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Review

Genetic influences on cognitive functions in the elderly: A selective review of twin studies

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ABSTRACT

In this review, we examined the published reports on the heritability of cognitive functioning in old age. Twenty-four papers from five study centers, comprising of participants with a mean age of 65 years and above were examined. The comparability of findings from different studies was compromised by the use of different measures for the same cognitive domain, and with large scale twin studies in cognitive aging limited to a few Scandinavian countries. While the results from cross-sectional samples appear to lend support for the notion that heritability of cognitive functions decreases in the elderly, the findings are best considered inconclusive. Longitudinal reports show little evidence for genetic effects, but an increase in unique environmental influences on the rate of cognitive change as age increases. In relation to the two prominent theories of cognitive aging, the genetic influence on processing speed as a major contributor to cognitive aging has been indicated in three reports, whereas the genetic relationship between executive functions and other cognitive functions has not been explored. Only two studies have focused on sex difference and did not find sex-specific genetic influence in cognitive abilities. This review indicates that there are complex relationships between heritability, environmental influence, and cognitive functions in the elderly. It highlights the need for more research, with consistent and appropriate cognitive measures, with data obtained from larger and more geographically and culturally diverse twin samples.

Contents

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1. Introduction

Aging is associated with changes in cognitive functioning, both in the general cognitive factor g, as well as in specific cognitive domains (Mattay et al., 2008). There is considerable inter-individual variability in these age-related changes, which is attributable to both genetic and environmental differences. Research in elderly twins may be a useful strategy to identify specific genetic and environmental factors, but until recently this strategy has been underutilized.

Twin studies represent a "natural experiment" for examining the contribution of genetic and environmental influences. 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. Since 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 environments", which represent those environmental factors that are specific to the individual and cause differences in pairs of individuals (Pedersen, 2000).

As a quantitative trait, the general factor of intelligence, g, has been a focus of much twin research. There are a number of reasons for this. G contributes to the cognitive domains of memory, executive functions, language, and executive functions. It is also a strong predictor of educational attainment, occupational achievement, aspects of health and health-related behavior, as well as longevity. As an intelligence phenotype, g has been considered as very stable across decades (Deary, 2008; Deary et al., 2009). Several twin studies of various age groups have indicated that heritability for g is significant. 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 (Singer et al., 2004). In another study, g increases from approximately 30% in very young childhood to as much as 80% in adulthood were reported (Deary et al., 2009). Plomin et al. (2008) stated that the average twin correlation of cognitive abilities of various age groups is 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 is 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 (Plomin et al., 1994).

While the genetic influences on g as a general cognitive factor are substantial, the environment would exert a similar and significant amount of influence on cognitive abilities. Environmental influences are divided into shared (common) and non-shared (unique) effects, and the former is considered not as important because of the "equal environment assumption" (McGue and Christensen, 2001) in twin studies. Shared environment refers to common household, family, school, and diet that are assumed to be common between the twin pair. Non-shared environmental influence refers to individual experiences of one twin that are unique to that twin. In the study of elderly twins, shared environmental influence is not considered important as a majority of twins would have lived separately since the beginning of early adulthood. This hypothesis also leads to another assumption that the discrepancy between larger MZ and smaller DZ twin correlations is due to greater genetic and not greater environmental similarity.

According to Salthouse's (1996) model of cognitive aging, it is the consequence of generalized slowing of perceptual and cognitive processes. It is argued that age-related deficits in specific cognitive domains, including memory, can be explained as a result of change in general information processing parameters, and consequently be predicted from performance on simple reaction time tasks. Consistent with this theoretical model, cross-sectional studies have demonstrated that age-related variance in measures of processing speed can explain up to approximately 80% of age-related variance in many cognitive abilities (Verhaeghen and Salthouse, 1997).

An alternative model of cognitive aging has been proposed by West (1996), Rabbitt (2000) and Rabbitt and Lowe (2000). The central tenet of this model is that age-related changes in cognition can be explained by localised and early age-related deterioration in the frontal lobes of the brain. As the frontal lobes are the neural substrates that are most closely associated with executive functioning, changes in these brain structures are argued to cause impaired executive functioning. Executive losses in turn lead to the well-documented changes in a range of cognitive processes, including memory. Most studies do identify age-related declines in executive functions such as inhibitory control and switching, particularly with novel tasks, and where working memory demands are high (for a review, see Phillips and Henry, 2008). There remains an ongoing debate as to the relative importance of more general changes in processing speed versus specific deficits in executive control as causative factors in cognitive aging.

Prior to 2006, there had been no study that specifically examined sex differences in the heritability of cognitive functioning in normal aging (Read et al., 2006). Non-twin studies had demonstrated that age-related cognitive decline was more pronounced in women than in men. Prevalence of Alzheimer's disease, in general, was higher in women than in men in many populations (Azad et al., 2007). However, it has been argued that the prevalence differences were an artifact of sex differences in longevity, and reflective of the higher life expectancy in women (Bachman et al., 1992).

So, do genetic factors continue to influence cognition well into old age? Data from Swedish twin studies (Pedersen, 2000) suggest that there is a decrease in genetic influence in the oldest old. Deary et al. (2009) cited studies that showed heritability of g increases with age. While the Swedish reports have been summarized by Pedersen (2000) and Finkel et al. (2005), a review of studies on the genetic influence of cognitive abilities of the elderly, inclusive of studies by other groups has not been published. Specifically, it remains unclear whether the genetic influence on a single cognitive domain, such as processing speed or executive control, contributes to the heritability of other general cognitive abilities.

The present review is an examination of published studies of elderly twins, aged 65 and older. The specific aims are: to integrate literature that has focused on quantifying how much variance in specific cognitive domains (including processing speed and executive control) is attributable to a heritable or genetic component; to examine the stability and/or change of genetic influence on cognitive functioning and the rate of change in longitudinal studies; to discuss the role of genetic influences in a single cognitive domain (processing speed and executive control) and their relationship with other aspects of cognitive functions; and, to examine twin data which may inform whether sex differences contribute to the genetic and environmental influences on cognitive aging.

