A Comprehensive Neuropsychiatric Study of Elderly Twins: The Older Australian Twins Study

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The Older Australian Twins Study (OATS) was recently initiated to investigate genetic and environmental factors and their associations and interactions in healthy brain ageing and ageing-related neurocognitive disorders. The study extends the classic MZ-DZ design to include one or two equivalently aged siblings for each twin pair and utilizes the rich resources of the Australian Twin Registry. The study has a number of distinguishing features including comprehensive psychiatric, neuropsychological, cardiovascular, metabolic, and neuroimaging assessments, a longitudinal design and links with a brain donor program. The study measures many behavioral and environmental factors, but in particular lifetime physical and mental activity, physical and psychological trauma, loss of parent early in life, later losses and life events, early-life socioeconomic environment, alcohol and drug use, occupational exposure, and nutrition. It also includes comprehensive cardiovascular assessment, blood biochemistry, genetics and proteomics. The socio-demographic and health data on the first 172 pairs of twins participating in this study are presented. Prevalence of mild cognitive impairment is 12.8% and of dementia 1.5% in the sample. The target sample size is 1000, with at least 400 pairs of twins aged 65–90 years. The cohort will be assessed every two years, with in-depth assessments being repeated. OATS offers an excellent opportunity for collaboration with other similar studies as well as researchers who share the same interests.

Keywords: twins, brain, ageing, cognitive function, MRI, mild cognitive impairment, mental disorder, cardiovascular health

Evidence suggests that environmental factors (E) act on a substratum of genetic endowment (G) to produce both age-related disease and healthy brain ageing (Kirkwood, 2002). The extended twin pair design is a potent methodology to explore these factors and their interactions. The twin method has been extensively utilized in children and young adults, but its application in the elderly has so far been limited (Harris, 2003). Notable exceptions are the Swedish Adoption/Twin Study of Aging (SATSA) (Lichtenstein et al., 2002), as well as other studies such as the Danish Twin Study (Christensen et al., 1999) and the NAS-NRC Twin Registry (DeCarli et al., 1999). Some smaller studies have also been reported on elderly twins (Barak, 2003; Karlinsky, 1992). These studies have yielded interesting data but the overwhelming opinion is that this resource has so far been under-utilized for research in older populations.

Some interesting insights have emanated from the studies of elderly twins in relation to brain ageing, including: (1) the concordance of Alzheimer's disease (AD) in MZ twins is estimated to be 80%, suggesting high heritability (Martin et al., 1996). The only gene that has been reliably shown to affect the risk of sporadic AD is apolipoprotein E polymorphism, and the heritability estimate suggests that the search for other genes should continue; (2) genetic factors are important in the development of white matter hyperintensities (WMHs), but single genes exert a small effect, and in all likelihood interact with risk factors such as hypertension and sex to manifest these effects (Atwood, 2004; Bergem, 1997). Genetic factors associated with WMH are poorly understood and are only beginning to be explored; twins present an excellent opportunity to advance this research

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(DeStefano, 2006); (3) according to one study, brain size, cerebrospinal fluid (CSF) and both WMH volumes and their anatomical distribution appear to have strong heritability, even in the elderly (Carmelli, 1998) but the hippocampus appears to be more influenced by environmental factors (Sullivan, 2001). These findings, which need to be replicated, have important implications for the study of the effects of ageing on the brain and cognition; (4) it has been shown that in late life, heritability of cognitive ability decreases and environmental factors become more important (Dolan, 1999).

Many findings supporting gene-environment interactions in ageing have also been reported in the literature. Head injury is recognized as a risk factor for Alzheimer's disease (AD), but one study found that this was only in the presence of the apolipoprotein E 4 (*APOE4*) gene. While one *APOE4* allele alone produces a ~5-fold increase in risk of AD (Rubinsztein and Easton, 1999), the presence of head injury increases the risk to 10-fold in its presence (Mayeux, 1995). Other similar studies of interaction of risk factors have been reported (Hunter, 2005).

