The genetics of cognitive ability and cognitive ageing in healthy older people

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Determining the genetic influences on cognitive ability in old age and in cognitive ageing are important areas of research in an increasingly ageing society. Heritability studies indicate that genetic variants strongly influence cognitive ability differences throughout the lifespan, including in old age. To date, however, only the genes encoding apolipoprotein E (APOE) and possibly catechol-O-methyl transferase (COMT), brain-derived neurotrophic factor (BDNF) and dystrobrevin binding protein 1 (DTNBP1) have repeatedly been associated in candidate gene studies with cognitive decline or with cognitive ability in older individuals. Genome-wide association studies have identified further potential loci, but results are tentative. Advances in exome and/or whole-genome sequencing, transcriptomics, proteomics and methylationomics hold significant promise for uncovering the genetic underpinnings of cognitive ability and decline in old age.

Human cognitive ability and non-pathological cognitive ageing

To speak of the ‘genetics of’ cognitive ability and cognitive ageing refers to the possibility that genetic differences cause some of the variation in these two phenotypes that is manifest in humans. To proceed, there must be clarification of the difference between cognitive ability and cognitive ageing, and of the phenotypes to be studied within each. Pathological states of cognitive decline (the dementias, other neurodegenerative conditions and prodromal states, such as mild cognitive impairment) are important research areas, and with their own research fields, including genetics. However, in the present overview, we focus on genetic contributions to normal, non-pathological variation in cognitive ageing. This is an important and large research area in its own right, in part because cognitive ageing affects people’s quality of life, predicts dementia and death, and is at this stage more likely to be open to amelioration [1,2]. We present evidence from twin studies that indicate that cognitive ability in old age is highly heritable. We then describe both candidate gene and genome-wide association studies (GWAS; see Glossary) that have attempted, with limited success, to determine the specific genetic variants that influence cognitive ability and cognitive ageing.

Cognitive ability and cognitive ageing

Consider the scores obtained by a 75-year-old individual in several mental tests; say, tests of memory, reasoning, speed of processing and so forth. This is an age at which the adult peak in such skills is typically well past [3,4]. Therefore, scores on any one test will be the combination of three things: the previous peak level of the ability, how much age-associated change there has been, and occasion-specific variance (including error variance). To separate the phenotypes of level and change in cognitive abilities, longitudinal studies are required in which people have taken mental tests on more than one occasion. This allows a cognitive trajectory to be computed for each subject. From a sample of such subjects, it is then possible to describe and find determinants of the differences in levels and rates of change in cognitive abilities. These are different things, probably with different determinants.

Glossary

Allele: one of two or more versions of a gene.
Candidate gene study: a study that investigates associations between genetic variants in a gene suspected of influencing a trait of interest (by virtue of the function or chromosomal location of the gene) and the trait.
Cognitive change: the change in cognitive score between occasions of measurement. Note that it is common to see ‘cognitive ageing’ referred to when only one occasion of measurement has taken place. This is a common error.
Cognitive level: cognitive score obtained on one occasion.
General intelligence (g): operationally, g is typically the first unrotated principal component (or factor) from a battery of mental tests administered to a sample of a population. It describes the near-universal finding that all mental tests tend to correlate positively.
Genome-wide association study: a hypothesis-free study whereby up to 1 million SNPs, spread throughout the genome, are investigated to identify genomic regions associated with a particular trait.
Intercept and slope: given a number of occasions of cognitive measurements, a regression equation can be applied to the longitudinal data of each individual to discover their starting level of cognitive ability (intercept) and trajectory of cognitive change (slope). Therefore, one can seek the antecedents [including genetics] and outcomes of the slope and trajectory. Note that the slope might be linear, quadratic or even more complex.
Single nucleotide polymorphism (SNP): a position on a chromosome where humans are known to differ with regard to which base pair occurs.
Cognitive phenotypes

How do we define cognitive phenotypes? If there were just, say, three types of mental work that brains performed, and if there was a perfectly valid test for each of them, this would be simple. One would apply these three tests each time one wished to assess an individual’s cognitive capabilities. This is not the case, however. There is no widely accepted taxonomy of brain functions that is isomorphic with mental tests. Therefore, what is available as phenotypes is a set of cognitive tests that are classified largely by their contents. To an extent, the contents do show isomorphisms with brain activation. Indeed, there tend to be their contents. To an extent, the contents do show isomorphisms with brain activation. Indeed, there tend to be two somewhat separate approaches to cognitive phenotypes, including how they are applied to ageing. The first is called the differential psychology (or psychometric) approach. It studies the multivariate associations among mental test capabilities and forms taxonomies of abilities based on correlations among cognitive skills [5] (Box 1). The second approach, called the cognitive or neuropsychological approach, relies more on lesion and brain imaging studies, and tends to focus on mental capabilities within a given domain of function [6]. In the present article, we largely use the differential psychology approach, as this is the approach almost exclusively employed in behaviour genetic studies and the bulk of molecular genetic studies seeking to explain individual differences in cognitive function and change in old age.