2. Methods

A computer-based search of Web of Science (Thomson Reuters, 2009) and PubMed databases was conducted using combinations of the following keywords: twins, heritability, cognitive abilities, cognitive functions, and cognitive aging or aging. In addition, a backward citation search was undertaken (i.e., references in each of the articles retrieved were checked). The searches were completed in March 2009.

Inclusion criteria for the review included: journal article, published in English, cognitive data collected on twins. The mean or median age of participants was 65 and above, which has been used as a cut-off for a majority of the published literature on the elderly, and old age is generally considered to begin at the age of legal retirement, which is approximately 65.

Cognitive measures would include the use of validated clinical cognitive assessments such as the Wechsler Scales or similar methods of assessment of cognitive functions. Reports that have used the Mini Mental Status Examination (MMSE) as the only cognitive measure, or based the assessment solely on telephone interviews were excluded from this review. Twin studies of the association between specific genes and cognitive functions, and brain structure and cognitive functions, were not included.

3. Results

Twenty-four published papers, with publication years ranging between 1992 and 2008 contributed to the present review. Details of the cross-sectional data from 23 samples, including demographic variables, are presented in the Tables 1 and 2, and contributing articles are indicated by an asterisk in the References section. For clarity of presentation, these reports are listed by study centers, with samples comprising subsets of twins from the same twin population. There were seven reports of longitudinal data. Three reports specifically examined the genetic relationship of processing speed and other cognitive abilities. There were two reports on sex differences in the heritability of cognitive functions.

The published reports have used the terms adult, adulthood, elderly, aging, cognitive aging, very old, over 70, over 75, over 80, adult aging, later in life, and second half of life span to describe their samples. For the purpose of this review, and as stated in the Methods section above, we included reports from samples of participants with mean or median age of 65 and above. Some investigators have used 65 as the cut-off for their cohorts: “younger old”: 64 to 80.6, “older-old”: 81.7 to 90 (Finkel et al., 2000a), age distinction between two cohorts: <65 and >65 (Finkel et al., 2005). One study, Finkel and McGue (2007) with a median age of 62 was included in this review, as it is the only known study which has specifically investigated the heritability of reaction time in the elderly.

A majority of the reports in this review had not considered g as an independent measure or construct. In the sample reported by McClearn et al. (1997), g was indexed by the first principal component of the various cognitive measures. Finkel and Pedersen (2004) reported g as a general cognitive factor which was created from principal component analysis. In Pedersen et al. (1994) “general cognitive ability” was referred to as g or IQ, and all the SATSA samples had used this term to include the first principal component derived from the various measures. Finkel et al. (2005) had referred to the general cognitive factor as IQ. Reynolds et al. (2005) reported that a measure of general cognitive ability was created by extracting the first principal component, referred to as g, from the cognitive measures. Finkel et al. (1995b) had reported a composite score for memory and referred to it as one of the components of general cognitive ability. Therefore, it appeared that concepts of g, general cognitive ability, IQ, have been used interchangeably to refer to each other.

All the samples reported have utilized the quantitative genetic analysis method for statistical analysis of twin data. This method allows for the proportioning of the total variance of a phonotypic variable into three different effects: additive genetic effects (A), common or shared environmental effects (C); and unique or non-shared environmental effects (E), which also include error of measurement. Another possible influence on the total variance is the dominant (D) genetic effects, which cannot be included in the same model with A. Effects of E has to be always considered in a model because it includes measurement error (Plomin et al., 2008). Two samples (Pedersen et al., 1992; Reynolds et al., 2005) had included “S” in their twin model, which refers to all twin similarity which cannot be explained by genetic factors or shared environments. This may be prenatal influence and similarity in adult life experience. As can be seen in Table 1 and 2, the majority of reduced models were AE models, that is, shared-environment (C) was not included in the final model.

Study samples, number of pairs of twins and individuals involved in the samples, demographic variables, best or final model from quantitative genetic analyses, cognitive tests and domains used were displayed in Table 1 (Swedish Adoption/

Table 1 – Samples, demographic variables, best twin model, and heritability of cognitive abilities — Swedish Adoption/Twin Study of Aging.

Sample	No. (pairs)	Age	Sex	Edu/IQ	Final Model	CS/FPC	Verbal ability	Spatial/fluid ability	Memory	Speed
Pedersen et al. (1992) (XS)	113 Mz 189 Dz	65.6 (8.4)	60% F		AESC	81% (AE)	58% Information (ACE) Synonyms (ACE) Analogies (AE)	46% Figure Logic (ES) Block Design (ACE) Card Rotations (ACE)	38% Digit Span (ES) Picture Memory (AE) Names and Faces (ES)	58% (AE) Digit Symbol Figure Identification (AE)
Plomin et al. (1994) (LG)	82 Mz 141 Dz	64.1 (7.5)			AE	80%	57% Same measures as above	46%	50%	60%
Finkel et al. (1995a) (XS)	31 Mz 51 Dz	71.6 (4.8)			AE	54%	43% Sp, 19% G=62% Information	32% Sp, 31% G=63% Block Design	28% Sp, 5% G=33% Digit Span	0% Sp, 49% G Digit Symbol
Finkel et al. (1995b) (XS)	30 Mz 51 Dz	72.4 (4.8)		a 1.5/101	AE	41%			12% G, 29% Sp=41% Digit Span 25% G Picture Memory 25% G Names and Faces	
McClearn et al. (1997) (XS) (OCTO twins)	110 Mz 130 Dz	b82.3	64% F	7.2 (2.4)	AE	62%	55% Information Synonyms	32% Figure Logic Block Design	52% Digit Span Picture Memory	62% Digit Symbol
	90 Mz 104 Dz				AE	53%	Information	Block Design		
Finkel et al. (2000a) (XS)	57 Mz 98 Dz	72.0 (5.4)	62% F		ACE		63% Information + Educ and Occupation	45% Digit Symbol and	Figure Logic+Illness Summary	
(OCTO twins)	68 Mz	83.3	63% F		ACE		24% Same measures	45% Same measures		
	82 Dz	(2.3)								
Finkel et al. (2005) (LG)	798 ind	c 65			AE		79% Information Synonyms Analogies	77% to 79% Figure Logic Block Design Card Rotations	77% Digit Span Picture Memory Names and Faces	77% to 79% Digit Symbol Figure Identification
Reynolds et al. (2005) (LG)	798 ind	at 65			ASCE	91%	70% Information 78% Analogies 75% Synonyms	80% Block Design 67% Figure Logic 74% Card Rotations	84% Picture Memory 52% Digit Span	85% Symbol Digits 78% Figure Identification
		at 80				76%				