The primary objective of this study is to establish a cohort of ageing twins and their siblings for the investigation of healthy brain ageing as well as age related cognitive disorders. Although the study is not strictly hypothesis driven, some specific hypotheses are being addressed: (a) the heritability of cognitive functions (episodic memory, working memory, frontal–executive function, information processing speed) decreases with increasing age; (b) cerebrovascular risk factors (hypertension, diabetes, smoking, high homocysteine, obesity, low physical activity) interact with genetic factors (e.g., *APOE4* and novel genes) in their association with WMHs; (c) total brain and grey and white matter volumes in the elderly are highly heritable, but the heritability decreases with age in both sexes; (d) the extent and rate of progression of WMHs are highly heritable, and the degree of heritability is different in the two sexes; (e) mental activity (i.e., brain reserve) interacts with genetic factors such as *APOE4* in its association with 'successful ageing' and mild cognitive impairment (MCI); (f) nutritional factors (e.g., calorie intake, antioxidant intake, plasma antioxidant measures, folic acid intake) account for a significant proportion of cognitive and motor discordance in MZ twins; (g) personality dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) continue to have high heritability in old age; (h) phenotypic discordance in elderly MZ twins is related to global and locus-specific differences in DNA methylation.

Materials and Methods

Participant Recruitment

Twins aged 65 years and older are being recruited through the Australian Twin Registry (ATR) as well as by a new recruitment drive by the authors. The ATR (www.twins.org.au) is a not-for-profit organization funded by the Australian government through the National Health and Medical Research Council. It maintains a national register of twin pairs and their relatives who are willing to participate in health related research. The ATR is the largest volunteer register of its kind in the world, with over 31,000 twin pairs registered. However, the number of aged twins is quite limited. According to a recent estimate, there are 849 MZ female twins, 377 MZ male twins, 573 DZ female twins, 209 DZ male twins and 641 DZ opposite sex twins aged 65 years and older registered with the ATR. Over 90% of these are in the three Eastern states of Australia (New South Wales, Victoria and Queensland), wherein recruitment for this study occurs. Since this is not a comprehensive listing, twins are also being recruited through advertisements, media campaigns, and by contacting clubs and networks of older citizens.

Potential participants are invited to participate by mail followed by telephone screening. The target is to recruit a minimum of 200 pairs each of MZ and DZ twins and one or two siblings for each pair (total sample size ~1000). The inclusion criteria are: age 65 years and older, ability to consent, having a consenting co-twin, having completed some education in English and being at least of low average IQ. The exclusion criteria include: diagnosis of malignancy or other life-threatening medical illness, inadequate English to complete a neuropsychological assessment and current diagnosis of an acute psychotic disorder. Subjects are excluded from the MRI component if they have a contra-indication for MRI, e.g. cardiac pacemaker, ferromagnetic foreign body or implanted device, or claustrophobia.

Ethics

Participants provide written informed consent. The study is 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 and a follow up every two years with targeted measures as described below. Assessment protocol is standardized across centers, with uniform training of research staff in the lead center. Assessment may be performed in a clinic room or the participant's home, according to the convenience of the participant. Twins are interviewed separately with the co-twin being interviewed close in time to his or her twin. MRI scans are performed within 3 months of the index assessment as much as possible. While participants are encouraged to complete all aspects of the assessment, the clinical and neuropsychological aspects comprise the core assessment, and other components are optional. The cardiovascular and metabolic assessment is performed at a second stage.

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Assessment

The following 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 PC, using a Microsoft Access database (2003; 2007).

Neuropsychological: A self-report subjective cognitive complaints questionnaire, and a comprehensive assessment using a computerized battery as well as paper and pencil tests: Premorbid Intellectual Functioning (NART) (Nelson, 1991); Attention: Mental Control and Digit Span from the Wechsler Memory Scale — Revised (WMS-R) (Wechsler, 1981); Memory: Logical Memory I & II from the WMS-R (Wechsler, 1981), Rey Auditory Verbal Learning Test (RAVLT) (Giles & English, 2002)], Benton Visual Retention Test (Benton, 1992), Picture location test (computerized, developed in-house); Visuospatial function: Block Design from WAIS-R (Weschler, 1987), copying simple designs; Language: an Australian adaptation of the Boston Naming Test (Kaplan et al., 1983); Executive function: Controlled Oral Word Association Test — phonemic/semantic (COWAT and Category) (Spreen & Benton, 1977), Trail Making Test B (Reitan & Wolfson, 1985), computerized Stroop test (adapted from Delis et al., 2004), Speed of Information Processing (Digit-symbol from WAIS-R (Wechsler, 1987), Trail Making Test A (Reitan & Wolfson, 1985), simple and complex reaction time (computerized test battery), fine motor skills from the Expanded Halstead-Retan Battery (grooved pegboard) (Heaton et al., 2005), Mini-Mental State Examination (Folstein et al., 1975) and GPCOG (Brodaty et al., 2002).

