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Research

Cognitive functioning in older twins: The Older Australian Twins Study

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Aim: *To examine the concordance rates of common medical conditions and neurocognitive performance in monozygotic (MZ) and dizygotic (DZ) older twins.*
Methods: *Twins aged ≥65 years and living in the three Eastern states of Australia were recruited through the Australian Twin Registry and underwent detailed neuropsychological and medical assessment.*
Results: *Assessments were conducted on 113 MZ and 96 DZ twin pairs, with a mean age of 70.5 years. MZ twins were more concordant than DZ twins for hypertension and asthma. MZ twins had higher correlations than DZ twins on most neuropsychological tests, with the exception of some tests related to processing speed. The concordance rate for mild cognitive impairment or dementia was 76.2% in MZ twins and 42.9% in DZ twins, a non-significant difference.*
Conclusions: *Except for some aspects of processing speed, most cognitive functions in older individuals show significant heritability. The heritability of neurocognitive disorders is, however, low.*

Key words: *ageing, brain, cognitive function, mild cognitive impairment, twin.*

Introduction

The ageing of the population has resulted in a major focus on cognitive functioning in older people. Not only does the prevalence of cognitive disorders see an exponential increase in the older age group, but normal ageing is also associated with changes in general cognitive abilities as well as in specific cognitive domains [1]. It is therefore important to examine the potential determinants of these age-related changes. Genetic and environmental factors have been suggested to be important, and the classical method of determining the relative contributions of the two is the study of twins. As identical or monozygotic (MZ) twins have all their genes in common, any difference between members of a pair would arguably be due to environmental differences. As fraternal or dizygotic (DZ) twins share only half of their genes, the importance of genetic effects can be estimated by comparing the similarity of identical and fraternal twins. The extent to which MZ twins are different provides an estimate of the importance of non-shared environment, which represents those environmental factors that are specific to the individual and cause differences in pairs of individuals [2].

Some interesting insights have emanated from the studies of older twins in relation to cognitive functioning. The concordance of Alzheimer's disease in MZ twins was estimated to be 40–60% in a review of different studies [3], about twice that seen in DZ twins. A more recent study, however, did not find any concordance in cognitive impairment in 32 MZ and 18 DZ female twin pairs aged 65–86 years (mean 70.2 ± 4.6 years), suggesting the importance of environmental factors [4]. Several twin studies of various age groups have examined the heritability for the general cognitive factor *g*. This genetic influence has been shown to increase linearly with age, from 20% in infancy to 40% in childhood, and to 60% in adulthood in one study [5]. In another study, increases from approximately 30% in very young childhood to as much as 80% in adulthood were reported [6]. Plomin and colleagues

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[7] stated that the average twin correlation of cognitive abilities of various age groups was 0.86 for MZ twins and 0.60 for DZ twins. The overall heritability of *g* was estimated to be 52%, and about half of the non-genetic variance for *g* was accounted for by shared environmental factors. With regards to specific cognitive abilities, it has been suggested that the more a test or measure correlates with *g*, the higher the heritability [8]. Data from Swedish twin studies [2] suggest that there is a decrease in genetic influence in the oldest old (mean age 83 years). Deary et al. [6] on the other hand, cited studies that showed heritability of *g* increases with age. The data about the heritability of cognitive function and cognitive disorders in old age therefore remain inconsistent.

The Older Australian Twins Study (OATS) was established in 2007 to investigate genetic and environmental factors in healthy brain ageing as well as age-related cognitive disorders. A cohort of twins aged ≥65 years, with both twins alive, willing to participate, and living in the three Eastern states of Australia, has been examined for their physical health status, neuropsychiatric health, neuropsychological functioning, brain imaging, genetics and proteomics. This is a preliminary report of the concordance of cognitive functioning and cognitive disorders in MZ and DZ twins.