Table 2 – Samples, demographic variables, best twin model, and heritability of cognitive abilities — LSADT, MTSADA, NHBLI, Italian study.

	No. (pairs)	Age	Sex	Edu/IQ	Final Model	CS/FPC	Memory	Speed	Executive Functions
Longitudinal Study of Aging in Danish Twins									
McGue and Christensen (2001) (XS)	168 Mz 235 Dz	79.7 (4.0)	71% F	>7	AE	d 54%	43% Word Recall *26% Digit Span*		*37% Category Fluency*
McGue and Christensen (2002)	408 Mz 582 Dz	75.7 (4.5)			AE				
(LG) Wave 1	56 ind					d e 76%	*Same measures*		*Same measure*
Wave 4	33 Mz 30 Dz 147 ind	85.6			AE				
McGue and Christensen (2007)	451 Mz	77.4	59% F		ACE	d e 39%	*Same measures*		*Same measure*
(LG) Wave 1	661 Dz	(5.5)							
Wave 6	18 Mz and Dz	89.4 (3.4)	70% F						
Minnesota Twin Study of Adult Development and Aging									
Finkel and McGue (1993) (XS)	93 Mz 67 Dz	66.6 (6.7)	52% F	12.5 (2.6)/103	AE	55%	56% Word Recall 48% Text Recall 64% Figure Memory		
Finkel et al. (1995b) (XS)	41 Mz 40 Dz	71 (6.9)	54% F	12.0 (2.3)/103	AE	59%	41% sp, 21% G=62% Digit Span 23% sp, 30% G=53% Text Recall 37% sp, 37% G=60% Figure Memory		
Finkel and McGue (2007) (XS)	185 Mz 131 Dz	b 62	60% F	13.4/ 103	AE AE CE			40% Mean Reaction Time 21% f movement time 0% g Decision Time	
Italian Study									
Giubilei et al. (2008) (XS)	35 Mz 58 Dz	67.6 (4.7)	61% F	11.2 (4.4)	AE AE DE DE		54% Story Recall		*79% Selective Attention* *56% Ravens CPM* *62% Verbal Fluency* *54% Category Fluency*
National Heart Lung Blood Institute									
Swan et al. (1999) (XS)	94 Mz 133 Dz	71.8 (2.9)	0% F	13.6 (2.8)	AE		56% Memory 0% Recognition		
Swan and Carmelli (2002) (XS)	80 Mz 78 DZ	71.3 (2.6)	0% F	13.7 (2.9)	AE	79%			34% Verbal Fluency (ACE) 68% Digit Symbol 50% Stroop Inhibition 50% Trail Making B
Lessov-Schlaggar et al. (2007)	94 Mz	72.7	0% F	13.1	AE				71% Digit Symbol
(LG) Wave 2	91 Dz	(3.0)			ACE				52% Stroop Inhibition
Wave 3	127 ind 56 Mz 57 Dz 111 ind	76.6 (1.9)							51% Trail Making B 82% Digit Symbol 61% Stroop Inhibition 43% Trail Making B

Mz=monozygotic, Dz=dizygotic, ind=individuals Edu=years of education. CS/FPC=composite score/first principal component. XS=cross-sectional, LG=longitudinal. A, C, E, D, S=additive genetics, shared environment, non-shared environment, dominance, correlated environment. Sp=effects specific to the individual measure, G=general effects through the general cognitive factor. *Italic*=no cognitive factor or domain, tests placed under domain by first author. a=scale from 1 (elementary school) to 4 (university +), b=median age, c=centering age, d=A influence on composite score of all 3 measures, e=average over waves, f=intraindividual movement time, g=intraindividual decision time.

Twin Study of Aging samples) and in Table 2 (Longitudinal Study of Aging Danish Twins, Minnesota Twin Study of Adult Development and Aging, and National Heart Lung Blood Institute) and an Italian study.

3.1. *Cross sectional twin reports on cognitive aging*

The majority of studies on the heritability of cognitive aging in twins were conducted within The Swedish Adoption/Twin Study of Aging (SATSA). Samples in their various samples are subsets of twins from the population-based Swedish Twin Registry. The other subset is the OCTO-Twin group which included Swedish twin pairs who were 80 years or older (McClearn et al., 1997). In the SATSA samples, various cognitive abilities were grouped under four cognitive domains: verbal ability, spatial/fluid ability, memory, and speed. In addition, a general ability factor was derived from these four domains. Age and sex were corrected for data analyses, and the exclusion criterion was dementia.