Personality: The NEO Personality Inventory (NEO PI-R) for assessing the five dimensions of personality, that is, Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness (Costa & McCrae, 1992).

Linguistic: Administration of a 5-minute Free Speech component whereby participants provide a narrative about one or more incidents in their past, and a 100-item Free Word Association component to assess linguistic cognitive decline in the Queensland sub-group of participants.

Informant interview: Informant questionnaire for cognitive decline in the elderly (IQCODE) (Jorm & Jacomb, 1989), confirmation of vascular risk factors (hypertension, history of dyslipidaemia, atrial fibrillation, smoking, obesity, diabetes) and previous hormone replacement therapy (HRT) use; Change In Cognition with Age Questionnaire (CICAQ), Clinical Dementia Rating Scale (CDR) informant section (Hughes et al., 1982), Bayer activities of daily living (B-ADL) scale (Erzigkeit et al., 2001), and Neuropsychiatric Inventory (NPI) (Cummings et al., 1994).

Nutrition: The Victorian Cancer Council food frequency questionnaire (Giles & English, 2002) is used, and biochemical measures of levels of vitamins and antioxidants are obtained.

Physical and mental activities: The Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) provides a quantitation of activities through the life span — frequency and complexity of occupations, mental activities, physical activities, and social relationships. This includes performance at school and college, hobbies, pastimes, etc.

Successful ageing questionnaire: An Australian adaptation of the San Diego Successful Ageing Questionnaire (Seeman et al., 1994) is used. This permits operationalization of definition of healthy or successful ageing, current functional abilities, social networks, involvement with community and contributions to extended family.

Blood collection: Blood (60mls) is collected to test for reversible causes of dementia, investigate correlates of cognitive function (full blood count, clinical chemistry screen, thyroid function tests, total antioxidant capacity, fasting cholesterol, homocysteine, iron, Vitamins B_{12}, C and E, folic acid, luteinising hormone (LH), and follicle stimulating hormone (FSH), and for DNA extraction and immortalization of lymphocytes using standard methods). Multiple genetic tests (apolipoprotein E polymorphism, zygosity testing, and so on) are planned, with a genome-wide association study in the future.

Medical records: A record of Medicare-funded consultations is obtained from the Health Insurance Commission of Australia after obtaining informed consent. In Australia, all outpatient medical consultations are at least partially Medicare funded and therefore provide a comprehensive record of health consultations by an individual.

Brain imaging: Structural MRI, and in a subset functional MRI (fMRI), is performed on a 1.5 T scanner. Siemens scanners with similar year of manufacture and upgrade, are being used in two centers (Melbourne and Brisbane), and a Philips scanner is being used in the third center (Sydney). Matching acquisition protocols are being used in the three centers, with standardization of in-plane resolution and slice thickness. A 3D phantom is used to detect variation across scanners (for correction of geometric distortion), and five volunteers are to be scanned on all three scanners for reliability measures. The standardized protocol is as follows: in-plane resolution 1×1 mm with slice thickness of 1.5 mm T1-weighted contiguous coronal sections through whole brain (T1-TFE sequence and 3D acquisition); T2-weighted fluid attenuation inversion recovery (FLAIR) 3.0 mm contiguous axial slices; diffusion tensor imaging (DTI) for whole brain in 32 directions; and susceptibility weighted imaging (SWI) in one center. Volumes of hippocampus, entorhinal cortex, parahippocampal gyrus and temporal neocortex are obtained using a standard tracing protocol. Automated segmentation of scans allows calculation of total grey matter, white matter, cerebrospinal fluid,

