Cognitive Function in Families with Exceptional Survival

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Abstract

The authors investigated whether cognitive function may be used as an endophenotype for longevity by assessing the cognitive performance of a family-based cohort consisting of one thousand three hundred and eighty individuals from 283 families recruited for exceptional survival in field centers in Boston, New York, Pittsburgh and Denmark. Cognitive performance was assessed in the combined offspring of the Long Life Family Study (LLFS) probands and their LLFS siblings as compared with their spouses' cognitive performance. Our results indicate that the combined offspring of the LLFS probands and their siblings achieve significantly higher scores on both digit forward and backward tasks (p=5E-5 and p=8E-4 respectively) as well as on a verbal fluency task (p=0.008) when compared with their spouse controls. No differences between groups were found for the other cognitive tests assessed. We conclude that LLFS family members in the offspring generation demonstrate significantly better performance on multiple tasks requiring attention, working memory, and semantic processing when compared with individuals without a family history of exceptional survival, suggesting that cognitive performance may serve as an important endophenotype for longevity.

Keywords

exceptional survival; cognitive performance; endophenotype

1. Introduction

An impressive and coherent series of epidemiological data in different populations (e.g., New England Americans, Mormons, Ashkenazi Jewish, Icelandic, Okinawan Japanese)

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indicate a clear familial component to longevity(Gudmundsson, et al., 2000,Kerber, et al., 2001,Perls, et al., 1998,Schoenmaker, et al., 2006,Willcox, et al., 2006). Various studies have documented the genetic nature of the familial component of exceptional survival, reinforcing the important role of genetic factors in survival chances at older ages. Studies in twins and in isolated populations have provided life span estimates heritabilities of 20-30% (Christensen, et al., 2006,Franceschi, et al., 2007,Herskind, et al., 1996).

In their study of inheritance of human longevity in Iceland, Gudmundsson and colleagues reported that first degree relatives of individuals who live longer than 95% of the population were twice as likely to also live to the 95th percentile when compared to controls (Gudmundsson, et al., 2000). Among siblings of probands in Utah families who reached the 97th percentile of exceptional survival, the ratio of recurrence risk of exceptional survival in first-degree relatives compared with the population prevalence (lambda) was 2.30 (Kerber, et al., 2001). Similarly, among Dutch families, mortality ratios for siblings, parents and offspring of long living participants were significantly lower when compared with the general Dutch population (Schoenmaker, et al., 2006).

Siblings of Japanese Centenarians experienced approximately half the mortality of their birth cohort-matched counterparts (Willcox, et al., 2006). In the New England Centenarian Study (Perls, et al., 2002), when survival of siblings of centenarians was compared to the 1900 American birth cohort, both males and females siblings of centenarians experienced lower mortality throughout life. The centenarian's male siblings had an average age of death of 76.7 years (70.4 years for females), while life expectancy for the U.S 1900 cohort has been estimated at around 51.5 years for males (58.3 years for females). Such elevated relative survival probability values support the hypothesis that these family members have genetic variations in common that is important to achieving exceptional longevity (McCarthy, et al., 1998).

Taken together these studies indicate a strong familial component to exceptional survival in which genetic factors play an important role by demonstrating that offspring of long-lived subjects have a significant survival advantage when compared to the population as a whole. However, exceptional survival is a complex phenotype likely resulting from the interaction of these genetic factors and environmental influences shared by family members.

The phenotypes that characterize exceptional survival are not fully established yet. Findings from elderly cohorts and centenarian studies have suggested that preservation of cognitive function has an independent and important association with survival. Cognitive impairment has been shown to be a robust predictor of mortality in diverse populations. Elderly individuals with mild as well severe cognitive impairment have an increased risk of death even after adjustment for a variety of health conditions, lifestyle factors and sociodemographic characteristics(Bassuk, et al., 2000,Dewey and Saz, 2001,Fried, et al., 1998,Gussekloo, et al., 1997,Kelman, et al., 1994,Liu, et al., 1990,Neale, et al., 2001,Smits, et al., 1999,Swan, et al., 1995). In studies of human twins and families, genetic influences on cognitive function are found to be substantial and to continue into old age(Finkel, et al., 1995a,Finkel, et al., 1995b,Lee, et al., 2004,McClearn, et al., 1997,McGue and Christensen, 2001,Pedersen, et al., 1992,Plomin, et al., 1994,Swan, et al., 1995,Swan, et al., 1999). About half of the variance in cognitive function can be accounted for by genetic differences. Plomin and colleagues (Plomin, et al., 1994) found heritability of verbal and speed of processing tests to be about 0.50 and 0.4 for memory and most studies have yielded heritability estimates for cognitive functions within this range.