Table 1 lists the samples from SATSA in chronological order of the reports published. The mean ages of the participants in the various samples ranged from 65 to 82. Heritability of verbal ability ranged from 0.55 (Confidence Intervals: 0.24, 0.81) in the OCTO-Twin study (McClearn et al., 1997) to 0.79 (Finkel et al., 2005), with the exception of 0.24 (0.09, 0.43) in one study (Finkel et al., 2000a), in which education and occupation were included as indices of verbal ability. Spatial/fluid ability had a genetic contribution ranging from 0.32 (CI: 0, 0.58, McClearn et al., 1997) to approximately 0.79 (Finkel et al., 2005). Heritability of memory functions generally ranged from approximately 0.30 (except 0.16 in an individual task) (Finkel et al., 1995b) to 0.77 for a composite score of three memory tests (Finkel et al., 2005). For processing speed, heritability ranged from 0.33 for mean age of 72 (Finkel et al., 1995a) to approximately 0.80 (Finkel et al., 2005). General ability, as the first principal component in the SATSA samples, ranged from 0.53 for age 82 (McClearn et al., 1997) to 0.91 at age 65 (Reynolds et al., 2005).

Table 2 lists the samples from other study centers. Twin studies of cognition were also conducted within the Longitudinal Study of Aging in Danish Twins (LSADT) (McGue and Christensen, 2001). The LSADT is a cohort sequential study of elderly same-sex twin pairs. Their samples have included participants with mean ages ranging from 77 to 80 years, and the cognitive measures included Digit Span, Word List Recall, and Category Fluency (McGue and Christensen, 2001, 2002, 2007). Age and sex were also adjusted for in their analyses. The heritability of the composite scores derived from these three measures ranged from 0.39 (0.21, 0.60) in McGue and Christensen (2007) to 0.76 (0.68, 0.82) (McGue and Christensen, 2002), with the lowest genetic influence revealed in the oldest group. The heritability of Digit Span as an individual measure was 0.26 (0, 0.48), and for Category Fluency was 0.37 (0.13, 0.49), whereas higher genetic influence of 0.43 (0.10, 0.57) was found for Word List Recall (McGue and Christensen, 2001).

Heritability of cognitive functions was also examined by the Minnesota Twin Study of Adult Development and Aging (MTSADA). In their twin samples, with individuals' mean ages ranging between 67 and 72, measures of memory function (including Digit Span, Text Recall, Word Recall and Figure Memory), heritability was found to range from 0.53 for Text Recall (Finkel et al., 1995b) to 0.64 for Figure Memory (Finkel and McGue, 1993). Genetic influence on a composite score for memory was reported to be 0.59 (Finkel et al., 1995b). As for speed, Finkel and McGue (2007) conducted the only known study on the heritability of simple and choice reaction time in the elderly. It was reported that genetic influence was 0.40 for mean reaction time, and 0.21 for intraindividual "movement time", whereas there was no genetic contribution to intraindividual "decision time" in these tasks.

The National Heart Lung Blood Institute Twin Study (NHLBI) consisted of all male twins who were World War II veterans, with mean ages over 70. Exclusion criteria in their twin reports (Swan et al., 1999; Swan and Carmelli, 2002) were history of documented stroke and/or a score of less than 23 on MMSE. Two of their reports purported to examine the genetic influence on executive functions. For those with a mean age of 71, heritability of executive functions (as represented by verbal fluency, Digit Symbol, Stroop inhibition, and Trail Making Test B) was estimated to be 0.79 (Swan and Carmelli, 2002). Age and education were adjusted for analyses in these two samples. In a more recent longitudinal report, in the first sample with a mean age of 73, genetic influence was stated to be 0.71 (0.63, 0.78), 0.52 (0.39, 0.63), and 0.51 (0.12, 0.66) for Digit Symbol, Stroop inhibition and Trail Making Test B respectively. As for the sample with mean age of 77 heritability estimates were 0.82 (0.75, 0.88), 0.61 (0.43, 0.74), 0.43 (0.08, 0.72) for Digit Symbol, Stroop inhibition and Trails Making Test B respectively (Lessov-Schlaggar et al., 2007). Participants in this sample were selected based on their proximity to the study sites. Genetic contribution to memory functions for the mean age of 72, as indexed by learning and memory, and recognition memory of a word list was 0.56 and 0 (zero) respectively (Swan et al., 1999).

A more recent study conducted in Italy (Giubilei et al., 2008), with a mean age of participants of 68, reported that the genetic contribution to memory (Story Recall) was 0.54, to selective attention was 0.79, and to verbal fluency and category fluency was 0.62 and 0.54 respectively.

Table 3 displays the measures used and cognitive domains assessed in various studies reviewed above. In the SATSA samples, speed was measured by Symbol Digit and Figure Identification. The former is a modified (oral) version of the Digit Symbol Coding Test of the Wechsler Adult Intelligence Scale, and did not require motor skills. Symbol Digit Test was considered as a measure of perceptual speed, an aspect of processing speed. The NHLBI studies used the Digit Symbol Coding Test in its standard manner (writing symbols to digits), but as a measure of executive control. However, it has also been described when used in another sample within the same study centre in another manner, that was, writing numbers to symbols. As for measures of memory, Digit Span was included with Picture Memory and Names and Faces Tests in the SATSA studies under specific cognitive ability of "memory". One of the MTSADA samples had also included Digit Span with Text Recall and Figure Memory as representing a cognitive factor. The NHLBI had used the Californian Verbal Learning Test in one of its investigation on the heritability of learning and recognition memory.

Table 3 – Tests used, domains, and sources in samples from different studies.

