Heritability of an Age-Dependent Categorical Phenotype: Cognitive Dysfunction

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We investigated the extent to which cognitive dysfunction is shaped by genetic or environmental influences, and whether these factors differ in women and men. All members of the Swedish Twin Registry aged 65 and older were screened by telephone using the TELE, a brief cognitive assessment instrument (Gatz et al., 2002), and the Blessed Dementia Rating Scale (Blessed et al., 1968) from relatives of those who scored poorly on the TELE. Data were available for 4308 pairs where both members responded and 5070 pairs where only one member was alive and participated. To analyze all available data, we used a raw data method extended to ordinal data. As the prevalence of cognitive dysfunction increases with age, we incorporated age-adjusted thresholds. The best fitting model from biometric analyses indicated 35% of the variation in liability to cognitive dysfunction could be explained by heritable influences and the remaining 65% by nonfamilial environmental influences. Differences by gender were not significant. As this is a normative population including cognitively intact individuals, preclinical dementia cases and demented individuals, the relative magnitude of genetic and environmental effects is of particular interest in light of high heritabilities found for dementias such as Alzheimer's disease. The findings emphasize the extent to which research is needed to uncover nonfamilial environmental influences on cognitive dysfunction in later life.

To study the heritability of cognitive dysfunction requires tackling two distinct issues: how to assess cognitive dysfunction using a single measure that includes those who are too impaired to answer for themselves, and how to best control for age relatedness when using such a measure in a twin design. Previous twin analyses examining quantitative mental status performance scores have indicated a moderate role for genetic influences with between 20 and 30% of the variance due to genetic factors (Brandt et al., 1993; Gatz et al., 2003). However, further analytical work is needed in this area of research. First, while proxy information is often sought when determining cognitive status, such information has not been included in prior biometrical analyses. Thus, those deemed untestable are excluded from the analyses although valuable information about level of dysfunction may be available from the informant. However, in order to make use of both self and proxy information, the scaling of the observed trait is necessarily ordinal. Second, greater cognitive dysfunction is associated with increasing age. In biometrical models of age-dependent traits, it becomes necessary to account for age in an appropriate way so as not to overestimate shared environmental effects. The present study combines mental status screening and proxy information into a single ordinal indicator of cognitive dysfunction and examines the effects of various age correction procedures on the resulting heritability of this ordinal scale.

Mental status tests differ from typical intelligence tests as well as from clinical diagnoses of dementing illnesses such as Alzheimer's disease. First, mental status scores aim to screen for adequate cognitive function rather than testing the upper limits of an individual's cognitive abilities, resulting in ceiling effects for most normal adults. Thus, little variation is seen in adult populations until after age 65 years and scores tend to be skewed by design. Furthermore, mental status tests are brief and global in contrast to tests that assess specific cognitive abilities. Secondly, mental status tests do not provide dementia diagnoses, as there are several additional neurological and behavioral criteria that must be considered in making diagnoses. The main goal of using mental status tests is to characterize the cognitive level of a population or to identify potential dementia cases for further finer-grained assessments. When applied to an entire population, mental status testing becomes the basis for asking, how heritable is cognitive dysfunction?

Heritability for general cognitive ability in older adulthood is high ranging from 60% (McClearn et al.,

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1997) to 80% (Pedersen et al., 1992), and heritability for Alzheimer's disease is likewise high at 74% (Gatz et al., 1997). However, tests of cognitive ability exclude those who are cognitively impaired, while evaluating heritability of a disease ignores all individual differences in those who do not meet diagnostic criteria for the disorder. There have been two prior large-scale studies of the heritability of mental status screening. Telephone interviews of over 4302 male twin pairs from the National Academy of Sciences (NAS) twin registry using the modified Telephone Interview for Cognitive Status (TICS-m) suggested that 32% of the variation in total scores was heritable and shared environmental variance accounted for 17% to 18% (Brandt et al., 1993). Analyses of telephone cognitive screening scores gathered on 13,519 Swedish twins aged 65 years and older indicated a heritability of 20% and a shared environmental influence of 9%, with no significant sex differences (Gatz et al., 2003). These two reports, however, excluded those who were too impaired to participate in mental status screening.

