



Genetic and Environmental Influences on Language Ability in Older Adults: Findings from the Older Australian Twins Study

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Abstract

We used a sub-sample from the Older Australian Twins Study to estimate the heritability of performance on three tests of language ability: Boston Naming Test (BNT), Letter/Phonemic Fluency (FAS) and Category/Semantic Fluency (CFT) Tests. After adjusting for age, sex, education, mood, and global cognition (GC), heritability estimates obtained for the three tests were 0.35, 0.59, and 0.20, respectively. Multivariate analyses showed that the genetic correlation were high for BNT and CFT (0.61), but low for BNT and FAS (0.17), and for FAS and CFT (0.28). Genetic modelling with Cholesky decomposition indicated that the covariation between the three measures could be explained by a common genetic factor. Environmental correlations between the language ability measures were low, and there were considerable specific environmental influences for each measure. Future longitudinal studies with language performance and neuroimaging data can further our understanding of genetic and environmental factors involved in the process of cognitive aging.

Keywords Genetic · Heritability · Twins · Aging · Language ability

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Introduction

Language or verbal ability is a crucial element of good communication skills, and as with most other cognitive domains, there is often an age-associated change in some aspects of language ability (LA) in late adulthood. Compared to research focused on the LA in children and adolescents, and especially research into its genetic and environmental determinants, LA in older age has received much less attention. Examination of the relative genetic and environmental contributions to LA in older age can help to understand the determinants of aging-related change in LA, which may lead to strategies to improve LA, and in turn may enhance effective communication and promote active social engagement, the latter being a facet of successful aging (Rowe and Kahn 1997). Further, examination of the relative genetic and environmental influences on LA can help to enhance our understanding of the basis of some neurodegenerative disorders.

Seven studies that examined heritability as well as the genetic and environmental contributions to verbal ability in older adults were conducted within the Swedish Adoption/Twin Study of Ageing (SATSA). The heritability estimates obtained from the SATSA were moderate to high, ranging from 0.55 (McClearn et al. 1997) to 0.79 (Finkel et al. 2005).

These studies used “Information” (a test of general knowledge), “Synonyms” (a test of word knowledge), and “Analogies” (a test of verbal reasoning ability) to index the “verbal” domain of cognitive functioning (Pedersen et al. 1992).

There are other aspects of verbal ability, such as verbal fluency and confrontation naming ability that involved lexical knowledge and lexical retrieval (Shao et al. 2014). These are sensitive to age-related cognitive decline as well as to the presence of neurodegenerative disorders such as Alzheimer’s dementia (Henry et al. 2004a). Verbal fluency, while commonly used in the clinical setting, has been relatively less examined in the context of behavioral genetics in older adults. It has often been used as a measure of executive function in research, and is considered to be associated with “fluid intelligence” (Roca et al. 2012). In twin studies of older adults, the genetic contribution to category (semantic) fluency was 37%, as reported by McGue and Christensen (2001) in the Longitudinal Study of Aging in Danish Twins (LSADT), with an average age of 80. Swan and Carmelli (2002) reported the genetic influence on letter (phonemic) fluency to be 34% in a study within the National Heart Lung Blood Institute (NHLBI), with participants’ average age 71. In an Italian twin study of older adults, with an average age of 68, the genetic contribution to verbal fluency was substantially higher than these previous studies, estimated to be 62% for letter fluency and 54% for category fluency (Giubilei et al. 2008). Findings from these twin studies have been reviewed in Lee et al. (2010).

In regard to confrontation naming, performance on this task had been shown to be strongly correlated with other aspects of verbal ability, such as reading ability, and in particular reading comprehension and reading fluency in school children (Luoni et al. 2015). The Boston Naming Test (Kaplan et al. 2001) is the most widely used test of this construct, and has been variously defined as a measure of word knowledge, word retrieval, semantic language, and verbal memory (Brouillette et al. 2011). BNT performance is significantly correlated with vocabulary, which is considered a “hold” (crystallised) test, relatively more resistant to the compromise of brain functions (Hawkins et al. 1993). In older adults, naming has been examined in studies focused on the neurocognitive functions of neurodegenerative disorders and other progressive language-associated disorders (Leyton et al. 2011). However, to our knowledge, no published study has explored the heritability or genetic influences on performance on visual confrontation naming in cognitively healthy, older adults.

While there is a substantial literature on the differences in cognitive performances between males and females, there has been very little research into sex differences in the heritability of cognitive abilities. Read et al. (2006) did not find sex differences in the heritability of cognitive abilities in the areas of “verbal”, “fluid” (intelligence), “memory”, and

“speed”. In Finkel et al.’s (2006) examination of genetic and environmental contributions to five cognitive measures, the results showed sex differences in the level of performance for all measures, but only “Synonyms” (a verbal test) showed higher heritability in males than in females. Therefore, conclusions regarding sex differences in the heritability of cognitive abilities cannot be drawn from the limited information available. Sex differences in the heritability of verbal ability, as indexed by verbal fluency and naming, have not been investigated.