Factors affecting age-associated cognitive decline

There are changes in population mean levels of cognitive test scores as people age, but what we are interested in here is the individual differences in these life-course changes and respect to ageing, an important distinction should be made between relatively age-sensitive cognitive domains (e.g., memory, speed of processing, spatial ability, and reasoning) and relatively age-resistant domains (e.g., verbal and numerical abilities) [50]. Furthermore, one might ask about the stability of cognitive differences, and whether age affects any or all of these three levels of cognitive variation. From youth (20 years) to later middle age (55 years) [51], and even from childhood (11 years) to old age (79 years) [52,53], there is high stability in people’s rank order of cognitive ability differences. In a study of male twins followed from age 20 to 55, genetic factors were responsible for the stability (and the same genetic influences were found at both ages) and non-shared environmental causes explained the changes [51]. With regard to how ageing affects cognitive abilities, a study of over 1200 people subjected to 12 mental tests for up to seven years found that 39% of the effect of age was on general cognitive function, 33% was at the level of domains (i.e. abstract reasoning, spatial visualization, episodic memory and processing speed) and 28% was at the level of the individual test [54]. Other longitudinal [55] and cross-sectional studies [3] also find this distribution of ageing effects across general and specific cognitive skills. To summarise: some ageing effects appear to be general and affect all cognitive skills, and some are more specific.

Box 1. The differential psychology approach to cognitive ability

Put simply, the differential psychology approach asks: do individuals differ in how generally smart they are, or do they tend to differ in their specific cognitive capabilities? Both are true to some extent, and the answer lies somewhere in between. This is based on the finding that all mental tests show positive covariation, and that there are groups of types of test that show higher correlations among themselves than with other mental tests. Therefore, the sources of variance (i.e. the thing that one is trying to explore genetic contributions to) are at least on three levels [5] (Figure I). Individuals differ in how generally mentally able they are; this is often called general intelligence, or g. Approximately half of the population variation in cognitive skills is captured by variation at this level. As long as there is a reasonable number of varied mental tests applied, this g factor ranks people almost identically even when it is based on different tests [47,48]. Individuals differ in how good they are in broad mental domains (e.g. memory, processing speed, visual perception, auditory perception, retrieval ability, etc.). They also differ in their specific cognitive skills. Therefore, one can seek genetic and other contributions to variation at each of these levels. The result is that additive genetic factors contribute approximately 70% or more of the influence on g in adulthood [7,47,49]. Other levels have high heritability too, but much of this is because they are highly correlated with g and so the genetic causes of g partly also cause these lower-level differences. With the effect of age was on general cognitive function, 33% was at the level of domains (i.e. abstract reasoning, spatial visualization, episodic memory and processing speed) and 28% was at the level of the individual test [54]. Other longitudinal [55] and cross-sectional studies [3] also find this distribution of ageing effects across general and specific cognitive skills. To summarise: some ageing effects appear to be general and affect all cognitive skills, and some are more specific.
what might cause them. Multiple factors have been proposed as possible determinants of individual differences in non-pathological, age-associated cognitive change [1]. A recent and thorough review examined over 100 observational studies, and many randomised controlled trials and systematic reviews [2]. The studies included nutritional, medical, socio-economic, behavioural, toxic and genetic factors. Firm evidence was lacking for most factors, but there appeared to be relatively robust evidence for risk of increased cognitive decline from the apolipoprotein E (APOE) ε4 allele, smoking and some medical conditions. There was also some evidence for the protectiveness of physical exercise and cognitive training.

With regard to studies of the genetic causes of differences in cognitive ageing, the simplest division of these is into behavioural and molecular genetic studies. Behavioral genetic studies typically examine twins and adoptees. They have been informative about how environmental and genetic causes affect mental test performance in old age. Mostly, they employ quite complex statistical modeling methods, but all are based on the facts that: monozygotic twins have 100% genetic similarity whereas dizygotic twins share, on average, 50%; and that adoptees share environmental but not genetic causes with their rearing family, and the reverse with their biological parents. Behavioral genetic studies have been used to explore whether genetic and environmental causes operate at the level of general intelligence (g) or specific cognitive domains, and have also explored causes of cognitive change as well as cognitive level within old age. It is important to repeat here that an association between a genetic variant and cognitive scores in old age is not the same as studying genetic contributions to cognitive ageing. Any association based on tests taken at a single time point might just represent an association with the life-long, stable trait of intelligence; to study ageing per se, it is important to show some association with individual differences in change across two or more occasions of measurement.

Heritability of cognitive ageing
The total variance (from genetic and environmental influences) in cognitive ability increases with age, possibly owing to stochastic effects. Although it might drop a little in advanced old age, there is also an increase in the percentage of this total variance that has a genetic component [7]. The contribution of twin studies to cognitive level and change in old age has been summarised extensively by Lee et al. [8]. As is found in earlier periods of life, the majority of the genetic variation is in general cognitive ability. The major cognitive domains also show high heritability, largely because they derive much of their variation from g. Memory in particular tends to have its own genetic causes in addition to those that derive from general cognitive ability [9].