One explanation for the lower heritability of mental status tests compared to either IQ or Alzheimer's disease diagnoses is the global nature of the brief mental status assessments. Another possibility is that there is heterogeneity of heritability in mediating phenotypes that lead to low mental status scores, such as vascular dementia versus Alzheimer disease (Bergem et al., 1997; Gatz et al., 1997). A last possibility is that not all individuals with low mental status scores are represented in these analyses, thus losing some important variation. In particular, individuals can be too impaired to be assessed using quantitative mental status measures, leading to missing data. If both twin and proxy information are combined into a single scale and a higher heritability is observed this might suggest that the lower heritability seen in prior studies is due to reduced variation because of systematic deselection of the low end of the mental status continuum. In other words, we might expect increased heritability, reflecting genetic influences for dementia not captured when only self-report measures are used.

In the present study, we sought to:

(1) examine biometrical models of cognitive dysfunction, measured on an ordinal scale which incorporates both self and proxy information.

(2) include a statistical correction for age so that similarity for age within twin pairs does not become confounded with shared environmental influences.

(3) examine whether there may be sex differences in the type and/or relative contribution of genes to cognitive dysfunction (sex-limitation).

Methods

Participants

All members of the Swedish Twin Registry aged 65 and older were screened by telephone for cognitive dysfunction (Gatz et al., 2005). Data from those with established zygosity were available for 4308 pairs where both members (or their informants) responded and 5070 pairs where only one member was alive and the individual or informant participated. The sample included more females than males (44% male, 56% female). The average age of the sample was 73.5 years (range 65 to 101 years).

The response rate to the screening was 71% out of a total population of 20,269 (Gatz et al., 2005). After excluding 253 for whom zygosity could not be established, there were 13,686 twins with available data. Of these, 10,212 were interviewed directly with no information from a proxy informant, 2200 had both direct screening interviews plus proxy information, and 891 had information from an informant alone with no direct interview of the twin. Of the remaining twins, 141 quit the interview before its completion and no informant was available, 181 were not interviewable due to physical illness and an informant was not available, and for 61 twins cognitive status had already been determined by a related concurrent study, using an essentially identical protocol (Gatz et al., 1997).

Zygosity determination was made on the basis of self-reported similarity assessed during screening or in previous waves of assessment of the Swedish Twin Registry (Lichtenstein et al., 2002). Zygosity distribution was 24% monozygotic (MZ) twins, 42% dizygotic (DZ) same-sex twins, and 34% unlike sex pairs.

Measures

Cognitive screening used the TELE, a brief telephone interview protocol with established validity for identifying cases of dementia (Gatz et al., 2002). Proxies were contacted only if there was poor performance by the twin or if the twin was unable to be interviewed. The proxy interview includes the Blessed Dementia Rating Scale (BDRS; Blessed et al., 1968) as well as other questions about health and daily functioning. The Blessed Dementia Scale (DS) is highly discriminative between nondemented and demented individuals, even in mild cases (Juva et al., 1997). The TELE incorporates the 10-item Mental Status Questionnaire (MSQ; Kahn et al., 1961), which has a large contribution from orientation items, supplemented by other cognitive items (counting backwards, recalling three words after a brief delay, and three similarities items) and by questions about health and daily functioning. An algorithm assigned ordinal scores from 0 (cognitively intact) to 3 (cognitive dysfunction) based upon total errors or errors across domains (MSQ, similarities or 3-word recall), informant BDRS scores, and reports by self or proxy of impairment in daily functioning due to memory or cognitive problems. Complete interview protocols are provided at http://www.usc.edu/dept/LAS/psychology/SCRAP Generally, those who were not impaired on any domain were coded '0', those with impairment in one domain were coded '1', those with impairment in two domains but where functional impairment was not confirmed by the informant were coded '2', and those