The aim of the present study was to explore the genetic and environmental contributions to performance in verbal or language ability tests that are sensitive to cognitive change in normal aging, that have not been commonly examined in older adults. In the context of our current study, we will refer to the performance in the three fluency and naming tests of interest as “language ability” (LA). The specific aims were firstly, to investigate the heritability of performance on three commonly used measures of LA: the Boston Naming Test (Kaplan et al. 2001), Letter Fluency Test (Benton and Hamsher 1976), and the Category Fluency Test (Goodglass and Kaplan 1987) in a cohort of older adult twins. Secondly, we aimed to examine the genetic and environmental influences on the variation and covariation between performances on the three LA measures and their genetic and environmental relationships. Thirdly, we would attempt to explore sex differences in the heritability of performances in these LA measures, to complement the limited research in this aspect of cognitive functioning.

Methods

Participants

Methodology of the Older Australian Twins Study (OATS) was previously described in detail in Sachdev et al. (2009). Briefly, participants aged 65 and above were recruited from the Australian Twin Registry, as well as through advertisements, media, and citizens’ networks. They were residents of the three Eastern states of Australia: New South Wales, Victoria, and Queensland. The inclusion criteria were: ability to consent to participate, having a co-twin who also consented to participate in the study, having completed some education in English, having at least low average intelligence (estimated $IQ \geq 80$), and a Mini-Mental Status Examination (Folstein et al. 1975) score of ≥ 24 . Exclusion criteria included life-threatening illness, acute psychosis, or inadequate English to complete the assessments.

There were 623 participants in Wave 1 (baseline) assessment. When the individual twins (without co-twins) and siblings were excluded, the present study sample comprised 506 individuals (253 complete twin pairs), 142 monozygotic

(MZ) twin pairs and 111 dizygotic (DZ) twin pairs. Table 1 shows the sample demographics. The average age was 70 (range 65–88), average years of education was 11 years (range 6–21 years) and the estimated mean IQ was 106 (range 77–128). Two participants with estimated IQ scores below 80 (77 and 79) were included in the present sample, as their performances on cognitive testing were generally within normal limits. There was an over-representation of female participants, with an approximate ratio of 2:1. There were three pairs of twins who were born overseas, all of whom had nominated English as their first language and were able to participate in the language-based assessments in OATS.

The current study sample was larger than the OATS samples in our two previous studies on the genetic and environmental influences on processing speed and executive functions, with sample sizes of 477 individuals [218 complete pairs, plus 41 individual twins, (Lee et al. 2012a)] and 472 participants [215 twin pairs and 42 individuals (Lee et al. 2012b)], respectively. All data and information across the three studies were drawn from the baseline phase of OATS.

Measures

Participants were administered a comprehensive battery of cognitive tests, which in addition to a measure of overall estimated IQ (NART, Nelson and Willison 1991), included tests that tap into the following specific cognitive domains: attention/concentration, verbal memory, visual memory, verbal/language ability, visuo-spatial ability, executive function, and processing speed. Three measures of LA, a global measure of baseline cognitive performance, and a measure of mood state were of interest in the present study:

1. Boston Naming Test (BNT, Kaplan et al. 2001)—this is a short-form of a test of visual confrontation naming. Participants were to name 30 pictures of line-drawings

of everyday objects. The number of correct items spontaneously named or named after semantic cueing was the score. The test–retest reliability of this 30-item version of BNT has been reported to be 0.90 (Dong et al. 2013).

2. Controlled Oral Word Association Test (COWAT, Benton and Hamsher 1976)—this test is also referred to as letter fluency test, phonological verbal fluency test, and phonemic fluency test. Participants were required to generate three word-lists, according to three designated letters (F, A, and S), 1 min for each letter, while abiding by the rules (no proper nouns, no numbers, and no derivative from words already given). This test is referred to as “FAS” from here onwards. The total number of words generated for the three letters (minus errors and repetitions) was the dependent measure.
3. Category Fluency Test (CFT, Goodglass and Kaplan 1987)—this test is also known as semantic fluency test. Participants were asked to name as many “animals” as they could within 1 min. The total number of animals named within the time limit was the score. The test–retest reliability for both the COWAT and CFT in an older adult sample has been estimated to be 0.70 (Harrison et al. 2000).
4. Global Cognition (GC)—This was created by combining the cognitive domain scores, formed as the average of the z-scores of the tests comprising each of the cognitive domains (attention/concentration, verbal memory, visual memory, visuo-spatial ability, executive function, and processing speed). As in our previous studies that examined the genetic and environmental influences in processing speed and executive functions (Lee et al. 2012a, b), the tests that form the cognitive domain being examined (LA in the current study) were not included in forming this composite measure.
5. Geriatric Depression Scale (GDS, Yesavage 1988)—a 15-item short version of the GDS was administered