Methods

Sample

Twins were recruited through the Australian Twin Registry as well as by a new recruitment drive by the authors. The inclusion criteria were age 65 years and older, residence in New South Wales, Victoria or Queensland, ability to consent, having a consenting co-twin, and having completed some education in English to be able to complete the questionnaires and neuropsychological testing in English. The exclusion criteria included: current diagnosis of malignancy or other life-threatening medical illness, intellectual handicap, and a current diagnosis of an acute psychotic disorder. The study was approved by the ethics committees of the Australian Twin Registry, University of New South Wales, University of Melbourne, Queensland Institute of Medical Research and the South Eastern Sydney & Illawarra Area Health Service.

Research design

Participants receive a comprehensive assessment at baseline (wave 1) and a follow-up every 2 years with targeted measures as described below. Only wave 1 data are being reported in this paper. Assessment protocols were standardised across the centres, with uniform training of research staff in the lead centre. Detailed methodology of the study has been published [9].

Assessment

The following areas are included:

Clinical: Sociodemographic data, medical and psychiatric history, detailed family history questionnaire, risk factors schedule, standard medical examination and a psychiatric assessment, including questionnaires for depression and anxiety. Data are entered directly onto a tablet personal computer, using a Microsoft Access database.

Neuropsychological: A self-report subjective cognitive complaints questionnaire, and a comprehensive assessment using a computerised battery as well as paper and pencil tests: Estimated premorbid intellectual functioning (from the National Adult Reading Test (NART)) [10]; Attention: Mental Control and Digit Span from the Wechsler Memory Scale – Revised (WMS-R) [11]; Memory: Logical Memory I from the WMS-R [11], Rey Auditory Verbal Learning Test (RAVLT) [12], Benton Visual Retention Test [13], Picture location test (computerised, developed in-house); Visuospatial function: Block Design from Wechsler Adult Intelligence Scale (Revised) (WAIS-R) [14], copying simple designs; Language: an Australian adaptation of the Boston Naming Test (two items were replaced: acorn and beaver with gum nut and platypus, respectively) [15]; Executive function: Controlled Oral Word Association Test – phonemic/semantic (COWAT and Category) [16], Trail Making Test B [17], computerised Stroop test (adapted from Delis et al. [18]); Speed of Information Processing (Digit Symbol from WAIS-R) [14], Trail Making Test A [17], simple and complex reaction time (computerised test battery), fine motor skills from the Expanded Halstead-Reitan Battery (Grooved Pegboard) [19], Mini-Mental State Examination [20] and General Practitioner assessment of Cognition (GPCOG) [21].

Informant interview: Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) [22], confirmation of vascular risk factors (hypertension, history of dyslipidaemia, atrial fibrillation, smoking, obesity, diabetes) and previous hormone replacement therapy use; Change in Cognition with Age Questionnaire (CICAQ), Clinical Dementia Rating Scale (CDR) informant section [23], Bayer activities of daily living (B-ADL) scale [24], and Neuropsychiatric Inventory (NPI) [25].

Consensus diagnosis of mild cognitive impairment and dementia

Individuals who met the following criteria were brought to a case conference to decide on a diagnosis: a score of at least 1.5 standard deviations below published normative data on a memory and a non-memory measure, or on two non-memory measures, or reduced neuropsychological scores and a decline in activities of daily living based on an informant interview. Consensus diagnoses were made by an expert team comprising neuropsychiatrists and neuropsychologists on the basis of the available clinical, neuropsychological, laboratorial and imaging data. If a participant met the criteria for diagnosis of possible dementia at baseline, he/she was excluded from the study. Dementia was diagnosed on the basis of DMS-IV criteria [26]. Participants were diagnosed with mild cognitive impairment (MCI) using the most recent international consensus criteria [27].