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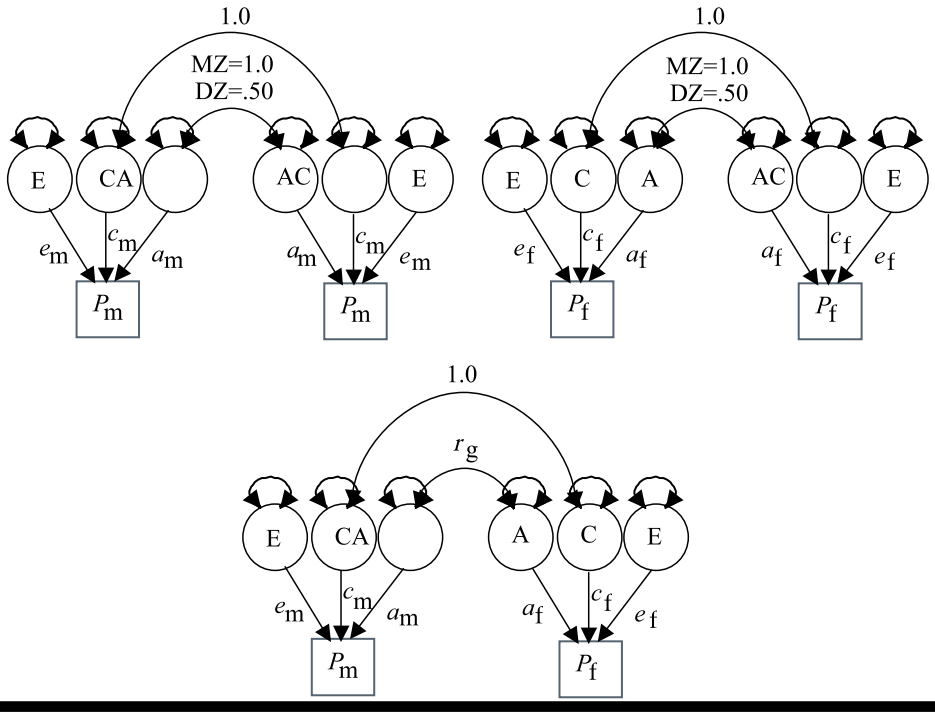

Figure 1

Biometrical sex-limitation model.

A = additive genetic influences, C = shared environmental influences, E = Nonshared environmental influences; f = female, m = male.

who performed poorly or were completely unable to be interviewed and had confirmed functional impairment were coded '3'.

Statistical Analyses

Biometrical analyses were conducted on raw ordinal data using Mx 1.55 (Neale et al., 1999) on a Mac OSX platform, where differential resemblance by zygosity and gender was compared (see Figure 1). Incomplete pairs were included into analyses as they contributed information for estimation of thresholds.

The assumption of the ordinal biometrical model fit is that there exists an underlying normally distributed liability to exhibit cognitive dysfunction for which at the observed level there are mutually exclusive ordinal categories (see Figure 2). Given that prevalence rates vary with age, we adjusted estimated thresholds for each level of impairment according to age of participant. Examples of age-adjustments to ordinal traits are beginning to appear in published biometrical studies (e.g., Foley et al., 2003). The Mx model for thresholds in the present case included regression of threshold on observed age at screening, using the definition variable approach (Neale et al., 1999). The Mx program used for the present analyses was adapted from a program provided by C. O. Gardner (personal communication, March 20, 2003). For greater interpretability age was centered and sex-specific age adjustments were permitted:

$$t(\text{Age}) = t_C + \beta(\text{Screen Age} - C) \quad [1]$$

where t(Age) denotes the age-specific threshold, t_C refers to the threshold observed at the centering age C, herein 65 years, and β refers to the regression coefficient of the centered age variable. Next, we extended the linear model of threshold adjustment to a linear plus quadratic model given that prevalence of cognitive dysfunction exhibits first an acceleration and then deceleration among the oldest-old (Gao et al., 1998):

$$t(\text{Age}) = t_C + \beta_1(\text{Screen Age} - C) + \beta_2[.5(\text{Screen Age} - C)^2] \quad [2]$$

where β_1 refers to the linear regression coefficient at the centering age and β_2 refers to the age-associated quadratic change of the prevalence rates. The Mx script with the quadratic age adjustment is available at www.psy.vu.nl/mxbib/.

