sensitivity of a Preclinical Alzheimer's Cognitive Composite (PACC) Based on Computerized Tests to Amyloid Load in Preclinical AD

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Introduction

It is now accepted that cognitive decline is a feature of preclinical Alzheimer's disease (AD) and that the efficacy of drug therapies designed to forestall the disease should be determined clinically by the extent to which amyloid related cognitive decline can be minimized. It is also agreed that cognitive composite scores should measure episodic memory and executive function, although there is still debate about which neuropsychological tests are most sensitive to amyloid related change. Most studies that have provided models for rates of amyloid related change in cognition have estimated effects based on the comparison of cognitively normal older adults with abnormally high amyloid (Aβ+) to those with low amyloid levels (Aβ-). Given that all individuals enrolled in clinical trials of preclinical AD will be Aβ+ a more appropriate estimate of possible treatment effects may be obtained through comparing individuals with vey high amyloid levels (Aβ++) to those with Aβ+. We therefore estimated the effect of reducing Aβ++ to Aβ+ on cognitive change over three years measured using different versions of the PACC in individuals with preclinical AD.

Methods

Sample: Data for subjects who had undergone amyloid imaging with positron emission tomography (PET) who met criteria for preclinical AD and who had undergone three years of neuropsychological assessment were drawn from individuals enrolled in the Australian Imaging Biomarkers and Lifestyle (AIBL) study. Aβ+ and Aβ++ were equivalent on all demographic variables except age where the Aβ++ was slightly older.

Neuroimaging classification: PET standardized uptake value ratio (SUVR) were calculated for each individual. Subjects with a SUVR between 1.4 and 1.9 were classified as Aβ+. Subjects with a SUVR of 1.9 or more were classified as Aβ++.

Table 1: Demographic characteristics of preclinical AD groups

	Aβ+ (n=62)	Aβ++ (n=42)	p
Sex N (%) Female	32 (52.5%)	26 (40.0%)	0.41
Age	73.78 (9.22)	78.31 (7.02)	0.04
Premorbid IQ	105.13 (9.78)	102.29 (8.27)	0.43
HADS depression	2.41 (2.24)	2.43 (2.34)	0.91
HADS anxiety	3.62 (3.2)	3.81 (2.82)	0.87
CDR sum of boxes	0.03 (0.47)	0.02 (0.61)	0.67
MMSE	28.91 (1.93)	28.74 (2.26)	0.53

Methods (continued)

Table 2: Preclinical Alzheimer's Disease Cognitive Composite (PACC) scores used in the current analyses

Composite score	Neuropsychological tests that contribute to composite
ADCS-PACC	WMS Logical memory (LM), California Verbal Learning Test Delayed Recall (CVLT), Digit Symbol Substitution Test (DSST), Mini Mental Status Examination (MMSE)
ADCS-PACC no MMSE	LM, CVLT, DSST,
ZAVEN	LM, CVLT, DSST, Verbal Fluency (VF)
Cogstate PACC	Cogstate One Card Learning Test (OCL), Cogstate One Back Test (OBK),

Computation of composite scores: For each neuropsychological test (Table 2) the group mean and standard deviation from the entire sample at baseline was used to standardize performance at the baseline and 36 month assessments. A composite score was then computed for each subject at each assessment by computing the average of the standard scores.

Computation of effect sizes for estimating effect of lowering amyloid: Linear mixed models (LMM) were used to compare slopes of change over 36 months for each PACC score between the Aβ+ and Aβ++ groups. Baseline scores were entered as covariates to adjust for any differences in previous neuropsychological assessment. Results of these analyses are summarized in Table 3.

Table 3: Group mean slopes for cognitive composite scores in Aβ+ and Aβ++ groups

Composite score	Aβ+ Mean slope	SD slope	Aβ++ Mean slope	SD slope	p
ADCS-PACC	-0.038	0.29	-0.21	0.29	<0.01
ADCS-PACC no MMSE	-0.078	0.27	-0.23	0.23	<0.01
ZAVEN	-0.042	0.24	-0.29	0.34	<0.01
Cogstate- PACC	-0.065	0.32	-0.39	0.45	<0.01

Results

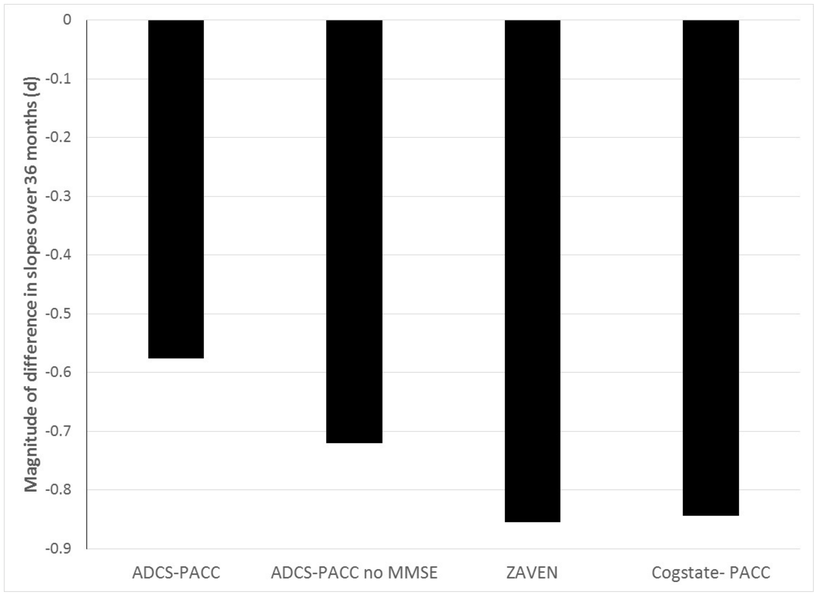

Fig 1: Magnitude of difference in slopes over 36 months between Aβ+ and Aβ++ groups for each PACC.

Figure 1 shows the differences in slope between the Aβ+ and Aβ++ groups for each PACC score. For each measure lower levels of abnormal amyloid were associated with a lower decline over 36 months. However, the figure shows that the difference in cognitive change between the Aβ+ and Aβ++ groups was smallest for the ADCS-PACC that included the MMSE. With the MMSE removed, the ADCS-PACC no MMSE, ZAVEN and Cogstate PACC all showed large magnitude differences between the Aβ+ and Aβ++ groups, with the ZAVEN and Cogstate PACC showing the greatest effects.

Conclusion

These data suggest that in preclinical AD lowering of amyloid levels will be associated with a reduction in the slope of cognitive decline over 36 months. The magnitude of this difference ranges between 0.5 and 0.8 depending on the cognitive composite measure used. These data therefore add to estimates of possible treatment effects derived from the comparison of individuals with abnormal and low Aβ and show that lowering Aβ will be associated with improvement in cognition. The data also suggest that addition of MMSE to cognitive composite scores reduces the sensitivity of those scores.