The Long Life Family Study (LLFS), a National Institutes on Aging sponsored multi-centered study, is a family-based cohort study of highly functional adults over age 90, their

siblings and their offspring, selected to study exceptional health and function well beyond what is expected in the general population. The primary objective of LLFS is to identify underlying genetic and non-genetic factors associated with exceptional familial longevity.

In the present study, we hypothesized that the LLFS offspring generation will show a cognitive advantage when compared to their spouse control group.

2. Material and Methods

2.1. LLFS cohort

The Long Life Family Study (LLFS) consists of families selected for exceptional survival phenotypes in the United States and Denmark. Recruitment of families into the LLFS was carried out by field centers located in Boston, New York, Pittsburgh and Denmark. Potentially eligible U.S.-based individuals and their families were identified through two main sources (1) mailings of study information to individuals aged 85 and above who were enrolled in the Medicare program and who reside in zip code areas located within a three hour driving distance from the three field centers, and (2) individuals who contacted the field centers in response to media events, including television appearances, newspaper stories, and advertisements. All potential participants were interviewed over the telephone to assess eligibility and willingness to participate in the LLFS. Family eligibility was assessed using the following criteria: 1) at least two living siblings over the age of 80, including the proband, 2) at least one living offspring of one of the two living siblings, 3) one living spouse of the offspring generation to serve as a control, and 4) demonstration of exceptional survival as measured by the Family Longevity Selection Score (FLoSS), a summary measure based on the survival experience of the proband and their siblings relative to what would be expected based on birth cohort specific life tables and the availability of alive subjects for study(Sebastiani, et al., 2009). A FLoSS score threshold of 7 or higher was used as inclusion criteria, which would exclude 99.5% of families in the Framingham Heart Study cohort. Among eligible families, those with exceptionally old living siblings were given highest priority. For analysis purposes, only probands who scored >=24 in the Mini Mental Status Examination test (MMSE) were considered cognitive healthy and therefore included in the analysis.

In Denmark, identification of potentially eligible probands and their families proceeded as follows. First, individuals who would be age 90 and above during the study recruitment period were identified in the Danish National Register of Persons, which contains current information on names, including past names such as maiden names for women, addresses, place of birth, marriages, and vital status. Second, using information on the place of birth and names, parish registers available in regional archives were searched to locate the parents of the elderly individuals in order to identify sibships. Based on the above information, potentially eligible families were identified and contact was made with potential probands to further assess the family's eligibility for and willingness to participate in the LLFS, using criteria parallel to those used in the United States.

2.2 Comparison cohorts

At the time of this analysis, the pedigree data included a total of 12,054 individuals (44% females) from 362 extended families distributed across 2 generations (LLFS proband and offspring generations). The average family size was 33 individuals, ranging from a minimum pedigree of 3 individuals to a maximum family size of 181 individuals. The present study was conducted in the LLFS offspring generation, for which we selected only the first degree offspring (sons and daughters) of the LLFS proband generation (probands and older siblings), along with the spouses of the offspring, leading to a sample size of 1639

individuals. After excluding those subjects from any of the collection sites with MMSE score<24 (N=17 individuals), the final sample consisted of: i) a combined LLFS offspring group (N=556) including sons and daughters of the LLFS probands older than 90 years of age and their older siblings and ii) a control group (N=752) consisting on the spouses of these LLFS offspring. Using partners of offspring of long-living subjects as the comparison group avoids potential cofounders since it is likely that they have a similar distribution of birth cohort, socio-economic, and geographical backgrounds. Table 1 shows the characteristics of both comparison groups.

2.3 Cognitive assessment

Cognitive performance in all individuals from both comparison groups was assessed with the following tests: 1) a brief version of the Logical Memory subset of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1981) consisting of only one paragraph to be recalled at immediate and delayed intervals; 2) Digit Span Forward and Backward, a widely used test of immediate auditory attention and working memory in which the participant is read number sequences of increasing length and asked to repeat them forward and backward; 3) Semantic fluency in which subjects were asked to name as many animals and vegetables as possible in two separate one minute trials.