Results

Phenotypic Distribution of Cognitive Dysfunction

Cognitive dysfunction is more prevalent with age (see Figure 3). The trend is generally linear but there is acceleration from 65 to 84 followed by deceleration. This pattern signals that a nonlinear age correction may prove most valuable in addressing the age-dependent nature of cognitive dysfunction.

Twin Similarity for Cognitive Dysfunction

Age-adjusted polychoric twin correlations were estimated by zygosity and sex using Mx 1.55 (Neale et al., 1999). While MZ twins are more similar than DZ twins, the difference between MZ and DZ was greater in the female pairs (see Table 1). The opposite-sex pair correlation was smaller than the geometric mean of the

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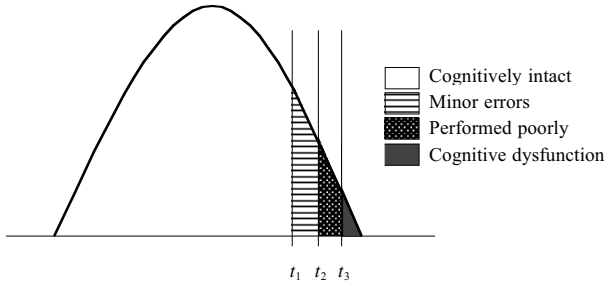

Figure 2

Underlying liability for cognitive dysfunction with thresholds indicated (t_n).

same-sex DZ pair correlations, .19 versus .22, respectively, raising the possibility of partial sex limitation. Nonetheless, the twin correlations were typically small to moderate, indicating that nonshared environment plays the largest role in cognitive dysfunction.

Biometrical Threshold Models

A series of nested models was fit with Mx 1.55 and compared using the chi-square difference test to examine the extent to which the age corrections reduced shared environmental variance in men and women (see Table 2, Models 1, 2 and 3). The effect of the quadratic age adjustment to the thresholds compared to no age adjustment was to reduce the shared environmental effect by over a third (see Table 3). There was a significant difference in fit between the linear and quadratic age models, with only a small difference in parameter estimates. The quadratic coefficient is nearly three times higher in women than in men, suggesting it may be of greater relevance to make the quadratic age adjustment in women than in men.

Table 1

Twin Polychoric Correlations by Zygosity and Sex and Age Group: Quadratic Age Correction

	MZM	MZF	DZM	DZF	OZ
Correlation: full sample	.26	.34	.19	.24	.19
Npairs$_{(TOTAL)}$	954	1285	1744	2355	3040
Npairs$_{(COMPLETE)}$	425	660	700	1036	1487
Correlation: 65–79 years	.24	.30	.19	.22	.18
Npairs$_{(TOTAL)}$	711	905	1379	1627	2611
Correlation: 80 + years	.33	.43	.23	.30	.24
Npairs$_{(TOTAL)}$	243	380	365	728	429

Note: MZM = monozygotic male twins; MZF = monozygotic female twins; DZM = dizygotic male twins; DZF = dizygotic female twins; OZ = opposite-sex dizygotic twins; Npairs = number of twin pairs.

A series of nested models was fit and compared using the chi-square difference test to examine the presence of sex-limitation or sex differences for cognitive dysfunction. There was no significant genetic sex-limitation effect (see Model 4, Table 2). The best fitting biometrical model constrains biometrical parameters across sexes and includes only additive genetic and nonshared environmental influences (see Model 5.2, Tables 2 and 3). Parameter estimates from the best fitting model indicate heritable influences explain 35% of the variation in liability to cognitive dysfunction with nonshared environmental influences explaining the remaining variation, 65%.

