



## Brief communication

## Exceptional memory performance in the Long Life Family Study

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## ARTICLE INFO

## Article history:

Received 29 April 2013

Accepted 1 May 2013

Available online 4 June 2013

## Keywords:

Long Life Family Study

Exceptional memory

Quantitative trait

Genetic variants

## ABSTRACT

Research to understand variability at the highest end of the cognitive performance distribution has been scarce. Our aim was to define a cognitive endophenotype based on exceptional episodic memory (EM) performance and to investigate familial aggregation of EM in families from the Long Life Family Study (LLFS). Using a sample of 1911 nondemented offspring of long-lived probands, we created a quantitative phenotype, EM (memory  $z \geq 1.5$ ), and classified LLFS families as EM and non-EM families based on the number of EM offspring. We then assessed differences in memory performance between LLFS relatives in the parental generation of EM families and those in non-EM families using multivariate analysis adjusted for APOE Apolipoprotein E genotype. LLFS relatives in the proband generation from EM families showed better EM performance than those from non-EM families ( $\beta = 0.74$ , standard error = 0.19,  $p = 1.4 \times 10^{-4}$ ). We demonstrated that there is a familial correlation of the EM endophenotype, suggesting that genetic variants might influence memory performance in long-lived families.

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## 1. Introduction

Human cognitive performance is highly variable. Family, twin, and adoption studies have documented strong evidence that genetic factors contribute to variation in the normal range of cognitive performance (Butcher et al., 2008; Deary et al., 2006). In contrast, little is known about the genetic factors that contribute to exceptionally high levels of cognitive performance. Quantitative genetic research in the normal range of cognitive variation has shown that virtually all cognitive tasks show appreciable heritability (Plomin and DeFries, 1998). For episodic memory (EM), for example, we and others (Johansson et al., 1999; Wilson et al., 2011) have consistently reported heritability estimates between 30% and 60%,

indicating that much of the observed variability in this cognitive domain is genetically influenced. Subsequent efforts have been aimed at identifying the specific genes responsible for the heritability of specific cognitive abilities. Most of the research has focused on conditions associated with cognitive disabilities because these conditions can provide important clues to the potential effect of genes on cognition. As a result, hundreds of single-gene defects have been described as impairing cognitive development (Freund and Reiss, 1991; Reiss et al., 1995). However, variability in normal cognitive function is most likely the result of many different genes interacting with each other and with nongenetic factors as well. In fact, genome-wide association studies of general cognitive ability have demonstrated that many genes of small effect make up 60% of the heritable variation in the trait (Butcher et al., 2008; Davis et al., 2010). Similarly, the majority of the research on exceptional cognitive abilities has explored the contribution of both genetic and environmental factors to the differences observed among individuals with exceptional abilities. As with estimates found for normal variation, findings from the small number of studies that

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have assessed cognitive exceptionality in twins reported high heritability estimates for high cognitive function (Haworth et al., 2009; Petrill et al., 2009; Plomin and Haworth, 2009; Saudino et al., 1994).

The biological pathways that influence longevity are still unknown. We and others (Barral et al., 2012; Fried et al., 1998; Korten et al., 1999; Schupf et al., 2003) have documented a significant association between preserved cognitive function and successful aging. It is likely that cognitive traits, such as exceptional memory, might represent 1 of the several endophenotypes contributing to exceptional survival.

In this study, we take into account the complex quantitative nature of cognitive performance and define a phenotype based on the exceptional performance of EM exhibited by offspring in the Long Life Family Study cohort. We aim to evaluate whether there is a familial clustering of the exceptional memory phenotype (EM) within Long Life Family Study (LLFS) families that would suggest its potential value for further genetic studies.

## 2. Materials and methods

### 2.1. LLFS cohort

Characteristics of the LLFS cohort have been described elsewhere (Barral et al., 2012).

### 2.2. Cognitive assessment: EM domain

Using the nondemented offspring of the LLFS probands as a normative sample ( $N = 1911$ ), we computed demographically adjusted z scores for 2 memory tests, immediate and delayed recall of story A from the Wechsler Memory Scale—Revised (Wechsler, 1987) using linear regression models adjusting for sex, age, and education. These demographically adjusted scores were then averaged to obtain the EM score.