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intracranial volumes and derivation of ventricular: brain ratio (VBR). Diffusion Tensor Imaging (DTI) will yield fractional anisotropy, mean diffusivity maps and data for tractography for anatomical connectivity and network studies (Schmitt et al., 2008). White matter hyperintensity (WMH) volumes and topography are obtained from FLAIR and 3D T1 images using a supervized but automated segmentation procedure (in-house software) (Wen & Sachdev, 2004). Blood oxygen level dependent functional MRI (BOLD fMRI) will be performed in a sub-sample (20 pairs each of MZ and DZ) using imaging protocols developed in our laboratory. The first uses visual paired associate memory with varying levels of task difficulty tailored to the participant. A motor task involving hand movements, based on Sirigu et al. (1996), has been developed to examine pre-SMA activation in subtle movement disorders.

Cardiovascular and metabolic assessment: Participants can choose an additional assessment in which they receive a more detailed cardiovascular and body composition assessment. The assessment comprises an arterial stiffness measure (pulse wave velocity), electrocardiograph, anthropometric measure (using bioelectrical impedance analysis), MRI of the abdomen to determine intra-abdominal and subcutaneous fat and MRS of the liver to determine liver fat content, and additional blood tests to determine insulin secretion and sensitivity, lipids and lipid peroxidation products, total nitrates, nitric oxide synthase, inflammatory markers and adipokines.

Resource utilization: Standard methods, including linkage to Medicare records and other centralized databases such as the Centre for Health Record Linkage (www.cherel.org.au) are used.

Brain collection: A brain donor program for participants is linked to the National Tissue Resource Centre (Brain Bank) (www.nnf.com.au). The long-term objective is to develop a brain bank from participants in this study to conduct neuropathological studies informed by the rich clinical data.

Follow-Up Assessment

Participants are to be reassessed after two years with shorter medical, neuropsychological and psychiatric assessments and MRI scans. Blood collection will be done at multiple time points for biochemistry and metabolic markers. Diagnosis of dementia, nursing home admission and death will be major endpoints.

Analytic Strategies

Establishing Phenotypes

The strength of our clinician-geneticist partnership is the careful work-up of participants for clinical and intermediate phenotypes, both 'global' and 'focal':

Healthy Ageing Related

Successful ageing: We operationalize this on the framework of reaching old age without having experienced serious chronic disease, and having maintained high levels of physical and cognitive functioning and community involvement (Seeman et al., 1994). Successful ageing is common in those with extreme longevity (Hitt et al., 1999), and evolutionary evidence suggests that longevity is genetically programmed (Kirkwood, 2002).

Physical health variables: We have particular interest in motor speed, gait slowing, grip strength and ventilatory capacity.

Grey matter, white matter, CSF and hippocampal volumes: Based on quantitative segmentation of MRI scans, these measures are related to healthy ageing as well as disease (Carmelli et al., 1998).

Cognitive function: We measure memory, frontal-executive function, visuospatial function, working memory and information processing speed using computerized tasks. We wish to examine the validity of autobiographical memory using twins (Ikier et al., 2003).

Personality dimensions: We use the NEO Personality Inventory (NEO PI-R) as a measure of the five dimensions of personality (Costa & McCrae, 1992).

Disease Related

Mild cognitive impairment (MCI): The high prevalence of MCI in the elderly population (rates of 3–20% depending upon criteria used) (Ophoff et al., 2002), makes it an important target. We define MCI using standard criteria, using both subjective reports and objective measures (Petersen, 2004; Winblad et al., 2004).

Dementia/Parkinson's disease: Our investigations allow the diagnosis of dementia and its subtyping into AD, Vascular Dementia (VaD), Dementia with Lewy bodies (DLB) and Fronto-temporal Dementia (FTD), as well as Parkinson's Disease (PD).

Cognitive decline: Changes in cognitive variables (see above) over two years.

Brain morphological change: Determine change in grey matter, white matter, total brain volume and hippocampal volume by repeat MRI.