A final analysis explored age group differences in genetic and environmental effects. The sample was split into young-old (65 to 79 years) and old-old (80 years and older). Polychoric correlations by age group are presented in Table 1. For each age group and gender we

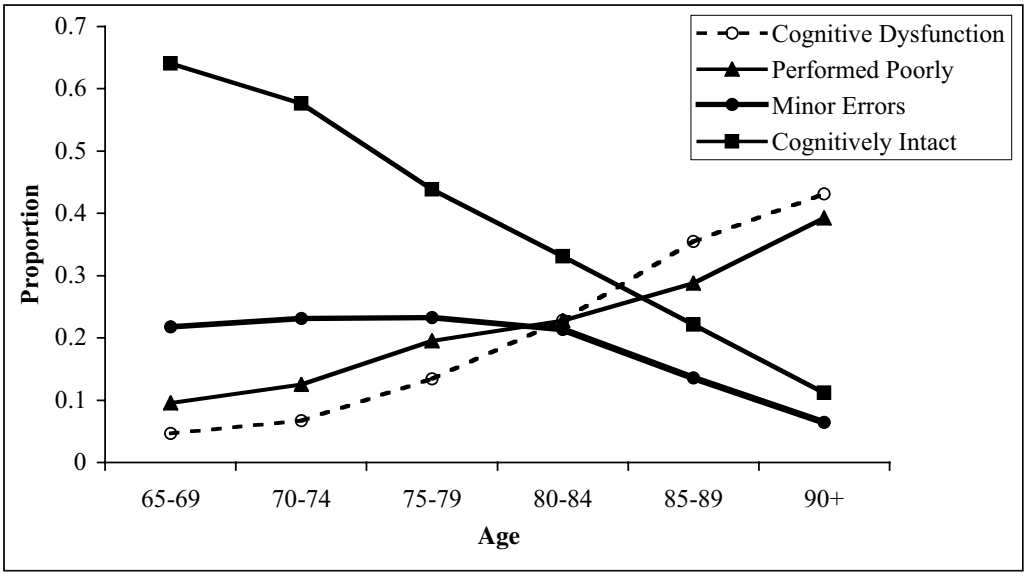

Figure 3

Phenotypic trends in cognitive dysfunction by age group.

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Table 2

Biometrical Models of Cognitive Dysfunction: Model Fit Statistics

Model	Model description	Age correction	–2ln(L)	# parameters	Compare models	$\Delta\chi^2$	*df*	*p*
1	Full, $r_g \leq .50$	Quadratic	31,224.79	17	—	—	—	
2	Full, $r_g \leq .50$	Linear	31,259.95	15	M2–M1	35.15	2	.000
3	Full, $r_g \leq .50$	None	33,126.54	13	M3–M1	1901.74	4	.000
4	$r_g = .50$	Quadratic	31,225.02	16	M4–M1	0.23	1	.891
5	m = f, $r_g = .50$	Quadratic	31,226.81	13	M5–M1	2.02	4	.363
5.1	A = 0	Quadratic	31,231.82	12	M5.1–M5	5.01	1	.025
5.2	C = 0	Quadratic	31,230.13	12	M5.2–M5	3.32	1	.068
5.3	A = C = 0	Quadratic	31,360.99	11	M5.3–M5	134.17	1	.000

Note: m = male; f = female; r_g = genetic correlation between opposite sex twin pairs; A = additive genetic influences; C = shared environmental influences.

allowed for separate estimates of heritable and environmental effects as well as linear and quadratic age effects. Full model results are presented in Table 4. Full model parameter estimates by age and gender suggest that heritability is increased by .09, or 9%, in the old-old group for men and women while shared environmental effects are generally consistent across gender and age groups. Nonshared environmental influences are smaller in the old-old group. Although these age group differences appear to be quite marked, there is little loss in fit when all biometrical parameters are constrained to be equal across young-old and old-old groups, $\Delta\chi^2(7) = 2.946$, $p > .85$.

Conclusion

Cognitive dysfunction shows some evidence of heritability (up to 35% in the best fitting model) but not as high as has been reported for diagnosed dementia, particularly Alzheimer's disease. Shared environmental effects were not significantly different from zero once age was accounted for, suggesting that genetic factors are the major contributor to familial similarity for cognitive dysfunction. Sex-limitation and sex differences in heritable or environmental influences were not significant. Given the large role of nonshared environment, the findings suggest additional research is needed to uncover individual specific environmental influences on cognitive dysfunction.