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Table 1: Sociodemographic characteristics of the sample

Variable	MZ ($n = 266$) Mean (SD) %	DZ ($n = 192$) Mean (SD) %	P†‡	DZ ($n = 74$) Mean (SD)%	P†§
Age (years)	70.58 (5.55)	70.42 (4.62)	0.749	70.61 (4.91)	0.948
Education	10.67 (2.76)	11.16 (3.37)	0.090	11.14 (3.35)	0.128
Sex (% male)	33.1%	27.6%	0.211	21.6%	0.014*
NESB	3.8%	2.1%	0.305	2.7%	0.570
Retired	71.1%	79.7%	*0.036*	82.4%	0.010*
Alcohol use	87.6%	83.9%	0.256	82.4%	0.151
Smoking (current & past)	38.0%	38.0%	0.959	39.9%	0.749

†Analysis of variance *p ≤ 0.05. ‡Comparison of all DZ with MZ twins. §Comparison of same-sex DZ with MZ twins. DZ, dizygotic; MZ, monozygotic; NESB, Non-English Speaking Background; SD, standard deviation.

Statistical analysis

Raw scores on cognitive tests are transformed into *z*-scores, based on this sample's means and standard deviations. Composite *z*-scores of particular cognitive domains are computed from the *z*-scores on individual tests comprising a domain, as indicated in the lower section of Table 3. The processing speed domain contained two factors obtained by a principal components analysis of the five tests comprising the domain: the first comprised the Digit Symbol, Trail Making Test A, and the Stroop Colour and Word Test; the second comprised simple and complex reaction time. The concordance between MZ twins and same-sex DZ twins is estimated as per cent concordance on a categorical construct or correlation between twin pairs on a continuous variable. The concordance in the two groups was contrasted using the χ^2 test for categorical constructs and analysis of variance for continuous variables. Heritability (h^2) was measured using Falconer's formula $h^2 = 2(r_{mz} - r_{dz})$, where r_{mz} is the correlation between MZ twins and r_{dz} the correlation between same-sex DZ twins.

Results

Sample characteristics

The sample comprised 113 MZ and 96 DZ pairs of twins; of the latter, 74 were same-sex pairs. The sociodemographic characteristics of the sample are summarised in Table 1. The mean age was approximately 70.5 years and nearly 70% of the participants were women. Competency in English was a requirement for participation, and only about 3% of participants were from a non-English-speaking background. Most of the participants had completed 10 to 11 years of education, and more than 80% of the individuals were retired.

Health characteristics

The concordance rates between MZ and same-sex DZ twins for the common medical conditions based on participant report are listed in Table 2. MZ twins were more likely to be concordant than DZ twins on a history of hypertension and asthma, but not on other medical disorders. The two groups did not differ on the prevalence of alcohol use or smoking. The concordance rates of depression or other mental health problems also did not differ between the groups, as was the case for self-rating of health as being fair or better.

Cognitive functions

The MZ and DZ twins did not differ significantly from each other on the means and variances of any of the cognitive measures. MZ had higher correlations than DZ twins on most neuropsychological tests, the only exceptions being simple and complex reaction time, Trail Making Test A and mental control, as shown in Table 3. The general intelligence factor *g* had a significantly higher correlation in MZ twins. Of the individual cognitive domains, memory, language and frontal-executive functions were correlated more highly in MZ twins, but not processing speed, as shown in the lower section of Table 3.

Diagnosis of MCI and dementia

Five (1.2%) individuals received a diagnosis of dementia, which consisted of one concordant MZ twin pair, two discordant MZ twin pairs and one discordant DZ pair. The consensus diagnosis of MCI was made in 59 (14.1%) cases, of which 44 (22 twin pairs) were concordant (15 MZ pairs and seven DZ pairs – three same sex and four opposite sex). Of the 15 discordant pairs with only one twin receiving a diagnosis of MCI, six were MZ and nine DZ (four same sex and five opposite sex). One MZ twin pair had dementia in one twin and MCI in the other. The concordance rates of presence or absence of MCI or dementia was 76.2% in MZ twins and 42.9% in DZ twins, a non-significant difference owing to the small sample size (Table 4).

Discussion

We present preliminary data from a large Australian study of twins aged ≥65 years with the objective of examining whether cognitive functions in older individuals are heritable. While formal measures of heritability are not presented, the difference between correspondence on a trait between MZ and DZ twins is considered to be evidence for the heritability of a trait. Our data suggest that cognitive functions in older people are highly heritable, with the possible exception of some aspects of processing speed.