Test used	Domain/specific ability	Source	Samples from Studies: Year published
Information	Crystallized/verbal	CVB (modified WAIS) Johnson and Molander (1964)	SATSA: 1992, 1994, 1995a, 1995b, 1997, 2000a, Finkel, 2005, Reynolds, 2005
Synonyms	Crystallized/verbal	Dureman-Slade (DS) Battery, Dureman et al. (1971)	SATSA: 1992, 1994, 1997, 2000a, Finkel 2005, Reynolds 2005
Analogies	Fluid and crystallized/verbal reasoning	WIT – III Westrin (1969)	SATSA: 1992, 1994, Finkel 2005, Reynolds 2005
Figure logic	Fluid/spatial reasoning	DS Battery	SATSA: 1992, 1994, Finkel 2005, Reynolds 2005
	Spatial		SATSA: 1997, 2000a, Reynolds 2005
Koh's block design	Fluid/spatial	DS Battery	SATSA: 1992, 1994, 1995a, 2000a
	Spatial		SATSA: 1997, Finkel 2005, Reynolds 2005
Card rotations	Spatial	Ekstrom et al. (1976)	SATSA: 1992, 1994, Finkel 2005, Reynolds 2005
Digit span			
Forward and backward	Memory	CVB (modified WAIS)	SATSA: 1992, 1994, 1995a, 1995b, 1997, 2000a, Finkel, 2005, Reynolds, 2005
	Memory	WAIS-R (Wechsler, 1981)	MTSADA: 1995b
	Cognitive	Developed for project	LSADT: 2001, 2002, 2007
Thurstone's picture memory	Memory	DS Battery	SATSA: 1992, 1994, 1995b, 1997, 2000a, Finkel 2005, Reynolds 2005
Names and faces	Memory	Colorado Adoption Project	SATSA: 1992, 1994, 1995b,
Immediate and delayed		DeFries et al. (1981)	Finkel 2005
Word list recall-12 items	Cognitive	Developed for project	LSADT: 2001, 2002, 2007
Word recall-36 items	Memory	Finkel and Fox (in press)	MTSADA: 1993
Logical memory	Memory	Wechsler Memory Scale	MTSADA: 1993
Immediate and delayed	Memory	Wechsler (1945)	MTSADA: 1995b
Immediate only			
Visual reproduction-immediate	Memory	Wechsler Memory Scale, 1945	MTSADA: 1993, 1995b
California verbal learning test	Learning and memory	Fridlund and Delis (1987)	NHLBI: 1999
Story recall	Memory	Novelli and Papagno (1986)	Italian Study: 2008
Mini-mental state exam	Cognitive screening	Folstein et al. (1975)	LSADT: 2001, 2002, 2007
	Overall functioning		NHLBI: 2002, Italian Study: 2008
Digit symbol (oral)	Perceptual speed	Modified WAIS	SATSA: 1992, 2000b
	Speed of processing		SATSA: 1994, 2000a
(Writing no. to symbols)	Perceptual speed		SATSA: 1995a
	Processing speed		SATSA: 1997
(Writing symbols to no.)	Perceptual speed		MTSADA: 1995a
Symbol digit modality test	Perceptual speed	Smith (1982)	SATSA: Reynolds 2005
Digit symbol substitution	Executive function	WAIS-R (Wechsler, 1981)	NHLBI: 2002, 2007
Figure identification	Perceptual speed	DS Battery	SATSA: 1992
	Processing speed		SATSA: 1994, Finkel 2005
Reaction time	Speed		MTSADA: 2007
Verbal fluency	Executive function	Benton et al. (1983)	NHLBI: 2002
Semantic fluency ("animals")	Cognitive	Developed for project	LSADT: 2001, 2002, 2007
Verbal and semantic fluency	Word generation	Borkowsky et al. (1967)	Italian Study: 2008
Trail making test B	Executive function	Reitan (1958)	NHLBI: 2002, 2007
Stroop colour–word test	Executive function	Stroop (1935)	NHLBI: 2002, 2007
Raven's CPM	Logical reasoning	Raven (1947)	Italian Study: 2008
Attentional matrices	Selective attention	Spinnler and Tognoni (1987)	Italian Study: 2008
Token test	Auditory comprehension	De Renzi and Vignolo (1962)	Italian Study: 2008

References for Source of Tests in "Footnote 2". Finkel 2005=Finkel et al., 2005,Reynolds 2005=Reynolds et al., 2005,CPM=Colored Progressive Matrices.

An observation relating to general cognitive ability, which was a composite score or first principal component score, was that it showed greater heritability than the individual measures or domains that it was derived from (Pedersen et al., 1992; Plomin et al., 1994; Finkel et al., 1995b; Reynolds et al., 2005; McGue and Christensen, 2001; Swan and Carmelli, 2002). In relation to this general ability measure, Pedersen et al. (1994) reported that 12 of the 13 tests in their 1992 sample

showed significant genetic influence which was independent of the genetic influence on general cognitive ability. There were two further reports (Finkel et al., 1995a,b) that described "specific effects" (from that individual measure) and "general effects" (through the common factor) contributing to the heritability of a cognitive measure, as shown in Table 1 and 2. The relationship between genetic influence on general cognitive ability and genetic influence on specific cognitive ability requires further examination.

To summarize across the above cross-sectional data from different centers, there appears to be a decrease in genetic influence with increasing age for verbal ability (0.79 for mean age 65, 0.55 for mean age 82), spatial ability (0.63 for mean age 71, 0.32 for mean age 82), and general ability (0.81 for mean age 65, 0.62 for mean age 80). In contrast, there appears to be an increase in genetic influence with age in processing speed: 0.26 for mean age of 72, and 0.62 for mean age of 82. Executive functions showed a similar trend with a heritability estimate of 0.34 (verbal fluency) and mean age 71, and 0.61 for mean age of 76. As for memory, the least (0.38) and highest (0.77) levels of genetic influence were found in different samples which had the same mean age of 65.

However, this summary of cross-sectional data had focused on the extremes of age difference, and included samples that have reported on single tests or combinations of tests that contributed to a cognitive factor. When examined in more detail, the heritability of verbal ability reported in two other samples was similar to those of mean age 82: 0.55 and 0.58, with mean ages of 65 and 64. Similarly, genetic influence of 0.76 had been reported for age at 80, which was similar to 0.81 reported for age 65. As for spatial ability, heritability of 0.45 was reported in two samples with mean age of 72. In addition, as can be seen in Table 3, different measures were used to represent a particular cognitive domain (such as different tests included in SATSA and MTSADA samples for memory), the same measure was included in different domains, and a particular test was used in various way in different samples. These render the findings across the different samples and study centers difficult to interpret and to compare.