White matter hyperintensity (WMH) volume and anatomical location: This is used as an intermediate phenotype for small vessel disease in the brain (DeStefano et al., 2006; Atwood et al., 2004; Bergem et al., 1997), cross-sectionally and its change. Standard procedures for genetic, imaging and biochemical analyses are used. Heritability analyses use structural equation modeling (Evans and Martin, 2000). The contributions of the latent variables are estimated as regression coefficients in the linear regression of the observed variables on the latent variables. Several widely available software programs, such as Mx (Dolan, 1999) or LISREL (Joreskog & Sorbom, 2001) allow the estimation of parameters by using normal theory maximum likelihood and weighted least squares. A useful estimator in the Mx program is the raw data likelihood estimator, which handles data from selected samples and from studies in which part of the sample might be missing as in longitudinal data. Changes in

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cognitive ability are examined using a latent growth curve model. We use: clinical and intermediate phenotypes for G and E analyses; motor speed and gait speed rather than a clinical diagnosis of Parkinson's disease; WMH volume rather than a diagnosis of VaD; episodic memory, working memory, processing speed measures, and volumetric brain measures etc and not dementia diagnosis. Refinement of phenotypes is one useful endpoint as it is germane to gene discovery.

Gene selection and analyses: Since we are studying complex traits, we will use a quantitative trait loci (QTL) approach. Candidate genes are selected on the basis of: (a) *a priori* hypotheses in relation to disease mechanisms; (b) genes known to code for specific disease-related proteins; and (c) from specific regions based on independent genome-wide scans. Strategies for optimization of candidate gene selection are used as described by Tabor et al. (2002) and have been used successfully by our group (Wilhelm et al., 2006; Blair et al., 2006). SNPs associated with a gene of interest are identified and those with allele frequency ≥ 5% are examined. SNP testing poses a multiple testing problem such that 'statistical significance' can be achieved only for the strongest effects. There are practical methods of dealing with this, such as ranking markers by proximity to candidate genes and by expected functional consequence (Carlson et al., 2004). Significance is addressed by permutation analysis of the observed data and by false-discovery-rate analysis (Storey & Tibshirani, 2003).

Power analysis: With 200 MZ and DZ twin pairs, we have power of 0.74 to detect additive genetics variance in the univariate case (df = 1) for heritability of 0.4 (Schmitz et al., 1998). In the multivariate case (df = 3, 6 or 10), heritability effects of 0.3 are detectable with power > 0.9 (Schmitz et al., 1998). The shared environmental correlations not only aid in the detection of c^2 but also of h^2. The addition of siblings increases the power. The average sibship of 3 is 3↔ and of 4 is 6–7↔, which is more informative (Dolan et al., 1999). For most of our analyses, we use a quantitative or marker-based approach which outperforms the dichotomized or trait approach used in some studies (Tenesa et al., 2005). After factoring in a 10% attrition over two years, rather than facing a decline in power due to decreased sample size, the longitudinal design actually helps increase power, through the use of the raw data option in Mx (Dolan, 1999), as our measures are expected to correlate over time.

Results

To date, 672 twin pairs, aged 65 years or older and living in New South Wales, Queensland, Victoria and the Australian Capital Territory, have been approached through the ATR. Of these, 263 twin pairs have been recruited, with an additional 32 twin pairs recruited through media campaigns and advertisements. Data collection is proceeding, and demographics and preliminary clinical data are reported for a total sample of 172 twin pairs (92 MZ, 80 DZ).

Table 1

Sociodemographic Characteristics of the Sample

Variable	MZ (*N* = 184) Mean (*SD*) %	DZ (*N* = 160) Mean (*SD*) %
Age (years)	71.48 (5.74)	70.33 (4.62)
Education	10.60 (2.76)	11.08 (1.14)
Sex (% male)	35.3%	32.9%
NESB	0.6%	1.6%
Retired	80.4%	86.8%
Learning difficulties	9.2%	9.6%
History of alcohol use	39.5%	29.4%
Past or current smoking	34.2%	40.4%

Note: MZ = monozygotic twins; DZ = dizygotic twins; NESB = Non-English speaking background.

Table 1 summarizes the sociodemographic characteristics of the sample. The majority of the participants are women. Since competency in English was a requirement for participation, there are very few participants from a non-English-speaking background. Most of them had completed 10–11 years of education, and over 9% reported learning difficulties. More than 80% of the individuals are retired.