Table 1 Characteristics of OATS participants at baseline assessment

	Total (n = 506)	MZ (n = 284)	DZ (n = 222)	<i>p</i>
Age (SD)	70.7 (5.5)	70.6 (5.6)	70.83 (5.35)	0.68
Sex: female (%)	328 (64.8%)	178 (62.68%)	150 (67.57%)	0.23
Education (years, SD)	11.17 (3.37)	10.99 (3.36)	11.39 (3.37)	0.20
Mood score ^a	1.79 (2.10)	1.68 (1.93)	1.89 (2.27)	0.27
GC	−0.002 (0.99)	0.02 (0.96)	−0.02 (0.99)	0.85
BNT	26.27 (3.32)	26.50 (3.22)	25.98 (3.42)	0.08
FAS	37.83 (12.25)	38.00 (11.98)	37.62 (12.62)	0.73
CFT	17.77 (5.07)	17.89 (5.14)	17.61 (4.99)	0.54

Means and standard deviations of GC, BNT, FAS, and CFT, and mood (GDS) score

MZ monozygotic, *DZ* dizygotic, *GC* global cognition (z-scores) *BNT* Boston Naming Test, *FAS* Letter Fluency Test, *CFT* Category Fluency Test (all raw scores), *SD* standard deviation

^aGeriatric Depression Scale score

to provide an index of mood state. A score of 5/15 or greater would be suggestive of depression.

Statistical analyses

Since the data for some of the variables were skewed, all variables were inverse normal transformed prior to analyses. T-tests for continuous variables for all other measures were used to compare means between MZ and DZ pairs. Equality of proportions of females between the two groups was compared using the Chi square test. All p-values were obtained using a permutation procedure with $N = 10,000$ (Fornito et al. 2011).

Five covariates were used in the analyses for heritability estimates as well as in multivariate genetic modelling. Age was included as a covariate because it is a recognised factor influencing most aspects of cognition (e.g. Glisky 2007). As one of our aims was to explore sex difference in the heritability of LA, sex was included as a covariate. As an individual's educational attainment can impact on their cognitive performance (e.g. de Azeredo Passos et al. 2015), hence it was included as a covariate. As a low mood can potentially impact on verbal production and fluency (e.g. Henry and Crawford 2005), the GDS score was also included as a covariate. Global Cognition was also used as one of the covariates in some of the analyses. We have only used main effects for these covariates and no interaction terms were used in genetic modelling.

The classic twin design was used to estimate the genetic and environmental contributions to the covariation between the variables. As MZ twins are 100% genetically concordant, and DZ twins only share 50% of their genes on average, this design allows for the proportioning of variance into additive genetics ("A") and environmental influences. The latter would either be "shared" between the twin pairs ("C") or unique to one twin of the pair ("E", and includes measurement error). If an MZ twin correlation is greater than the corresponding DZ twin correlation, "A" influence is suggested. If DZ correlation is more than half the MZ correlation, a "C" (shared environmental) effect is indicated.

Structural equation modelling (SEM, Neale and Cardon 1992) was used to estimate the heritability and genetic correlations. Twin SEM was conducted with different models fitted to the data using the full information maximum likelihood estimation in OpenMx (2.0.1) R package (Boker et al. 2011), making use of paired twins only. In the univariate analysis, a full Cholesky ACE model was fitted first and subsequently AE, CE and E models were fitted and compared with the Cholesky ACE model.

In a post-hoc analysis, we also examined the genetic parameters between male and female samples, using a heterogeneity model. Different set of parameters for the likelihood functions for male, female and opposite sex pairs

were considered under this model. The test of homogeneity between male and female samples was examined using the likelihood ratio test, comparing the heterogeneity model against the homogeneity model with the same set of parameters for both genders. Further, to examine heritability as a function of age, the gene-environment interaction model (Purcell 2002) was fitted. In this model, age effect is incorporated in to the A, C and E path coefficients.

The genetic and environmental correlations among the three LA tests were examined using multivariate SEM. We began with the full Cholesky ACE (CholACE) model, followed by independent pathway (IP) and common pathways (CP) models. For the Cholesky, IP and CP models, we have also considered the model without the C component (AE model). The Akaike's Information Criterion (AIC, Akaike 1987) and the p values from the $-2LL$ (minus two times log-likelihood) statistics were compared between nested models and the full model to assess model parsimony.