3.2. *Longitudinal data and genetic influence on rate of change in cognitive aging*

In order to assess heritability and the genetic and environmental influence in the rate of change, complex statistical analyses were employed: cross-sequential analysis (Finkel et al., 1998) or cohort sequential design (McGue and Christensen, 2002), latent growth curve analysis (Reynolds et al., 2002, 2005), individual growth curve analysis and biometric growth curve analysis (McGue and Christensen, 2007). Growth curve analysis allows for the consideration of "intercept" (level of performance) and "slope" (rate of decline). Lessov-Schlaggar et al. (2007) conducted multivariate genetic analysis to determine the correlation of genetic and environmental influences on performance across time points. Univariate analysis was then used to establish the contribution of genetic or environmental influences on the changes of decline.

Plomin et al. (1994) examined the SATSA longitudinal data of twins over two assessments, mean ages 64 from Pedersen et al.'s (1992) sample and 66, three years apart. Results showed stability in the heritability of the general cognitive ability measure of approximately 0.80 on both occasions. It was found that genetic factors accounted for approximately 90% of this stability. As for the individual cognitive domains which constituted general cognitive ability, the average heritability estimates over the two testing occasions were approximately 0.60, 0.50, and 0.40 for verbal ability, spatial ability and processing speed respectively.

Using both cross-sectional and longitudinal twin data, with six cohorts and three measurement times, Finkel et al. (1998) used cross-sequential analysis to determine the genetic variance over time for various cohorts. The cognitive measures consisted of the 13 tests included in the SATSA battery. The mid-point age for the youngest cohort was 55, and for the oldest 75. Their analysis revealed a definite decrease in genetic variance over time, especially for the older cohorts (mid-point ages: 67, 71, and 75). Genetic influence decreased from approximately 80% at measurement 1, to 60% at measurement 3 for the older cohorts. There was also an increase in environmental variance for the two oldest cohorts.

The latent growth model was used to examine the sources of influence (genetic or environmental) on individual difference on "ability levels", as compared to the "rate of change" in a subset of SATSA twins (Reynolds et al., 2002). Three cognitive domains were included in the analyses: spatial ability (Block Design), memory (Thurstone's Picture Memory), and perceptual speed (Symbol Digit). Results here suggested that genetic influences were of greater importance to individual variability in ability level. As for the rate of change, it was found that there was a larger, mainly non-shared environmental component for the rate of change.

In examining further the decrease in genetic influence in cognitive functioning in aging, Reynolds et al. (2005) employed biometric latent growth curve models to examine the sources of variability for ability "level" and "change" for verbal ability, spatial ability, memory, and processing speed in a SATSA sample. Cognitive data on 10 cognitive measures under the four cognitive domains of the SATSA cognitive battery as well as g, derived from first principal component of the cognitive measures, was obtained over four occasions and spanning 13 years. Mean ages on the four testing occasions were 64.9, 65.4, 68.3, and 70.8 respectively. Results indicated that genetic variation was more significant than non-shared environmental variation for ability level at the age of 65. As for the changes in genetic and environmental variance with age, non-shared environmental variance was found to generally increase with age, whereas genetic variance usually decreased with age. The above pattern of change, however, did not apply to two of the memory measures (Digit Span and Picture Memory) and one of the verbal measures (Information), in which genetic influence increased with age.

The Danish group (LSADT) has published two reports on the heritability of cognitive aging. The first study (McGue and Christensen, 2002) involved twins over 70 years of age, assessed across four testing occasions. Cognitive performance was examined with Category Fluency, Digit Span, and a 12-item list recall. The mean age at the first testing occasion was 76 and at the third follow-up was 85.6. The results indicated that the overall level of cognitive functioning was high in

genetic influence (0.76), but heritability estimates for the rate of linear change in cognitive performances was low (0.06). With additional cohorts, their second report (McGue and Christensen, 2007) involved the same cognitive measures, but over six testing occasions and with mean ages of 77 at the first wave and 89 on the fifth follow-up. This report indicated that the genetic contribution to the levels of cognitive function was significant (0.39), and for the heritability of the rate of change was 0.18, indicating greater environmental influence.

Genetic and environmental influences in individual variation in executive functions and decline over time was investigated with the NHLBI all male twins (Lessov-Schlaggar et al., 2007). Three tests: Digit Symbol, Trail Making Test B (time to completion), and Stroop inhibition task (number of correct responses within 45 s), were used to index executive control. The mean ages for each testing occasion were 63, 73, and 77 respectively. Digit Symbol performance was shown to have increased genetic influence over the three occasions (0.69, 0.71. and 0.82 respectively). Genetic influence on Stroop inhibition was also shown to increase from 0.52 to 0.61 over two testing occasions (four years apart). However, the level of performance of Trail Making Test B showed a decrease in genetic influence from 0.51 to 0.42 over two occasions. The longitudinal change in performance decline for all three tasks (over a four year period) was reported to be completely attributable to non-shared environmental factors.

Taken together, data from longitudinal research appears to indicate that there is stability over time in the genetic influence in general cognitive ability as well as in specific cognitive measures of verbal ability, spatial ability, memory, and processing speed for the relatively younger-old (mean age 65) groups. However, there is a decrease in heritability for the older and oldest cohorts (mean ages 70 s and 80 s) over time, and an increase in unique (non-shared) environmental influence. As for the rate of change, there is relatively little genetic contribution but more unique environmental influence with increasing age. It is also interesting to note that the rate of change in performance decline from the second to the third testing occasion for all three measures of executive functions in the NHLBI sample was entirely due to unique environmental influence.