The main medical and neuropsychiatric conditions in this group are listed in Table 2. It is noteworthy that depression and other mental health problems are common in this group. Results of neuropsychological assessment are available for 92 MZ pairs and 76 DZ pairs. Preliminary data analyses of some of the neuropsychological variables are displayed in Table 3. As can be seen, the percentile equivalent of their group mean scores of both the MZ and DZ groups are comparable, and both groups have performed well within the average range in all the cognitive domains examined. On the adjusted MMSE, 3.3% of the MZ and 1.2% of the DZ twins scored < 24/30 suggesting possible dementia. MMSE scores were adjusted on the basis of previous research which suggests that individuals > 75 years or with low education or from a non-English speaking background are disadvantaged in their performance on MMSE (Anderson et al., 2007). By consensus, seven (2.1%) participants were diagnosed with dementia according to the DSM-IV criteria. No twin pair was concordant for dementia, but one twin of a dementia case was diagnosed with mild cognitive impairment (MCI).

The standard criteria for defining MCI (Winblad et al., 2004) were applied to participants who demonstrated cognitive impairment in one or more cognitive domains during the cognitive assessment. The diagnoses of MCI were made at consensus meetings attended by four or more investigators. Eleven individuals were diagnosed with amnestic single domain MCI (aMCI), and 11 were classified as amnestic multiple domain MCI (amdMCI), giving a prevalence of

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Table 2

Medical and Functional Status of the Sample

Variable	MZ (*N* = 184)	DZ (*N* = 160)
History of depression	21.7%	16.2%
History of other mental health problems	17.9%	14.4%
Parkinson's disease	1.6%	1.2%
Previous stroke/transient ischemic attack	5.4%	6.0%
Other heart problems	26.7%	20.5%
Epilepsy	2.2%	1.8%
Diabetes	10.9%	9.6%
Thyroid problems	15.2%	10.2%
Hypertension	56.5%	55.1%
[1]Adjusted MMSE score < 24	3.3%	1.2%
B-ADLs1 — cognitive impairment	0.8%	0.9%
B-ADLs2 — cognitive impairment	3.3%	1.8%

Note: B-ADLs = Bayer activities of living scale (objective information); MMSE = Mini Mental Sate Examination
[1]According to Anderson et al., 2007

Table 3

A Summary of the Neuropsychological Test Scores for the Sample

		MZ (*N* = 184)			DZ (*N* = 152)[§]		
Cognitive domains	Test/s	Mean raw scores (*SD*)	Mean Scores*	Percentile	Mean raw scores (*SD*)	Mean scores*	Percentile
Estimated IQ		106.33 (10.85)			104.34 (14.07)		
Attention	Digit span forward	6.54 (1.30)	*z* = 0.26	58–62	6.48 (1.34)	*z* = 0.235	58–62
Memory (verbal)	RAVLT Recall	7.61 (3.17)	s = 10.87	62	8.11 (3.47)	s = 11.27	66
Memory (visual)	Benton VRT	12.56 (1.90)	*t* = 49.09	46	12.47 (2.04)	t = 48.26	42
Visuo–spatial	Block Design	24.00 (7.90)	s = 10.70	58	24.80 (9.27)	s = 10.76	58–62
Language	Boston Naming Test	26.28 (3.54)	*z* = –0.31	38	25.72 (3.97)	*z* = –0.45	31–34
Frontal/executive	COWAT (FAS)	36.98 (12.63)	*z* = 0.25	58–62	35.52 (11.96)	*z* = 0.01	50
	Digit span backward	4.06 (1.24)	*z* = 0.10	54	4.68 (1.25)	*z* = 0.19	58
Processing speed	Trail Making Test A	40.00″ (17.70″)	*z* = 0.28	62	39.07″ (13.10″)	*z* = 0.24	58–62
	Digit symbol	54.09 (13.72)	s = 10.71	58	55.76 (13.46)	s = 10.90	62

Note: [§]Data incomplete for eight subjects.
**z* scores (*z*), scaled scores (s) and t-scores (t) are age and education corrected.
The values are based on the exclusion of outliers (top and bottom 5% of performance in the particular test).

amnestic MCI of 22/336 (6.5%). Eighteen individuals were classified as nonamnestic single domain MCI (nMCI), while four were diagnosed with nonamnestic multiple domain MCI (nmdMCI), giving a prevalence of non-amnestic MCI of 22/336 (6.5%), and a total MCI prevalence of 13.0%. The concordance for MCI was 44% in MZ and 32% in DZ twins.