Results

Sample characteristics

As can be seen in Table 1, there were no significant differences between the MZ and DZ twins in their average age, years of education, proportion of females, or their mood status (all p values were > 0.05). Means and standard deviations of the participants' performance on the three LA variables BNT, FAS, CFT and their GC scores are also shown here. There were no significant differences between the MZ and DZ twins on any of the measures of LA, or on their global cognitive functioning (GC).

Heritability estimates

Table 2 shows the heritability estimates and intraclass correlations under the univariate ACE model. The heritability estimate was high for FAS (0.59), moderate for BNT (0.35) and low for CFT (0.20). Education and GC were significantly associated with performance on all measures. GDS (mood) was not associated with any of the LA measures. Age was significantly associated with CFT and sex was significantly associated with BNT (Supplementary Table 1). Contributions from all the shared environment components were very small, and hence the AE model was found to be the parsimonious model. Education and GC had a significant impact on the heritability of all the LA measures, as the heritability estimates without these covariates were higher than the estimates with these covariates (Supplementary Table 2). Specifically, GC and education had a large impact on the heritability of CFT, as the estimate was doubled without

Table 2 Intraclass twin correlations (ICC) for MZ and DZ twins, heritability estimates, and model summary

	ICC MZ (95% CI)	ICC DZ (95% CI)	A (95% CI)	C (95% CI)	E (95% CI)	P-AE	P-CE	P-E	Sig. of covariate
GC	0.69 (0.60, 0.76)	0.38 (0.30, 0.53)	0.61 (0.29, 0.76)	0.07 (0.00, 0.37)	0.31 (0.24, 0.40)	0.69	8.59E-05	0	1,1,1,1,NA
BNT	0.35 (0.20, 0.48)	0.17 (0.10, 0.24)	0.35 (0.02, 0.47)	0.00 (0.00, 0.26)	0.65 (0.53, 0.79)	1	0.039	2.34E-05	0,1,1,0,1
FAS	0.59 (0.48, 0.68)	0.30 (0.24, 0.39)	0.59 (0.36, 0.68)	0.00 (0.00, 0.24)	0.40 (0.32, 0.52)	1	6.48E-05	5.00E-15	0,0,1,0,1
CFT	0.20 (0.04, 0.35)	0.10 (0.02, 0.24)	0.20 (0.00, 0.35)	0.00 (0.00, 0.24)	0.80 (0.65, 0.96)	1	0.30	0.05	1,0,1,0,1

ICC MZ intraclass correlations monozygotic twins, ICC DZ intraclass correlations dizygotic twins, GC global cognition, BNT Boston Naming Test, FAS Letter Fluency Test, CFT Category Fluency Test. A (heritability), C (shared environment), and E (unique environment), standardised variance components obtained using the ACE model. P-AE, P-CE and P-E denote p values from likelihood ratio test comparing ACE model versus AE, CE and E models, respectively. P-CE also represent p value for heritability (testing of component A=0 is equivalent to testing heritability of zero). Sig of Covariate significance of covariate at p<0.05 for age, sex, education, mood, Global Cognition, respectively, indicated as string: 1=significant; 0=not significant and NA=not applicable

these covariates. The heritability of GC, adjusted for age, sex, education and GDS, was also found to be high (0.70).

In order to investigate the possibility that FAS had a much higher heritability than CFT was due to the former being a total score of three 1-min tests, while the latter is the score of a 1-min test, the scores for the three letters were analysed individually. Overall, the heritability estimates for F (0.46), A (0.43), and S (0.43) individually were lower than the heritability of FAS total (0.59), though these remained more than twice as high as CFT (0.20), as shown in Supplementary Table 3.

Sex heterogeneity and age moderation

A sex heterogeneity model was fitted to contrast the difference in heritability estimates between the male and female samples, with age, education, mood and GC entered as covariates. As shown in Table 3, the heritability estimates were generally higher in women for all LA variables. Except for BNT (p value: 0.03), the test of homogeneity of parameters between male and female samples indicated that the heritability estimates between the two groups were similar (p value > 0.05). Though the test for homogeneity of parameters between pooled samples against separate estimates in male and female samples was rejected for BNT, there was

a considerable overlap between the confidence intervals for heritability in both samples.

Across the age range of 65–85 years (the approximate age range in our data), the variation of heritability of the LA measures was examined using the age moderation model. The heritability of LA measures as a function of age were plotted in Fig. 1. Heritability of FAS increased with age and approached 75% at 85 years. Although there was a moderate increasing trend for CFT and decreasing trend for BNT across the age range, the heritability of both of these measures were approximately 27% at 85 years.

Multivariate modelling

The phenotypic correlation matrix, derived from the full saturated model, between traits and between twins is shown in Supplementary Table 4. The correlations of FAS with BNT and CFT were similar, and the correlation between BNT and CFT was slightly higher than their correlations with FAS. GC had high correlations (>0.5) with the LA measures, with the highest correlation observed with CFT.