Our data are consistent with published cross-sectional studies of cognitive function in twins. In the Swedish Adoption/Twin Study of Aging (SATSA), with participants in the age range 56 to 82 years, the heritability of verbal abilities was reported to be 0.79 and of spatial/fluid abilities about

Table 2: Concordance rates (% pairs with the same classification) between MZ and same-sex DZ twin pairs on common medical and psychiatric conditions based on self-report

Variable	MZ twin pairs Total pairs = 133		DZ twin pairs Total pairs = 96		χ^2	*P*	Fisher's exact test
	n†	Concordance (%)	*n*†	Concordance (%)			*P*
Stroke	8	0.0	4	0.0	—	—	—
Transient ischaemic attacks	10	20.0	9	0.0	2.01	0.156	0.474
Heart problems	50	34.0	22	13.6	3.16	0.076	0.092
Myocardial infarction	15	40.0	6	0.0	3.36	0.067	0.123
Angina	22	22.7	7	0.0	1.92	0.166	0.296
Atrial fibrillation	9	44.4	3	0.0	2.00	0.157	0.491
Hypertension	73	72.6	43	39.5	12.37	0.00004	0.001
High cholesterol	70	57.1	41	48.8	0.73	0.394	0.434
Diabetes	20	35.0	10	40.0	0.07	0.789	1.00
Head injury	38	13.2	12	33.3	2.52	0.113	0.191
Asthma	21	38.1	11	0.0	5.59	0.018	0.029
Arthritis	66	56.1	39	64.1	0.66	0.418	0.538
Anaemia	17	17.6	18	5.6	1.26	0.261	0.338
Thyroid problem	31	29.0	11	18.2	0.49	0.482	0.696
Parkinson's disease	3	0.0	2	0.0	—	—	—
Epilepsy	4	0.0	1	0.0	—	—	—
Alcohol use	109	85.3	54	75.9	2.18	0.140	0.191
Smoking (current & past)	54	57.4	31	51.6	0.27	0.605	0.655
Depression history	33	30.3	14	28.6	0.01	0.906	1.00
Sleep apnoea	12	16.7	3	0.0	0.58	0.488	1.00
Other mental health problem	32	18.8	21	0.0	4.44	0.035	0.070
General health (good or better)	85	45.9	42	57.1	1.43	0.232	0.261
General health (fair or better)	115	87.0	58	91.4	0.738	0.390	0.459

†Number indicates pairs in which one or both members are affected. DZ, dizygotic; MZ, monozygotic.

0.79 [28], and in the OCTO-Twin study (Individual differences among the oldest old: OCTO-Twin), with a mean age of 83 years, it was 0.55 and 0.32, respectively [29]. In the SATSA, the heritability of memory ranged from 0.30 to 0.77 for a composite score of three memory tests, from 0.33 to 0.80 for processing speed [28], and from 0.53 to 0.91 for general ability [30]. Data from the Longitudinal Study of Ageing in Danish Twins (LSADT) [31], the Minnesota Twin Study of Adult Development and Aging (MTSADA) [32] and the National Heart Lung Blood Institute Twin Study (NHLBI) [33] are largely consistent. Finkel and McGue [34] reported on the heritability of speed measures, with 0.40 for mean intraindividual variability in reaction time and 0.21 for movement time, and no heritability for intraindividual decision time. We similarly found low heritability for processing speed, especially reaction time, in our sample. These data also suggest a reduction of heritability with age, which was not examined for this paper.

It is noteworthy that different cognitive functions have different levels of heritability, suggesting that the determinants of these functions must be examined differentially. In our study, processing speed was examined as two factors, with one factor comprising reaction time not showing any heritability. To our knowledge, only the MTSADA group has examined the genetic influences on intraindividual variability of Simple and Complex Reaction Time, with a slightly younger group of twins (median age = 62). Heritability of decision time and movement time in their study was found to be low, 0% and 21%, respectively. There is no relevant study to date which had examined the genetic influence in Trail Making Test A, and Stroop reading and Stroop naming trials in older people. Heritability of Digit Symbol Coding, when examined in the NHLBI studies was estimated at 68% (mean age 71) and 82% (mean age 77), which is in keeping with our finding of higher heritability for factor 1 compared to factor 2 of processing speed. The low heritability of reaction time may be related to the age-related changes in reaction time, which possibly have environmental rather than genetic determinants. Slowing of processing speed is a major concomitant of ageing [1,2], over and above other cognitive functions, and environmental factors as well as the accumulation of brain pathology account for its reduced heritability in older people. There is also the possibility that reaction time is more sensitive to measurement error due to motivational and emotional factors. However, this finding needs to be replicated before further inferences can be drawn.