### 2.3. EM quantitative trait

In the normative sample, the EM distribution had a mean value of 0.002 (standard deviation [SD] = 0.96), ranging from a minimum z score of  $-3.04$  to a maximum z score of  $3.26$  (Fig. 1). We used a threshold of 1.5 SD above the mean score to declare that an individual has exceptional memory (EM z score  $\geq 1.5$ ). We used this threshold to identify EM subjects in the entire offspring generation of the LLFS cohort (nondemented offspring and their unrelated nondemented spouses,  $N = 2547$ ). Based on the number of offspring with EM, we categorized the LLFS families as families with and without exceptional memory, EM families (families with at least 2 EM offspring) and non-EM families (families with 1 or none EM offspring).

### 2.4. Comparison groups

We investigated differences in memory performance of probands and their siblings in EM families and probands and their relatives in non-EM families. Secondary analysis assessed differences in performance for 3 comparison groups: (1) spouses of the LLFS' offspring in the EM families versus spouses of the LLFS' offspring in the non-EM families; (2) offspring of the non-EM families versus the entire group of spouses in the offspring generation; and (3) offspring of the EM families versus the entire group of spouses.

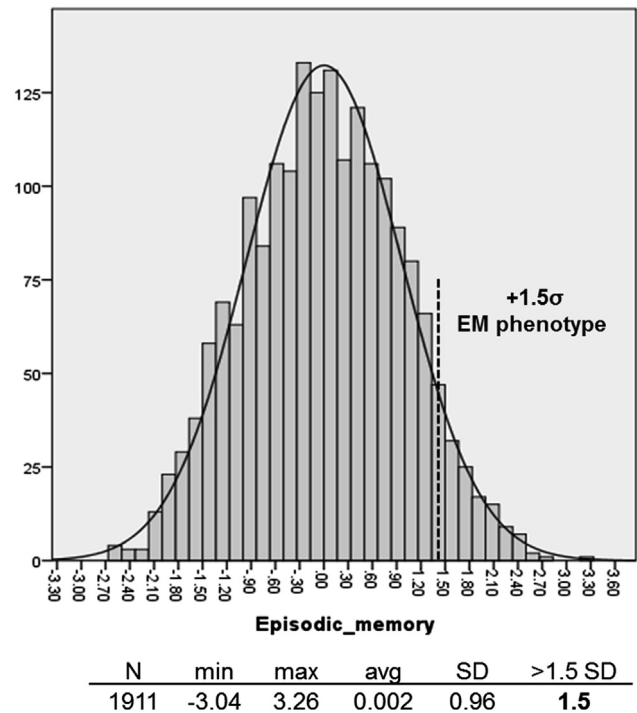


Fig. 1. Episodic memory distribution in the normative sample of nondemented offspring of Long Life Family Study probands.

### 2.5. Statistical analysis

To assess differences in memory performance between the different comparison groups, we used general linear models and generalized estimating equations (GEEs). For those group comparisons involving relatives of the LLFS' probands, GEE allows adjustments for differences in family size and accommodates the dependence among related individuals without assuming the joint distribution of the whole family. All multivariate analyses were adjusted for APOE genotype—genotypes at the APOE locus were recoded into 2 categories after excluding heterozygous individuals'  $\epsilon_2\epsilon_4$ : (1) having no APOE  $\epsilon_4$  allele and (2) having at least 1 copy of the APOE  $\epsilon_4$  allele. Analyses were not demographically adjusted as the dependent variable was already adjusted for age, sex, and education.

## 3. Results

The LLFS dataset used in this study was restricted to families without missing values for the cognitive tasks and demographic variables considered, consisting of 2971 subjects from 557 two-generation LLFS families. When our selection criterion was applied to the entire offspring generation of the LLFS cohort ( $N = 2547$ ), we identified 18 EM families ( $N = 405$  subjects) and 539 non-EM families ( $N = 2566$  subjects). Table 1 summarizes the results from the different linear models considered. Results from our primary comparison analysis showed that probands and their siblings in EM families achieved significantly higher scores on EM compared with probands and their siblings in non-EM families—estimated average EM of 0.56 (standard error [SE] = 0.19) vs.  $-0.18$  (SE = 0.05),  $p = 1.4 \times 10^{-4}$ . Secondary analysis showed that spouses of the LLFS' offspring in EM families demonstrated no significant difference in performance compared with spouses from non-EM families (estimated average EM of 0.20 [SE = 0.08] vs. 0.02 [SE = 0.04],  $p = 0.069$ ). The non-EM offspring have significantly worse memory

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