In order to obtain the genetic correlations among the three LA measures, the saturated Cholesky model, followed by IP and CP models were considered. The model fit comparisons with the Cholesky ACE model and the other models are summarised in Table 4. Comparisons of the AIC and

Table 3 Heritability estimates under the sex heterogeneity model

	Female ICC MZ (95% CI)	Female ICC DZ (95% CI)	Male ICC MZ (95% CI)	Male ICC DZ (95% CI)	Male–female ICC DZ (95% CI)	Female h ² (95% CI)	Male h ² (95% CI)	P
BNT	0.39 (0.21, 0.53)	0.19 (0.11, 0.40)	0.33 (0.08, 0.53)	0.23 (0.05, 0.47)	−0.02 (−0.35, 0.31)	0.38 (0.00, 0.53)	0.19 (0.00, 0.53)	0.03
FAS	0.67 (0.54, 0.77)	0.34 (0.27, 0.43)	0.48 (0.27, 0.64)	0.24 (0.14, 0.51)	0.22 (0.03, 0.31)	0.67 (0.45, 0.77)	0.48 (0.00, 0.64)	0.50
CFT	0.33 (0.12, 0.50)	0.17 (0.06, 0.30)	0.06 (0.00, 0.29)	0.06 (0.00, 0.29)	0.02 (−0.10, 0.13)	0.33 (0.00, 0.50)	0.01 (0.00, 0.26)	0.36

ICC Intra-class correlations and h² heritability for male and female, BNT Boston Naming Test, FAS Letter Fluency Test, CFT Category Fluency Test, obtained using heterogeneity ACE model. P=p value from likelihood ratio test of homogeneity, common variances and co-variances versus separate parameters for males and females. Covariates: age, education, mood, global cognition

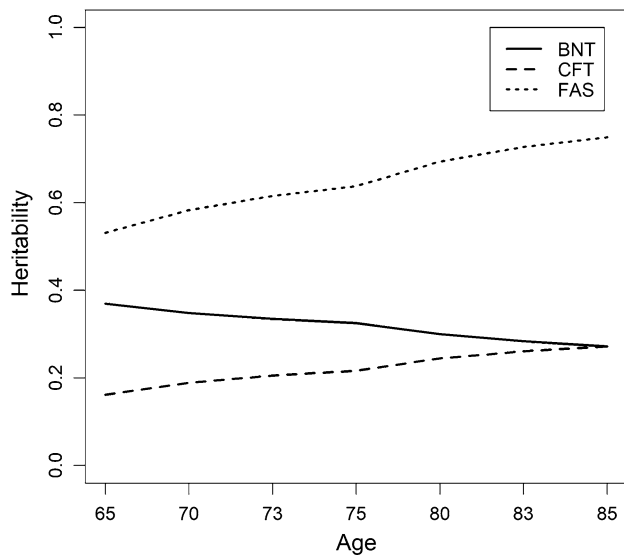


Fig. 1 Estimated age-associated change in heritability based on gene by age interaction univariate ACE model

p values for model parsimony showed that the common pathway models without the shared environment components provided the best fit for the data. The estimated path coefficients from one latent factor common pathway model (ComAE) are represented in Fig. 2.

Table 5 shows the phenotypic, genetic, and environmental correlations, using one latent factor common pathway model (ComAE). The genetic correlations amongst the LA variables were low for FAS and CFT (0.28) and for FAS and BNT (0.17). High genetic correlation was found for BNT and CFT (0.61). The environmental correlations amongst the three LA measures were all low, ranging from 0.10 to 0.16.

The heritability (additive genetic variance) of the latent factor was 0.60 and the environment variance is 0.40. The proportion of variance accounted for by the additive latent

factor for BNT, FAS and CFT to the total additive variance respectively are 38, 8 and 100%. Total additive genetic variance for CFT was explained by the latent genetic factor and there was no specific genetic variance for the CFT. The proportion of variance explained by the additive genetic variance (heritability) for the three tests were 35, 59 and 21% respectively, consistent with the heritability estimates from the univariate heritability analysis.

In a separate analysis, to examine the extent of genetic and environmental correlations of GC with the three LA variables, we fitted a four variable Cholesky ACE model adjusted for age, sex, education and mood score, followed by the AE model. Under the Cholesky AE model, the genetic correlation of GC with BNT, CFT and FAS respectively were 0.62, 0.70, 0.44 and the corresponding environmental correlations were 0.19, 0.14 and 0.16.

Discussion

The primary aim of the present study was to examine the heritability of verbal performances in three commonly used LA tests in a community sample of older adults. We also aimed to explore the variation and covariation amongst performances on these LA tests and their relationships with each other. In addition, we explored the possibility of sex differences in the heritability of performances on these LA tests. A summary of our findings is displayed in Table 6.