Discussion

OATS is a major new initiative that has brought together geneticists and researchers in neuropsychiatry of the elderly to examine key issues in cognitive ageing and dementia. It uses the extended twin pair design to examine heritability of brain imaging and cognitive parameters. It also recognizes that the examination of genetic factors alone cannot account for many chronic diseases in the elderly and environmental factors are important considerations — alone and in interaction with genetic factors. The study is designed to delineate a number of neuropsychiatric phenotypes with great precision. It incorporates detailed neuropsychological, physical and neuroimaging assessments, as well as the collection of indepth lifestyle, mental and physical activity and dietary information. The rich data so obtained will assist in the delineation of new gene x environment interactions across a range of measures.

An additional advantage offered by the study is its longitudinal design, with planned assessments every two years. The prospective assessments reduce the limitations of cross-sectional diagnostic assessments, which can be unreliable in the determination of predementia syndromes (Anstey et al., 2008). They also permit the careful description of any exposure to risk

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factors, and the complete characterization of the cognitive syndrome at onset and progression following risk exposure. This is important in complex diseases in which genes with small effect interact with environmental factors. The study will provide the data to study multiple disease outcomes in the elderly in relation to brain and cognition. The longitudinal nature of the study will permit the collection of biospecimens (blood, DNA, brain images) over time without bias in relation to disease outcome.

The large proportion of participants is recruited through the ATR. The representativeness of the sample in relation to elderly individuals in the community is not known. With a mean age nearly 71 years, this is a relatively young old cohort. Nearly two-thirds are women, while the ratio of men to women in this age group was 4:5 in the 2001 Census (Trewin, 2003). This is a predominantly English-speaking cohort even though 22% of older Australians were born in a country with a language other than English and only 45% of these spoke English well (Trewin, 2003). About one in five individuals reported a history of depression. As this does not distinguish between major and minor depression, the rates are not inconsistent with those reported in the general population (Trollor et al., 2007). Rates of vascular risk factors such as hypertension, diabetes, smoking, and heart disease were high, as is usual for an elderly population. The rate of dementia by consensus diagnosis was 2.1%, even though the proportion scoring <24 on the MMSE was slightly higher.

Since a major focus of this study is on cognitive impairment, it is important to note the profile of cognitive performance in the sample. Performance on most tests is in the average range, but 13.0% met the international consensus criteria for MCI (Winblad et al., 2004). This was about equally distributed between amnestic and non-amnestic MCI. The rates of MCI vary from 3–26% in various studies, but the best prospectively designed cohort studies report rates of 12–18% in nondemented individuals over the age of 65 years (Petersen, 2004). Our rates are therefore on the lower end of the reported range, possibly due to the relatively young age of our sample. The relative proportion of amnestic and non-amnestic MCI is not well established in the literature. The concordance in MCI diagnosis of 44% in MZ twins relative to 32% in DZ twins is difficult to interpret considering the low reliability of MCI diagnosis. Decline over the next few years of follow-up will provide a more accurate estimation of the heritable component of genetic decline in older individuals.

The cohort design of this study is not without its limitations. Since the study involves a commitment to extensive investigations over a long period of time, only the more motivated individuals are likely to volunteer, thereby introducing a referral bias. Bias is also likely to be introduced in such a study by exposure suspicion and diagnostic suspicion, but these can be overcome by systematic assessments and standardized procedures following extensive training of researchers. This is one feature of the assessments in the Older Australian Twins Study. The depth of assessment comes at a cost which is not just fiscal and borne by the research budget, but a cost in time generously donated by our participants, who have demonstrated an eagerness to be part of this project. We trust this approach will be fruitful in the understanding of the determinants of the ageing process and of age-related degenerative disorders.

The Older Australian Twins Study (OATS) offers an excellent opportunity for collaboration with other similar studies as well as researchers who share the same interests. Since initiation of the study, we have developed collaborations with other researchers in a number of areas including the genetics of atrial fibrillation, falls risk and linguistic markers of cognitive decline. The data will eventually be made available to other researchers who share our interests in brain ageing.

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Appendix A

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