The present study included the broadest range of cognitive function by creating an ordinal scale that incorporates both twin and informant information. Full model heritability estimates differed very little from previous analyses examining quantitative TELE scores from the same population but without including proxy information (Gatz et al., 2003). However, full model heritability estimates for men in the present study were lower than the results previously reported for over 4000 male twins aged 62 to 73 participating in the NAS, again based on quantitative scores from twins only, without including informants (Brandt et al., 1993). In addition, Brandt et al. (1993) reported a relatively high contribution for shared environment, similar to our models before including age correction. However, the results for the younger part of our sample did not show higher heritability in comparison to the older part of our sample.

Our results do not support our prediction that including proxy reports would lead to higher heritability estimates for cognitive dysfunction than are typically found for mental status screening. We still found modest heritability as compared to heritability estimates for either IQ measures or dementias including

Table 3

Biometrical Models of Cognitive Dysfunction: Model Parameters

Model	Description	Age correction	Males					Females					
			a^2	c^2	e^2	β_{age}	β_{age^2}	a^2	c^2	e^2	β_{age}	β_{age^2}	r_g
1	Full, $r_g < .50$	Quadratic	.14	.13	.74	–.05	–.001	.20	.14	.66	–.04	–.003	.36
2	Full, $r_g < .50$	Linear	.14	.13	.74	–.05	(0)	.20	.15	.65	–.04	(0)	.35
3	Full, $r_g < .50$	None	.18	.21	.61	(0)	(0)	.21	.28	.51	(0)	(0)	.42
4	$r_g = .5$	Quadratic	.17	.09	.74	–.05	–.001	.21	.13	.66	–.04	–.003	(.5)
5	m = f, $r_g = .5$	Quadratic	.20	.11	.69	–.05	–.001	.20	.11	.69	–.04	–.003	(.5)
5.1	A = 0	Quadratic	(0)	.24	.76	–.05	–.001	(0)	.24	.76	–.04	–.003	(.5)
5.2	C = 0	Quadratic	.35	(0)	.65	–.05	–.001	.35	(0)	.65	–.04	–.003	(.5)

Note: m = male; f = female; a^2 = additive genetic influences; c^2 = shared environmental influences; e^2 = nonshared environmental influences. Values in parentheses are equated to value shown.

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Table 4

Biometrical Model of Cognitive Dysfunction With Age Moderation: Model Parameters by Age Group

Model description	Age group	Males					Females					
		a^2	c^2	e^2	β_{age}	β_{age^2}	a^2	c^2	e^2	β_{age}	β_{age^2}	r_g
Full, $r_g < .50$	65–79 years	.10	.14	.76	–.03	–.004	.16	.14	.70	.00	–.008	.34
	80+ years	.19	.14	.67	–.10	.005	.25	.18	.57	–.10	.003	.37

Note: m = male; f = female; a^2 = additive genetic influences; c^2 = shared environmental influences; e^2 = nonshared environmental influences. Values in parentheses are equated to value shown. The –2ln(L) fit of the model was 31,147.759 with 34 parameters estimated. A submodel constraining a^2, c^2, e^2 and r_g to be equal across age groups resulted in a –2ln(L) fit of 31,150.705 with 27 parameters.

Alzheimer's disease. The difference in heritability for Alzheimer's disease and cognitive dysfunction is etiologically plausible. Cognitive dysfunction is a condition with numerous potential causes including life style and habits and other medical conditions (e.g., psychiatric diseases, vascular diseases, metabolic disorders). Many of these causes have a limited genetic component (e.g., vascular disease). In contrast, Alzheimer's disease is a specific, well-defined anatomo-pathological disease with a clear genetic component. We do not believe that including those with lifelong low intellect can explain the findings, as the proxy interview specifically asks how changes in memory and thinking interfere with activities of daily living and those scoring '3' were confirmed as having functional impairment not present earlier in life. Future research should consider the premise that the etiological heterogeneity of phenotypes that lead to low mental status scores lead to low to moderate heritability for cognitive dysfunction. In pursuing this work, we have demonstrated the feasibility of age-adjustment for an ordinal phenotype when dealing with an age-related phenomenon.

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