Of the three LA tests, heritability was found to be highest for the phonemic fluency test (FAS), estimated to be 59%. This estimate can be considered similar to Giubilei et al.'s (2008) study, but much higher than the estimate reported in the all men NHLBI study (Swan and Carmelli 2002). Discrepancies between different studies could partly be explained by sex differences, as there is a trend for in the heritability estimates in our study to be higher for women for

Table 4 Model fitting results for all variables, in the order of BNT, FAS, and CFT

Comparison with Cholesky ACE model	−2LL	df	AIC	Δ −2LL	Δdf	<i>p</i>
CholACE	3843.69	1482	879.69			
CholAE	3843.71	1488	867.71	0.02	6	1
IndACE	3843.72	1482	879.72	0.04	0	0
IndAE	3843.74	1488	867.74	0.05	6	0.9999
IndA	3851.87	1491	869.87	8.18	9	0.5163
ComACE	3844	1485	874	0.31	3	0.9579
ComLcAE	3844	1488	868	0.31	6	0.9994
ComAE	3844	1489	866	0.31	7	0.9998

−2LL −2 log likelihood, Δ −2LL difference in −2LL when compared to the Cholesky ACE model, AIC Akaike Information Criteria—used for model parsimony, CholACE and CholAE Cholesky ACE and AE models, IndACE and IndAE Independent pathway ACE and AE models, ComACE and ComAE Common pathway ACE and AE models, ComLcAE Common pathway model with A, C, E common latent factors and A and E specific factors. Best fitting model in bold

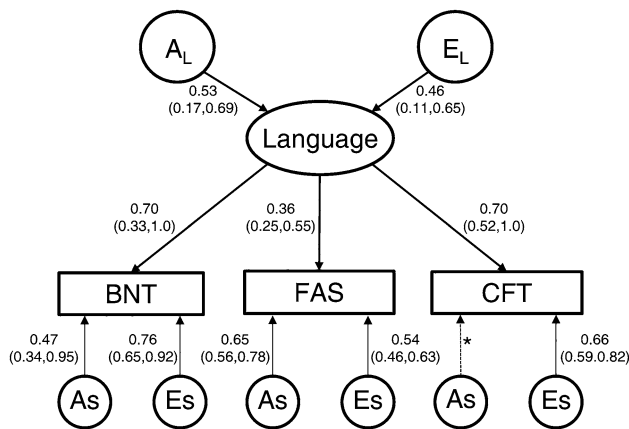


Fig. 2 Best fitting one factor common pathway model showing genetic and environmental influences on BNT, FAS and CFT. A: common genetic factor; A_s : specific genetic influence; E: common environmental factor; E_s : specific environmental influence. Non-significant pathway is shown in dashed line

all LA tasks. The heritability estimate for category fluency (CFT) was 20% in the present study, substantially lower than that of Giubilei et al.’s (2008) study but closer to that of the LSADT study (McGue and Christensen 2001). The present study was the first to investigate heritability of confrontation naming (BNT), where a moderate heritability estimate of 35% was found.

While it may not be appropriate to make a direct comparison of the heritability estimates of our findings with those

of the SATSA, it is interesting to note the greater (55–79%) genetic influences on their verbal tests (of general knowledge, word knowledge and verbal abstract reasoning) and the lower heritability (20–59%) found in our language test of fluency and naming, when fluency and naming also involved word knowledge and semantic memory. This could be further investigated in the context of “crystallised” intelligence and “fluid” intelligence, given that some of the tests used in the SATSA to represent verbal ability are considered to be associated with the former, and the language tests in our study are more representative of the latter.

Our findings on the heritability of LA performance complement two previous publications from OATS, which reported on the heritability of measures of processing speed (Lee et al. 2012a) and executive functions (Lee et al. 2012b). Comparing the heritability estimates of 35–62% for measures of speed and 29–63% for measures of executive functions, the heritability estimates of LA (20–59%) appear to be within a similar range. It should be noted that the same measure of verbal fluency (FAS) had been used in both our executive functions and the current LA studies, and their heritability estimates are similar at 62 and 59% respectively. It has been suggested that the verbal letter fluency test is a multifactorial measure of cognitive functioning. It has often been used as a measure of fronto-executive functions (Lezak et al. 2012) and letter fluency (such as FAS) has been associated with focal frontal cortical lesions (Henry and Crawford 2004). However, it has also been reported that performance in verbal fluency test is correlated with

Table 5 Phenotypic, genetic, and environmental correlations of BNT, FAS, and CFT

	BNT	FAS	CFT
Phenotypic			
BNT		0.13 (0.05, 0.20)	0.28 (0.20, 0.37)
FAS			0.17 (0.08, 0.27)
Genetic			
BNT		0.17 (0.01, 0.30)	0.61 (0.23, 0.97)
FAS	Environmental	0.10 (0.00, 0.18)	0.28 (0.10, 0.47)
CFT		0.16 (0.02, 0.27)	0.12 (0.01, 0.21)