2.4 Health Status assessment

Since health is a critical factor that may influence both exceptional survival and cognition, we assessed the health status of all individuals in our analysis by using an approximation of Charlson's weighted index of comorbidity (Charlson, et al., 1987). The twenty-six conditions influencing survival in our study population were given a weighted score based on the relative mortality risk. The sum of weighted scores of all the conditions present in each subject was summed to create the final comorbidity score for each individual. The comparison of the comorbidity score between the two groups lead to a 2×11 contingency table, in which only the first 6 cells have values >5. To prevent increased Type II errors derived from the small number of observations, we combined those cells with low counts to create comorbidity grades. Tables 2a and 2b shows comorbidity score and comorbidity grades for both comparison groups.

2.5 Statistical analysis

Differences in sex between the two comparison groups were assessed using a Fisher exact test. T-tests were used to examine differences in age, years of education and sex, respectively, between LLFS family members and the spouse control group. To assess differences in cognitive performance between the two comparison groups, we used Generalized Estimating Equations (GEE) to adjust for the relatedness of the LLFS offspring by treating family membership as a cluster. All multivariate analyses were adjusted for age, sex, education and health status by using the derived comorbidity index. We additionally used polynomial logistic regression to compare the proportions of the two groups in the highest tertile of each of the assessed cognitive tests, using the same covariates.

3. Results

We found significant differences in sex, age and education when comparing both groups. The proportion of females among the offspring of the LLFS proband generation was higher compared to the percentage among their spouses (60.9% vs. 48.8%, p=0.002).Sons and daughters of the LLFS probands were, on average, 2 years older than their spouses (64.4 versus 62.4 years, t=11.056, p=0.001) and had, on average, almost one more year of education (12.9 years vs 12 years; t=17.468, p<0.001) compared to the spouse controls.

When comparing the performance among individuals with cognitive data, sons and daughters of the LLFS probands performed significantly better than spouse controls on digit forward (adjusted mean=8.55 vs adjusted mean=7.83, p=4.5E-05) and backward tasks (adjusted mean=6.76 vs. adjusted mean=6.17, p=4E-04) and a category fluency (vegetables) task (adjusted mean=15.52 vs. adjusted mean=14.65, p=0.008) adjusting for age, sex, education and health status as potential cofounders (Table 3a). No differences were found for the other cognitive tests assessed.

Furthermore, compared to their spouses controls, LLFS offspring were 2.35 times more likely to have scores in the highest tertile of digit span forward (OR=2.35, 95%CI: 1.6-3.5), 2.11 times more likely to have scores in the highest tertile of digit span backward (OR=2.11, 95%CI: 1.4-3.2), and 1.5 times more likely to have scores in the highest tertile of category fluency vegetables task (OR=1.54, 95%CI:1.01-2.35).

4. Discussion

The LLFS is a multi-center effort to enroll families with multiple living and exceptionally old individuals. The assessment of cognitive function carried out in these families provides the possibility of examining whether the preservation of cognitive abilities in very old age represents a key characteristic of the overall phenotype of successful aging. We found that aspects of cognitive performance were stronger in the offspring of individuals selected for exceptional survival than in their spouse control group. Our results are broadly consistent with previous findings in younger cohorts of exceptional survival (Duff, et al., 2009,Hagberg and Samuelsson, 2008,Johansson and Berg, 1989,Ramsay and Reynolds, 1995,Siegler, et al., 1982,Small and Backman, 1997), and show that this cognitive advantage is also present in their offspring generation.

Interestingly, the cognitive differences between the performance of LLFS and comparison groups appeared to be somewhat selective. Specifically, we found that offspring of the LLFS proband generation showed significantly better performance on the digit span task than the comparison group not selected for familial longevity. This difference was driven by higher scores on both the forward component (immediate auditory attention) and backward component (mental manipulation) of the digit span task, and was seemingly independent of global cognition, as performance on other measures such as episodic memory tasks was comparable across groups.

We also found that offspring of LLFS proband generation outperformed their spouses-controls on the vegetable fluency test but not the animal fluency task. The reason for this discrepancy remains unclear, and could reflect random statistical variability, particularly given the relatively comparable effects sizes of longevity on both fluency tasks. However, it should be acknowledged that animal and vegetable fluency tasks appear to place demands on different cognitive processes(Ventura, et al., 2005a,Ventura, et al., 2005b) and can be selectively impaired in clinical populations(Hart, et al., 1985,Samson, 2003). The primary difference between the tasks involves the relative importance of processing sensory versus functional information about the items to be named, with sensory features being particularly important for animal knowledge. As such, it is also possible that the cognitive processes which disproportionately contribute to vegetable rather than animal fluency are more clearly implicated in the cognitive endophenotype of longevity in this sample.