One would expect the high heritability of most cognitive functions, implying the role of additive genetics in their variance, to be reflected in the concordance of MCI and dementia diagnosis. The rate of dementia of 1.2% in this sample is lower than the reported prevalence of about 3% at the mean age of 72 years [35]. This is possibly due to a bias against the recruitment of individuals with dementia into the study. The rate of MCI of 14.1% is, on the other hand, not too dissimilar from a rate of 16% reported in the Canadian Study of Health and Aging [36] and the Mayo Clinic Study of Aging [37]. The number of individuals with dementia was too low to examine its heritability. MCI, on the other hand, did not show a statistical difference in the concordance rates in MZ and DZ twins, although the con-

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Table 3: Difference in MZ and DZ (same sex) correlations on cognitive measures and domains

Broad domains	Measures	*r* (MZ) *n* = 119	*r* (DZ) *n* = 65	*z*	*P*	h^2
Premorbid IQ	National Adult Reading Test	0.79	0.38	4.27	0.000	0.83
Cognitive screening	Mini-Mental State Examination (MMSE)	0.39	–0.12	3.38	0.004	1.01
Attention	Digit Span Forward	0.55	0.15	2.97	0.002	0.80
Working memory	Digit Span Backward	0.56	0.20	2.73	0.003	0.72
Abstract reasoning	Similarities (SIMIL)	0.54	0.23	2.35	0.009	0.62
Visuospatial	Block Design (BD)	0.67	0.35	2.83	0.002	0.64
Verbal memory	Logical Memory (Immediate) (LM1)	0.46	0.07	2.72	0.003	0.79
	Logical Memory 2 (Delayed) (LM2)	0.55	–0.02	4.06	0.000	1.13
Verbal learning	Rey Auditory Verbal Learning Test (RAVLT)					
	5th trial (T5)	0.66	0.18	3.88	0.00	0.95
	Immediate Recall	0.60	0.25	2.78	0.003	0.71
	Delayed Recall (T7)	0.60	0.19	3.18	0.001	0.82
	Learning over trials	0.39	0.33	0.44	0.330	0.11
	Total Learning (TL)	0.65	0.25	3.3	0.001	0.80
	Recognition	0.40	0.00	2.69	0.004	0.80
Visual memory	Benton Visual Retention Test (BVRT)	0.22	0.10	0.78	0.218	0.24
Phonemic fluency	Controlled Oral Word Association Test (COWAT)	0.70	0.13	4.68	0.000	1.14
Semantic fluency	'Animals'	0.61	0.14	3.61	0.000	0.94
Naming	Boston Naming Test (BNT)	0.57	0.27	2.36	0.009	0.60
Processing speed	Mental Control	0.50	0.50	0.00	0.500	0.00
	Digit Symbol Coding (DS)	0.65	0.44	1.93	0.027	0.42
	Trail Making Test A (TMTA)	0.35	0.31	0.29	0.386	0.08
	Trail Making Test B (TMTB)	0.54	0.30	1.87	0.031	0.47
Naming speed	Stroop Colour Naming (Stroop 1)	0.48	0.71	–2.32	0.010	–0.47
	Stroop Word Reading (Stroop 2)	0.51	0.33	1.4	0.081	0.36
Inhibition	Stroop Word-Colour (Stroop 3)	0.52	0.07	3.22	0.001	0.90
Fine motor speed	Grooved Peg Board	0.50	0.26	1.8	0.036	0.48
Reaction time (RT)	Simple RT (SRT) (median)	0.39	0.19	1.4	0.081	0.39
	Complex RT (CRT) (median)	0.40	0.44	–0.31	0.378	–0.08
Language	COWAT, animals, BNT	0.66	0.21	3.65	0.000	0.90
Memory	LM1, LM2, RAVLT (T5, T7, TL), BVRT	0.70	0.08	4.96	0.000	1.24
Processing speed	DS, TMTA, Stroop (1, 2, 3), SRT, CRT	0.63	0.49	1.29	0.099	0.28
PS factor 1	DS, TMTA, Stroop (1, 2, 3)	0.64	0.48	1.48	0.069	0.32
PS factor 2	SRT, CRT	0.51	0.43	0.65	0.258	0.16
gf	Similarities, BD	0.69	0.38	2.82	0.002	0.62
g	Similarities, BD, memory	0.76	0.33	4.12	0.000	0.86

