

INTRODUCTION

The clinical syndrome of Alzheimer's disease (AD) is preceded by a prolonged and currently irreversible pre-clinical phase characterized by neuropathological, functional, structural, metabolic and cognitive changes typical of AD.

In spite of the evidence for a pre-clinical phase in the development of AD, little is known about the time of onset or the specific neuropsychological pattern of cognitive changes occurring in asymptomatic persons.

Identification of early cognitive changes are important because mild cognitive deficits in asymptomatic persons have been shown to be predictive of subsequent AD.

This has been most clearly established in adults aged 65 and older for predictive intervals of approximately 2-8 years. Reductions in memory as well as abstract reasoning, verbal fluency and executive function have also been found to be predictive of dementia.

Early identification of cognitive changes are also important for interventions designed to alter the disease course.

PURPOSE OF STUDY

Our focus is the effect of family history of AD on cognitive course in clinically asymptomatic middle-aged individuals.

The purpose of this investigation is to determine whether distinct and clinically meaningful profiles of cognition can be detected in this group.

PARTICIPANTS & METHODS

Subjects included:

- 536 asymptomatic middle-aged individuals with a parent with AD (median age = 53 years).
- 130 control participants with a negative family history of AD whose parents survived to at least age 70 without AD or other memory disorders.

All research participants were administered a comprehensive test battery. Cognitive domain scores were constructed based on a review of the clinical neuropsychological literature and examination of distributional properties of raw test scores (see Table 1).

ACKNOWLEDGEMENTS

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RESULTS

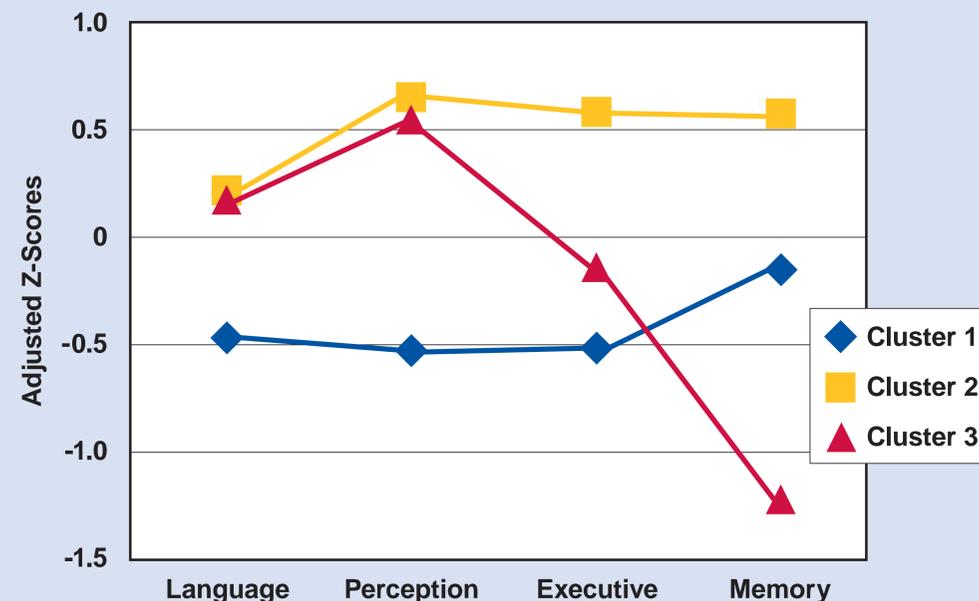
TABLE 1. NEUROPSYCHOLOGICAL TEST BATTERY

Domain	Test
Language	Boston Naming Test (BNT) WASI: Vocabulary
Perception	WASI: Blocks WASI: Matrices
Executive Function	WAIS III: Letter-Number Sequencing Trail Making Test (B)
Memory	Rey Auditory Verbal Learning Test (AVLT): • Total Score • Delayed Score

TABLE 2. DEMOGRAPHIC CHARACTERISTICS OF THE 3 CLUSTER GROUPS

Characteristic	Cluster 1 Low Average Cognition	Cluster 2 Above Average Cognition	Cluster 3 Memory Impaired
Age (years)	51.30	53.64	54.65
Female gender, % (n)	74 (186)	94 (146)	60 (47)
Education (years)	15.90	16.46	15.68
N	249	211	78

FIGURE 1. MEAN CLUSTER PERFORMANCE ACROSS COGNITIVE DOMAINS



DATA ANALYSES

Raw scores were converted to age, gender and education adjusted z-scores based on the controls and mean cognitive domain scores were derived (language, perception, executive function, memory) for middle-aged individuals with a parent with AD.

Mean domain scores were then subjected to cluster analysis. Ward's hierarchical agglomerative clustering method was used with squared Euclidean distance as the index of pair-wise similarity-dissimilarity between participant profiles.

RESULTS

Three cognitive profiles were identified (see Figure 1 & Table 2):

- **Cluster 1: Low Average Cognition** (n = 249)
Characterized by significantly lower scores than controls in language (p = .0001), visuoperception (p = .0001), and executive function (p = .0001) with average memory.
- **Cluster 2: Above Average Cognition** (n = 211)
Characterized by significantly higher scores than controls across all four cognitive domains (all p's = .0001 to .017).
- **Cluster 3: Memory Impaired** (n = 78)
Characterized by significantly worse (p = .0001) verbal memory compared to all groups and (p = .0001) better visuoperception domain compared to controls.

Differences in APOE and history of head injury and other neurological disorders were not significant among the clusters.

There were no significant differences on BMI, blood pressures, history of heart disease, HTN, high cholesterol, stroke, diabetes, or diagnosis of depression.

No significant differences were found on exercise, alcohol or tobacco use.

A significant difference was found in homocysteine. Cluster 3 (Memory Impaired) had higher homocysteine than the other two clusters.

Cluster 3 (Memory Impaired) had more people with a prior history of learning disabilities.

CONCLUSION

Among asymptomatic persons at risk for AD, cluster analysis reveals three distinct cognitive profile types.

One cluster is characterized by clear relative impairment in episodic memory performance.

Whether different cognitive trajectories will be associated with these cognitive profile types over time remains to be determined.

This hypothesis will be tested by reassessing subjects four years after their baseline evaluation.