3.3. *Genetic relationship between processing speed and other cognitive abilities*

Finkel and Pedersen (2000) examined the genetic influences on cognitive functions in adulthood, in the context of the relationship between perceptual speed and cognitive aging in a subset of SATSA twins. It was reported that 90% of the age-related variance in the four cognitive domains: crystallized (Information), fluid (Block Design), memory (Picture Memory), and spatial (Card Rotation) was shared with perceptual speed (Symbol Digit and Figure Identification). Seventy percent of genetic variance in cognitive domains was shared with perceptual speed. Perceptual speed and the cognitive factor (constructed from the four cognitive domains) also shared larger genetic effects in common with increasing age.

To investigate the role played by measures of processing speed in explaining the longitudinal pathway of change for cognitive abilities and the genetic influences on those trajectories, Finkel and Pedersen (2004) used four measures of cognitive abilities from the SATSA battery. These were crystallized ability (Information), fluid ability (Block Design), memory (Picture Memory), and g, a general cognitive factor (created from principal component analysis). It was reported that when the effect of perceptual speed (Symbol Digit) was removed from the other cognitive measures, the pathway of decline was less severe. It was reported that a substantial portion of the genetic variance for the cognitive measures was accounted for by the genetic contribution to processing speed. Their results also suggested that environmental influence increased in late adulthood.

Another study on the genetic and environmental influences on the longitudinal association between processing speed and cognitive ability was conducted by Finkel et al. (2005). Results of their multivariate genetic analyses on the longitudinal data on three cognitive domains (verbal ability, spatial ability, memory) suggested that there were significant genetic influences on the initial level of performance for the three cognitive factors, half shared with processing speed (Symbol Digit and Figure Identification) and half independent of speed. Genetic influence on the decline in the specific cognitive abilities was not significant. As for accelerating (faster rate) age changes, there were minimal genetic influences for verbal ability, but strong genetic influences for the spatial and memory domains. Environmental influences for all three cognitive factors were largely independent of environmental influences on processing speed.

There has been, to our knowledge, no other group which had examined the relationship between heritability of processing speed and other cognitive abilities. Based on the findings from the two earlier SATSA samples (Finkel and Pedersen, 2000, 2004) and their own report, Finkel et al. (2005) drew the following general conclusions regarding the genetic influence on the relationship between processing speed and cognitive aging. Firstly, a significant proportion of genetic influence on cognitive ability arises from genetic influence affecting processing speed. Secondly, this effect is more prominent in late adulthood. Thirdly, it is the accelerating age changes in cognitive performance that share genetic variance with processing speed, and not the linear age changes. It should be noted that these conclusions were limited to processing speed, as indexed by performance on the oral report of digits to symbols, and was considered as perceptual speed by the SATSA.

3.4. *Sex differences in the heritability of cognitive abilities*

In their study of SATSA twins, with mean age groups (by sex and zygosity) of 76 to 80 years, Read et al. (2006) found sex differences in mean levels of performance, with women performing worse than men among the oldest participants in the sample. However, they did not find significant differences in heritability or sex-specific genetic influences in general cognitive abilities (verbal, fluid, memory, and speed). The same genetic effects were involved for men and women, and the magnitude of genetic effects was similar for both sexes. Finkel et al. (2006) examined the genetic and environmental contributions to sex differences in the level of cognitive performance and the rate of decline in a SATSA sample. While the results showed sex differences in the mean level of performance for five, and the rate of decline in two of

the cognitive measures, only Synonyms (in the verbal domain) demonstrated sex differences in the genetic and environmental influence to mean level of performance, in that heritability was higher in men than in women. Clearly, there is a lack of research into sex difference of cognitive functions in twin studies of the elderly for conclusive comments to be made.

4. Discussion

In this paper, we review the published studies on elderly twins, 65 and above, to examine genetic influences on individual variation in cognitive aging. Studies of heritability of cognitive functions across the life span have shown that genetic effects on cognitive functions increase linearly with age from childhood, with genetic influences greatest in older adulthood (Singer et al., 2004). This current review of twin studies on the elderly indicates that there may in fact be a more complex relationship.

Cross-sectional studies seem to suggest a decrease in heritability of g, from 80% at the mean age of 65 to 60% at the mean age of 82. This pattern of reduction in genetic influence appears to be the trend for verbal and spatial abilities. Processing speed and executive functions seems to show an opposite trend of increase in genetic influence as age increases. As for memory, the extent of genetic influence as the individual ages is equivocal. However, these comments are made when only the extreme ages were considered. In addition, data are mostly obtained from samples from the same study centre, with one cognitive measure confounding another, and with measures labeled under different cognitive domains in different samples. Further, the comparability between studies has been compromised by the heterogeneity of the samples across studies, with different inclusion and exclusion criteria. Therefore, the issue of whether heritability increase or decrease with age after 65, is inconclusive.

Longitudinal twin studies have generally indicated that there may be stability over time in the genetic influence on the "levels" of performance in general cognitive ability, as well as in more specific cognitive domains (verbal ability, spatial ability, memory, and processing speed) for the younger old with mean age of 65. Non-shared environmental influences seem to increase in their importance, suggesting a shift in relative influence after this age. There is a decrease in genetic influence over time in the older cohorts, with mean age of 70 s and 80 s. There is little genetic effect in the "rate" of change, but increase in unique environmental influence with increasing age.

Apart from genetic and environmental influences, impending death is another factor associated with cognitive decline in the elderly (Wilson et al., 2003). Cognition undergoes a period of terminal decline in the final years of life and this significantly contributes to age-related loss of cognitive ability. In examining cognitive data over time, Pedersen (2000) observed that for twin pairs who had participated in all three waves of the studies, cognitive performance was relatively stable. However, there was a slight and subsequently steeper decline in performance between the first two (of three) occasions for pairs in which either or both twins ceased their involvement with the study after wave two, with the twin pairs participating in only the first assessment performing at the lowest level. The implication here is that individuals who were unwell at the first assessment were too ill to participate, or died before the subsequent assessments. The timing of entry into terminal decline is considered to be associated with environmental factors, which might also be associated with "selection bias" in longitudinal studies (Finkel et al., 2000a).