DZ, dizygotic; MZ, monozygotic; PS, processing speed.

Table 4: Concordance rates for the diagnoses of MCI or dementia in MZ and DZ twins

Diagnosis	MZ twins		DZ twins		χ^2	*P*	Fisher's exact test
	n	Concordance	*n*	Concordance			
MCI or dementia	21	76.2%	7	42.9%	2.67	0.102	0.165
Dementia	3	33.3%	1	0.0%	0.44	0.505	1.00

DZ, dizygotic; MCI, mild cognitive impairment; MZ, monozygotic.

cordance in MZ twins was higher. The discrepancy may be owing to the fact that the diagnosis of MCI depends upon the individual reaching a certain cut-off for impairment in one or more cognitive domains, and there is some arbitrariness in imposing this categorical distinction on a continuum. In dementia, there is an added consideration of functional impairment due to the cognitive deficit, and there is some subjectivity in such an assessment. In a 1997 review of genetics of Alzheimer's disease [3], it was reported that the concordance of dementia in MZ twins in different studies was 40% to 60%, which was twice that seen in DZ twins. In a subsequent study [4], it was reported that ageing-related cognitive impairment was not different between MZ and DZ twins. Another possible reason for the low heritability of MCI is the heterogeneity of the diagnosis. This can possibly be reduced by subtyping MCI into amnestic and non-amnestic types, but the numbers in our sample are too small for such a sub-analysis.

Low heritability measures using the twin design does not necessarily mean that the additive genetic variance in MCI or dementia is small. It only means that of all the observed variance in the diagnosis, only a small proportion is caused by variation in genotypes. The conclusion from our study is limited by the small numbers with a diagnosis, and the study will become more informative on this count with follow-up in the second wave. The high heritability of individual cognitive functions, in contrast with MCI or demen-

tia diagnosis, suggests that in the search for genetic determinants the use of cognitive functions as phenotypes may be more appropriate.

Another noteworthy finding from our study is the heritability of hypertension in contrast with a range of other medical conditions. In a recent review of the literature [38], the heritability of systolic and diastolic blood pressure was found to be in the range of 0.50 to 0.60, with the rest of the variance attributed to non-shared environmental factors. The heritability measures are influenced by a number of environmental factors, including education [39] and other sociodemographic factors. Significant heritability was also noted for bronchial asthma, but this was not the case for a large number of medical conditions. More detailed exploration of this is yet to be carried out in this study.

Conclusion

This is the first Australian study of older twins to examine cognitive functioning in this group in some detail. The study shows that most cognitive functions in older individuals show significant heritability, with the exception of some aspects of processing speed. The heritability of a neurocognitive disorder is, however, lower, possibly due to the complex determination of these diagnoses which take both the severity of cognitive deficit and its functional impact into account. The heritability of hypertension is noteworthy and this has implications for cerebrovascular diseases and dementia in older people. More detailed exploration of genetic and environmental factors on cognition in older people should be carried out in future studies.

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Key Points

1. Hypertension and asthma in older people show significant heritability.
2. Most cognitive functions in older individuals show significant heritability.
3. The heritability of mild cognitive impairment is low.

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Appendix I

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