Phenotypic correlations are presented first. Genetic correlations (above diagonal) and Environmental correlations (below diagonal), with 95% confidence intervals in parentheses. All estimates are obtained using common factor model with single common genetic and environment components from Fig. 2

Table 6 Summary of findings

- Heritability estimates varied among three measures of language ability (LA): FAS highly heritable (0.59), BNT moderately (0.35), and CFT least heritable (0.20). Level of education and GC had significant influences on LA performances
- Age moderation model showed heritability of FAS increased with age to 75%, whereas heritability of BNT and CFT showed a mixed trend to converge at 27% at 85. There was suggestive evidence that heritability estimates were higher for LA among women
- A latent factor (AE) model best explained the genetic and environmental correlations among the LA measures. There were little genetic correlation between FAS and the two other LA measures. BNT and CFT had relatively lower heritability estimates, but shared a higher genetic correlation

other cognitive measures such as word knowledge, auditory attention span, and memory (Ruff et al. 1997). Henry et al. (2004) have noted a language component in this task, and more recently, Whiteside et al. (2016) examined the main cognitive structure underlying two verbal fluency tests, and found that letter fluency (FAS) and category fluency (CFT) both loaded completely onto the “language” factor and not the “executive functioning” factor.

As the heritability estimates were 59, 35, and 20% for FAS, BNT, and CFT respectively, 41, 65 and 80% respectively of the variance in the performance in these three LA tests can be attributed to a combination of environmental factors and measurement error. Some potential environmental factors influencing performance in the LA measures were suggested in a discordant MZ co-twin study of this cohort (Lee et al. 2014). Specifically, greater participation in cognitive activities and better odour identification ability were associated with better performance in the LA tests, whereas poorer performance was associated with higher body mass index. It should be emphasized that these environmental factors have been identified from discordant MZ twin pairs, and there are also genetic influences in odor identification (Finkel et al. 2001), participation in cognitive activities (Lykken et al. 1993) and body mass index (Pérusse et al. 2000). In our study, the environmental correlations between the three LA measures were very low, suggesting that there is little shared environmental influence between the performances on these tests.

The phenotypic correlations between the three LA measures are low to moderately low (0.13–0.28). These may partly be explained by the fact that performance in these tasks involved different brain regions. Letter fluency (FAS) has reportedly been associated with activation in the frontal structures (Abrahams et al. 2003), and specifically for strategic word retrieval (Baldo et al. 2006). However, in the latter study of lesion symptom mapping, the temporal cortex was found to be involved in category fluency (CFT) when retrieval of words was restricted by semantics. Consistent with this view, in their meta-analysis which focused on the pattern of impairment observed following focal lesions, Henry and Crawford (2004b) argued that category fluency may impose greater demands on temporal neural substrates than letter fluency. As for confrontation picture naming (BNT), when substantial demands are placed on semantic memory and semantic knowledge, areas of the temporo-occipital cortices and the inferior frontal gyrus appear to be particularly activated (Abrahams et al. 2003). However, in a more recent study of older adults (in another cohort within our Centre), which examined cerebral gray matter correlates of the same three LA measures in our study, found that either unilateral or bilateral frontal and temporal lobes volumes were associated with performance in these three tests (Zhang et al. 2013).

The genetic correlations between the three LA measures were low to moderately low for FAS and BNT (0.17) and for CFT and FAS (0.28), but moderately high for BNT and CFT (0.61). These findings on genetic correlations, together with the results of genetic modelling, which demonstrated that one common factor could explain the covariation between performances in these three tasks, suggest that performance on these tests share the same genes or the same set of genes. In addition, under this one common factor model, there is relatively less genetic influence to the performance in CFT and BNT, with less than half of their genetic variance (none in CFT and 22% in BNT) due to genetic influence specific to itself. In contrast, for the performance on FAS, approximately half of the genetic influence was specific to itself. This disparity of high and low genetic correlations between performance on the three tests could be due to the fact that performance on both the BNT and CFT involves “semantics”, which is subserved by temporal lobe structures, and FAS is relatively more associated with frontal lobe structures, as discussed above. In addition, there appears to be relatively lower heritability for CFT and BNT, and their heritability is primarily shared through the common latent language factor. The influence of the latent language factor on FAS is comparatively low. Therefore, it would seem that performance on these three tests might have different underlying brain structures or brain networks, with BNT and CFT showing greater overlap.