As noted, there were inconsistencies between the two studies by McGue and Christensen (2002, 2007), in that the genetic influence on the levels of performance was 75% (4 waves) and 39% (6 waves), and the heritability of the rates of change was 6% and 18% respectively. While the magnitude of these discrepancies can be partly attributed to the addition of cohorts in the second report, the reduction in genetic influence on the levels of performance over the two reports could also be explained by the effects of terminal decline and selection bias, as demonstrated the reduction in sample sizes from intake to the final follow-up.

It is unfortunate that the results of this review do not allow for the comparison of the two theories of cognitive aging. Processing speed as a mediator or factor involved in the heritability of cognitive aging has been the focus of much twin research, and has gained support from the studies reviewed. Several SATSA reports have concluded that processing speed is more strongly heritable than other cognitive functions, and it may be considered as "genetic informative" data for cognitive aging. It has also been considered as the major marker of cognitive change in their non-twin studies of aging. In contrast, the possibility that age-related loss in selective attention and maintenance of attentional set is associated with reduced performance in other cognitive domains (what may be regarded as a "frontal system" hypothesis) has only been alluded to by Finkel et al. (2000b).

A limitation in the current literature pertaining to twin studies of cognitive aging is the inclusion of one or two tasks as measures of one aspect of processing speed. Salthouse (2000) has pointed out that there are at least six different measures of "speed": decision speed, perceptual speed, psychomotor speed, reaction time, psychophysical speed, and time course of internal responses. As different studies used different measures and examined different aspects of processing speed, it makes combining and comparing results difficult and likely contributes to some of the discrepancies noted between individual studies. Similarly, the different memory tests used in various samples place different demands on cognitive functioning, and the variability in the use of instruments to assess "memory" renders the comparison of findings from different studies problematic. This may also contribute to the equivocal findings of genetic influence in memory in this review.

While an examination of the heritability of executive functions has been attempted by the NHLBI studies, the measures used have confounded assessment of this construct with speed. Thus, although intended to study executive functions (inhibition and cognitive flexibility), time to complete and number of errors made in performing relatively complex timed tasks were used as the dependent measure, without consideration of a "baseline" speed component which did not impose demands on executive control. This

methodology may therefore have led to the questionable conclusion that the heritability of executive functions in the elderly is high (approximately 80%). When considered as speeded tasks, the genetic influence on these "executive function measures" in the NHLBI studies would lend support to the aforementioned observation in this review that processing speed seems to show an opposite trend of increasing genetic influence with increasing age. Therefore, in order to test the relative heritability of executive functions versus processing speed and thereby evaluate the two competing models of cognitive aging, there is a need for research to identify relatively pure indicators of each of these constructs.

It is also not possible to draw definite conclusions regarding sex difference in the heritability of cognitive functions. From the two studies on this issue that has been reviewed, and with their relatively small samples, no significant sex difference in heritability of general cognitive abilities was found. One of the reasons for the lack of focus in sex difference may be the generally disproportionate numbers of males and females in twin samples, with approximately one-third and two thirds of the samples comprising males and females respectively. Other twins study centers involved only male twins (NHLBI) and same-sex twin pairs (LSADT) in their study samples, thus limiting the opportunity to explore this issue.

A further limitation of the current literature is the disproportionate reliance on Scandinavian studies. In particular, heritability of verbal and spatial abilities, and the relationship between processing speed and other cognitive abilities were only explored by the SATSA centre. Although two published reports had drawn comparisons between SATSA and MTSADA samples, the cognitive measures used were not consistent across the two samples. McGue and Christensen (2001) have suggested that relative to many other countries, the Danish health system would have provided better health care for elderly people, thereby increasing the environmental influence in cognitive aging. It would be important to see if their findings and those of the other Scandinavian countries, of increased environmental influence can be replicated when investigations are extended to other Western and non-Western countries. This may also elucidate the role played by different governments and their policies in the prevention and reduction in risk factors associated with cognitive impairment in the elderly.

The findings from this review indicate a significant role for non-shared environmental factors in cognitive aging. This is not only due to their increased influence with increasing age on most of the cognitive domains, but also in view of the findings that there was no genetic contribution to intraindividual decision time in reaction time tasks, and that the rate of change on all the executive functions measures in the NHLBI study was entirely due to unique environmental influences. The genetic influence on verbal ability in a SATSA sample (Finkel et al., 2000a) was reduced to 0.24 from generally above 0.55 in other samples when education and occupation was included with Information under the same domain, suggesting the importance of non-shared environmental factors. Some of these environmental factors such as mental activities, physical exercise, educational attainment and occupational background, are potentially modifiable and should be investigated. Moreover, much larger samples would be required to detect shared environmental influences, as underpowered twin samples can misleadingly inflate the contribution of genetic influence. While shared environmental influences may exist in these models from the samples reviewed, it would require a large number of twin pairs such as more than 1000 pairs of each zygosity to detect these effects (Swan and Carmelli, 2002).

Finally, collaborative research between study centers, would increase the sample size and provide better statistical power for more sophisticated statistic analysis of data, such as meta-analysis. Collaboration would also be beneficial for the study of genetic influence and sex differences in cognitive aging, as the necessary sample size of opposite sex twin pairs required for research in this area would be more readily achieved. Consistency of measures used in examining the different cognitive domains would improve the comparability between studies. Further, the study of heritability in cognitive functioning in the elderly is only the initial stage of disentangling the genetic and environmental determinants of cognitive aging. Identifying specific genes and environmental risk and protective factors, and their interactions, as well as their neuroimaging correlates (see Mattay et al., 2008) and molecular correlates (see Deary et al., 2009), would be areas of interest, and present challenges to current and future research.

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