INTERACTIVE EFFECTS OF FAMILY HISTORY OF AD AND CHILDHOOD LEARNING PROBLEMS ON MIDLIFE MEMORY PERFORMANCE

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BACKGROUND

Risk of Alzheimer's disease (AD) is increased for persons who have a 1st-degree relative with AD. Early life factors such as lowered mental ability during childhood may also increase AD risk. We studied learning problems during childhood as a potential moderator of cognitive performance in middle-aged persons with a parental family history of AD.

METHODS

Subjects were 783 cognitively intact adult children of parents with AD and 282 control participants without a family history of AD, enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP), a prospective longitudinal study.

Procedures included a health and lifestyle questionnaire, a baseline battery of neuropsychological tests (Table 1), laboratory evaluations and APOE genotyping.

Participants were asked if they had any learning problems in school. Fourteen percent answered "yes" or "don't know". These subjects were asked additional questions to determine the type and severity of learning problems. Answers to six of these questions (Table 2) were combined to form a single index of childhood learning problems (LP) equal to the proportion of questions with a "yes" response.

The sample overall was middle-aged (mean = 53 years), well-educated (median = college graduate), and almost entirely non-Hispanic white (98%). Age, education, and gender did not differ for LP and non-LP subgroups, but depressive symptoms (CES-D scores) were higher in the LP group.

RESULTS

The percentage of subjects who reported LP was higher for AD children than for controls (14% vs. 8%, $p < .05$). And, among subjects who reported a personal history of LP, the percentage who reported that one or more 1st-degree family members also had LP was higher for AD children than from controls (77% vs. 39%, $p < .01$).

Relationships between LP index scores and each of five factor-analytically derived cognitive domains were examined in regression analyses that included the following predictors: age, education, gender, depression symptom score (CESD), and LP group, as well as an LP x Family History interaction term.

A significant main effect of LP was observed on three of the five cognitive domains (Figure 1): Verbal Ability ($\beta = -1.97$, $t = -2.69$, $p = .007$), Working Memory ($\beta = -1.80$, $t = -2.90$, $p = .004$), and Speed and Flexibility ($\beta = -1.03$, $t = -2.21$, $p = .028$).

There was no significant effect of LP on Visuospatial Ability scores.

For the *Verbal Learning and Memory* domain, the *Family History group x LP interaction* effect was statistically significant (β -1.58, $t = -2.75$, $p = .006$). Childhood LP was associated with lower memory performance for AD children, but not for Controls (Figure 1).

TABLES & FIGURES

TABLE 1. NEUROPSYCHOLOGICAL TESTS BY COGNITIVE DOMAIN

Cognitive Domain	Test
Verbal Ability	• Wechsler Abbreviated Scales of Intelligence (WASI) Vocabulary and Similarities subtests • Wide Range Achievement Test-3: Reading scale • Boston Naming Test
Visuospatial Ability	• WASI Block Design and Matrix Reasoning subtests • Judgment of Line Orientation • Wisconsin Card Sort -64 items: perseverative errors
Working Memory	• Wechsler Adult Intelligence Scale-III: Digit Span, Arithmetic, and Letter-Number Sequencing subtests • Controlled Oral Word Associations
Verbal Learning & Memory	• Rey Auditory Verbal Learning Test: Sum recalled on learning trials and delayed recall
Speed & Flexibility	• Stroop Color Word Test: Interference trial • Trail Making Test: A and B

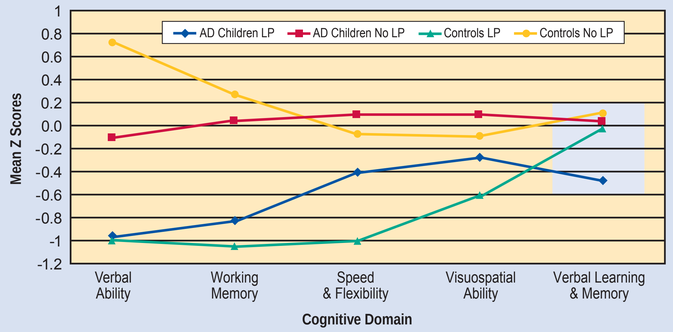
Note: Domains were identified by linear multi-factor analysis using a confirmatory model (Dowling et al., ICAD, 2008). Cognitive scores defining each latent factor were first transformed into z-scores, and factor loadings were used to compute a weighted linear combination of the transformed cognitive tests.

TABLE 2. QUESTIONNAIRE ITEMS COMPRISING THE LEARNING PROBLEMS (LP) INDEX SCORE

Did you have any learning problems in school?
Did the learning problems affect all of your schoolwork or only certain subjects?*
Did you start school late for your age or repeat any grades?
Did you have to work harder than your classmates on school tasks (e.g., spend more time on homework)?
Did you have more trouble with school work than your brothers or sisters?
Did you get any special help (e.g., remedial classes or tutoring) because of the learning problem?

*Coded "yes" if any specific subjects were identified.

FIGURE 1. MEAN COGNITIVE DOMAIN SCORES FOR AD CHILDREN AND CONTROLS WITH AND WITHOUT LEARNING PROBLEMS



CONCLUSIONS

Childhood learning problems emerged as significant predictors for several dimensions of cognitive performance at midlife.

For most cognitive domains, LP was associated with a mild-to-moderate lowering of scores among both AD children and Controls.

By contrast, on verbal learning and memory – the cognitive domain most sensitive to beginning stages of AD – LP was associated with lower midlife performance only among AD children. This raises the possibility that AD children with a history of LP may be especially vulnerable to memory decline.

Persons with LP may be entering middle age with reduced cognitive reserve. It is also possible that AD children with LP have combined genetic vulnerabilities that may accelerate cognitive decline.

STUDY STRENGTHS & LIMITATIONS

WRAP focuses on an important at-risk group — AD children — and has a substantial sample size.

To our knowledge, these analyses are the first to test for potential interactions between family history of AD and an early life ability factor in determining adult cognition.

Limitations include reliance on self-reports to determine LP, the small number of controls with LP, and absence of longitudinal data to determine change in cognition over time or emergence of clinical AD. Statistically significant associations between LP and multiple cognitive domains (e.g., Verbal Ability) tend to support the validity of LD self-reports. Continued recruitment of controls will lead to a larger control sample with LD, and longitudinal reassessments are currently underway.

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