One of our aims was to explore the possible effect of sex difference on the heritability of LA in older adults. A sex heterogeneity model (with age, education, mood and GC as covariates) demonstrated a trend for greater heritability estimates for women than men for all the three verbal measures, with the sex difference significant for confrontation naming (BNT: 0.19 and 0.38, for men and women respectively). If the present results are shown to be robust, the finding of sex difference in the genetic influence in language performance would have practical implications for maintaining cognitive health in older age. For instance, some intervention strategies for enhancing LA may provide more benefit for men, as there is relatively less genetic influence on LA for men than women. Nevertheless, the differences in the heritability estimates in women and men in FAS and CFT were not significant, and should only be regarded as a trend. Also, our sample has a high proportion of female and therefore, a larger sample in an independent cohort would be necessary to definitively address the question of sex difference.

Performances in CFT and BNT were shown to have large environmental contributions, at 80 and 65%, respectively (including measurement error). Level of education was a significant factor in the performance in these two tasks in our study, and higher education has been considered a factor associated with verbal fluency tasks in several studies (e.g. Tombaugh et al. 1999). As mentioned

above, we have previously reported that odor identification ability, participation in cognitive activities, and body mass index are associated with language ability (Lee et al. 2014). In a study of cognitively intact older adults, social isolation and self-reported feelings of loneliness were found to be associated with greater cortical amyloid burden, an indicator of pre-clinical Alzheimer's disease (Donovan et al. 2016). Further exploration of the mechanisms underlying these associations and other environmental factors in older age could be informative. In particular, these could be translated into interventions to improve or optimise verbal communication through amelioration of word-finding difficulty as detected in performances in the LA tests, thereby promoting social engagement and interaction, contributors to successful aging.

Our analysis using the age moderation model revealed an increase in heritability of FAS and a trend for increasing heritability of CFT with age, whereas the heritability for BNT decreases with age. These findings do not support the observation that there is a trend for heritability of cognitive functions to decrease with age in cross-sectional samples in a selective review of genetic influence on cognitive functions in older twins (Lee et al. 2010). Our findings are also incongruent with expectations from a meta-analysis of cognition across the lifespan with longitudinal twin and adoption studies (Tucker-Drob and Briley 2014), which found that genetic stability of cognition to be very low in very early life but markedly increases in childhood, with their exponential model suggesting ultimately “nearly perfect” longitudinal stability from early adulthood to beyond age of 80. Nonetheless, the heritability of CFT and BNT, both approximating 27% at age 85, is consistent with the heritability of verbal ability (as measured with other verbal tests) reported in the meta-analytic studies in Reynolds and Finkel (2015).

Findings from this study have implications for exploring genetic influences in neurodegenerative disorders. Language difficulties, such as in word-finding, impaired naming ability, and loss of semantic knowledge or memory, have commonly been reported in a clinical setting. These are also prominent features in language-associated neurodegenerative disorders, such as variants of Primary Progressive Aphasia in Fronto-temporal dementia, as well as Alzheimer's disease. Our findings can be informative for gene discovery, in that performances in CFT and BNT are likely to share many of the same genes or the same set of genes. Performance in these LA measures can potentially be useful endophenotypes for language-associated neurodegenerative disorders, mediating between genotype and phenotype (cerebral changes). This is especially so given that it has long been recognised that clinical manifestations of cognitive decline can precede dementia, such as due to Alzheimer's disease, by several years (Amieva et al. 2005).

It is important to acknowledge the cross-sectional nature of this study, which limits interpretation of findings in relation to causality. Future longitudinal studies are therefore needed, as these would prove informative on the possible change in genetic influence along the trajectory of cognitive aging. The fact that the fluency and naming ability examined in this study represent only some facets of language and verbal ability, limits the generalizability of our findings to other aspects of verbal ability. If there were more measures, such as vocabulary and verbal abstract reasoning ability included in this study, it is possible that more than one genetic factor would be found. It is also possible that FAS and GC, and FAS and executive functions may share some genetic variation, although we have not attempted to separate the sources of genetic variation from these factors. Future investigations with genetic modelling on performance on the three LA tests and their neuroanatomical correlates (frontal and temporal lobe structures) in this cohort of OATS would further our understanding of the relationship between genetics, brain function, and brain structure. Further exploration into sex differences in LA with a larger sample would help to clarify the difference in heritability of verbal, language functions between sexes.

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Compliance with ethical standards

Conflict of interest T. Lee, A. Thalamuthu, J. D. Henry, J. N. Trollor, D. Ames, M. J. Wright, P. S. Sachdev and OATS Research Team declare that they have no conflict of interest.

Ethical approval All procedures/assessments performed in this study involving human participants were in accordance with, and approved by the Human Research Ethics Committee (HC No. 12599) of the University of New South Wales, Australia.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Informed consent Informed consent was obtained from all individual participants included in the Older Australian Twins Study.

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