The association between digit span performance and survival has been documented previously in an early study examining the robustness of terminal decline (Johansson and Berg, 1989). Individuals who exhibited superior baseline performance in both forward and backward digit span showed longer survival than individuals with low performance.

However, other aspects of cognition have been linked with survival as well, including verbal and visual memory and performance IQ (Siegler, et al., 1982), verbal understanding, short term memory and learning capacity (Hagberg and Samuelsson, 2008). In one of the most comprehensive studies of cognition and mortality in older adults, aged 75 to 95 years, two cognitive tasks, immediate recognition and category fluency predicted death after three years of follow-up (Small and Backman, 1997). Finally, performance on 9 out of 12 cognitive measures at baseline in a large sample of elderly adults (average age of 73 years) predicted mortality during follow-up (Duff, et al., 2009).

Taken together, these studies suggest that multiple aspects of cognition are likely to be relevant in the identification of a cognitive endophenotype for longevity. The longevity-differences seen on the digit span task in the current study suggest that both basic and complex attentional processes, the building blocks of many cognitive capacities, may be key features of a cognitive endophenotype for longevity. The fact that the LLFS offspring generation is relatively younger (average age of 64 years, approximately 31 years younger than their long-lived parental generation) supports the hypothesis of cognitive ability as a heritable component of the exceptional survival phenotype.

The current findings complement a number of earlier studies that have linked preservation of cognitive functioning with successful aging. In several studies, individuals who were classified with severely impaired cognition, had a more than three times higher risk of dying compared with those who scored in the high normal range (Fried, et al., 1998,Korten, et al., 1999) for memory, vocabulary and visuospatial abilities (Anstey, et al., 2001,Hassing and Backman, 1997,Shipley, et al., 2008,Small, et al., 2003). Although a sizeable portion of this effect can be attributed to other known risk factors such as age and health status, it is noteworthy that cognitive function remained a significant predictor of survival even after adjustment for these other factors (Pavlik, et al., 2003).

Moreover, several prospective studies from our group have found that neuropsychological tests independently predict death in older adults(Cahn-Weiner, et al., 2000,Carlson, et al., 1999,Lavery, et al., 2005,Owsley, et al., 2002,Royall, et al., 2004). We previously investigated the relationship of cognitive functions to familial aggregation of survival showing that the rate of decline in cognitive function during old age had strong effects on survival in the probands (Schupf, et al., 2005). We also observed that siblings of elderly probands with slow rates of decline in memory, cognitive function and activities of daily living skills were one-half as likely to die as siblings of probands with rapid rates of decline (Schupf, et al., 2003). Additionally, we found that heritability of memory and a select group of cognitive functions was high, suggesting that they might serve as an endophenotype related to successful aging (Lee, et al., 2004).

The mechanisms that generate the association between cognitive functioning and survival in the elderly are not well understood and the literature to date is no consistent, with multiple studies and contradictory results. Most likely, a large part of the discrepancies may be explained by different sources of variability (demographic, cognitive assessment, study design and statistical methods).Therefore, replication studies using different tests and different samples would be crucial to further validate the association between preserved cognitive function and exceptional survival. Currently, researchers are just beginning to explore the potential of cognitive performance as an endophenotype for longevity. Moving forward, we aim to use the cognitive endophenotypes identified in this sample to estimate the genetic contribution to exceptional survival. Strong genetic influences will suggest that genetic analyses of exceptional survival endophenotypes may help to identify genetic variants associated with longevity.

Finally, exceptional survival is a complex phenotype, most likely influenced by multiples endophenotypes, such as functional ability among others. To further identify exceptional survival endophenotypes, a principal component analysis carried out in both proband and offspring generations of LLFS cohort (Matteini, et al., 2010) showed that combined measures of different trait domains (pulmonary, physical metabolic and cardiovascular functions) are important for functional longevity, suggesting pleiotropic effects among the different longevity endophenotypes. Further studies would be needed to better characterize the interaction patterns between different endophenotypes, such as cognitive and functional, to better elucidate how their joint effects contribute to the exceptional survival of LLFS members.

Acknowledgments

7. References

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Table 1

Demographic characteristics of the comparison groups

Group	N	Females (%)	Mean age (SD)	Mean education (SD)
LLFS offspring	305	60.9	64.4 (7.0)	12.9 (2.9)
Spouses-control	434	48.8	62.4 (8.6)	12.0 (3.3)

Table 2a

Prevalence of comorbid conditions among offspring of LLFS proband generation and their spouses-controls

Score	Conditions	LLFS Offspring	Spouses-control
1	Coronary artery disease [a]	23	33
	Congestive heart failure	2	2
	Stroke or cerebrovascular disease	6	9
	Chronic pulmonary disease [b]	95	127
	Chronic Liver disease	0	0
	Peptic ulcer disease	0	0
	Peripheral vascular disease	0	0
	Mild liver disease	0	0
	Connective tissue disease	107	137
	Diabetes	17	31
	Hemiplegia	0	0
2	Moderate to severe renal disease	0	0
	Diabetes with end organ damage	2	14
	Any prior tumor	64	82
	Leukemia or Lymphoma	1	1
3	Moderate to severe liver disease	6	9
6	Metastatic solid tumor	1	3
	AIDS (not only HIV positive)	0	0
Total		324	448

[a] Includes myocardial infarction, heart attack, coronary angioplasty, coronary artery bypass

[b] includes chronic bronchitis, emphysema or chronic obstructive pulmonary disease, pulmonary fibrosis

Table 2b

Comorbidity grades distribution in the two comparison groups

Comorbidity grade	1	2	3	4	total
spouses-controls	308	119	32	12	471
Offspring LLFS	218	94	17	5	334
Total	526	213	49	17	805

Table 3a

Cognitive performance descriptives and Generalized Estimating Equations results for sons and daughters of LLFS probands or their sibling and their spouse's controls

Cognitive test	group	N	Mean	95%CI	B	95% CI	p-value
Logical Memory IA	LLFS Offspring	305	13.19	12.7, 13.7	0.13	−0.56, 0.81	0.718
	spouses-controls	434	13.03	12.6, 13.5			
Logical Memory IIA	LLFS Offspring	305	11.76	11.3, 12.2	0.30	−0.39, 0.99	0.391
	spouses-controls	434	11.47	11.0, 11.9			
Digit Forward	LLFS Offspring	305	8.55	8.3, 8.8	0.66	0.37, 0.96	1.E-05
	spouses-controls	434	7.83	7.6, 8.1			
Digit Backward	LLFS Offspring	305	6.76	6.5, 7.0	0.59	0.26, 0.91	4.E-04
	spouses-controls	434	6.17	6.0, 6.4			
Category Fluency Animals	LLFS Offspring	305	22.08	21.4, 22.8	−0.31	−1.21, 0.59	0.497
	spouses-controls	434	22.32	21.8, 22.9			
Category Fluency Vegetables	LLFS Offspring	305	15.52	15.0, 16.1	0.90	0.24, 1.56	8.E-03
	spouses-controls	434	14.65	14.3, 15.0			

Table 3b

Result from the polynomial logistic regression analysis to compare highest tertile of cognitive tests between LLFS offspring and spouses controls

Digit span forward

	B	SE	Exp(B)	95%CI	Sig
group	0.85	0.20	**2.35**	1.58,3.49	**0.000**
sex	0.00	0.20	1.00	0.68,1.49	0.986
age	0.02	0.01	1.02	0.99,1.04	0.153
edu	−0.32	0.04	0.73	0.67,0.79	0.000
HI	−0.14	0.07	0.87	0.76,1.01	0.067

Digit span back ward

	B	SE	Exp(B)	95%CI	Sig
group	0.75	0.21	**2.11**	1.41,3.16	**0.000**
sex	−0.48	0.21	0.62	0.41,0.93	0.022
age	0.00	0.01	1.00	0.98,1.03	0.849
edu	−0.35	0.04	0.71	0.65,0.77	0.000
HI	−0.09	0.08	0.92	0.79,1.06	0.258

Category Fluency vegetables

	B	SE	Exp(B)	95%CI	Sig
group	0.43	0.21	**1.54**	1.01,2.35	**0.042**
sex	−1.86	0.22	0.16	0.10,0.24	0.000
age	0.06	0.01	1.06	1.03,1.09	0.000
edu	−0.14	0.04	0.87	0.81,0.94	0.000
HI	0.06	0.09	1.06	0.89,1.27	0.498