Much of the information about genetic causes of ability differences in old age has come from various samples based on the Swedish Twin Registry. For example, the Swedish Adoption Twin Study of Ageing estimated the heritability of g at approximately 80% in the mid-60s, and showed a high correlation between g loadings of tests and their heritability [10]. Longitudinal study of this sample tested on multiple occasions over 13 years separated the genetic and environmental causes of the level and slope of cognitive functions [11]. The heritability of cognitive level was very high, with most of the rest being caused by unique and non-shared environmental effects. Whereas g still accounted for substantial genetic contributions to the cognitive domains, an interesting finding was that the heritability in fluid and/or spatial ability decreased somewhat with age, whereas that of memory increased. The slope of cognitive function with age had linear and quadratic aspects. The causes of differences in the former were almost entirely the influence of a unique environment, whereas the quadratic aspect (accounting for a much smaller proportion of variance than the linear effect) had some genetic influence. Analyses of the genetic effects on the four cognitive domains in the SATSA tests (verbal, spatial, memory and speed) over a period of up to 16 years found significant genetic influences on the intercepts, but not on the slopes [12]. However, genetic influences did affect cognitive slopes via intercept–slope correlations; that is, there were genetic influences on cognitive level, and individuals starting at different cognitive levels did not decline at the same rates. These complex analyses came to an important conclusion concerning genetic contributions to age-related cognitive changes: that genetic variance in processing speed is largely responsible for the variation that occurs at a later time point in other cognitive factors. Therefore, researchers interested in determining genetic factors that influence cognitive ageing should look for those that influence processing speed.

The Swedish study with the oldest subjects (the OctoTwin Study) reported that the heritability of g was 62% at a median age of 82 years, with the heritability of cognitive domains being between 32% and 62% [13]. The non-genetic variance was caused by non-shared environmental factors. Further analysis of this sample found that the genetic contributions to the cognitive domains of verbal ability, spatial ability, speed of processing and memory were largely those that caused differences in g [9].

Similar results and conclusions were derived from studies of the Longitudinal Study of Aging Danish Twins [14–16]. It should be stressed that the cognitive test battery in this study was small: the number of animals that could be named in 1 min; forward and backward digit span; immediate and delayed recall of a 12-word list. Even so, at initial assessment, when subjects had a mean age of 80 years and were all over 75 years, the additive genetic contribution to the cognitive composite score was 54%, with the remainder owing to non-shared environment, which is similar to that from the comparable Swedish study [13]. Follow-up of this sample to include four waves of cognitive testing showed a heritability of 75% for cognitive level but almost zero for cognitive change [15]. The heritability estimate for slope using data from a subsequent wave was 18%, but still non-significant: most of the contribution to change appeared to come from a non-shared environment [16]. Note that this higher heritability estimate for level is because level is a latent trait summarising four individual waves of testing, each of which had heritabilities typically of approximately 50%; the estimate was lower at a subsequent follow-up [16]. Note also that the total retest time
was no more than 6 years, which does not allow much time for any genetic or environmental factors to influence cognitive change.

A US study of male twins between 69 and 80 years old reported a heritability of 79% for a latent trait of executive control [17]. The contributing tests to this trait (digit symbol, stroop, trail making and verbal fluency) make it likely to be a reasonable measure of $g$.

In summary, the Swedish Twins-based and other studies have demonstrated that heritability of $g$ and the major cognitive domains is still high in old age and that the heritability of the latter is due substantially to influences on the former. It is important to note that heritability studies have been more revealing for cognitive level than for cognitive change. Cognitive change tends to suffer from a poor phenotype: being studied over too-short periods of time with insufficient assessments [8]. Having established high heritability of cognitive level in old age, and with the jury still being out on genetic contributions to cognitive change, it has been important to seek the specific genes that contribute to cognitive differences in old age. Here, we consider several approaches, including candidate gene studies and GWAS. Several more recent promising approaches are summarised in Box 2.

**Candidate genes**

Several approaches have been taken to identify candidate genes to test for association with both cognitive ability in older people and age-related cognitive decline. Generally speaking, selected genes have previously been associated with age-related diseases, traits and mechanisms. Many of these genes have been implicated in cognitive ability and cognitive ageing, but few findings have been replicated. Selected examples of candidate genes, for which there are multiple positive associations, are given below. We first discuss candidate gene studies in the context of normal cognitive function in elderly subjects [18]. However, a meta-analysis failed to find strong evidence for an association between $COMT$ and cognition, finding only suggestive evidence that methionine homozygotes score slightly higher on cognitive ability tests [20].

**Neurocognitive disease**

The genetic contribution to Alzheimer’s disease (AD) has been widely studied. Genes associated with the rare early-onset form of the disease include those encoding amyloid precursor protein (APP), presenilin 1 ($PS1$) and presenilin 2 ($PS2$), but none has been definitively associated with cognitive function or age-related cognitive decline in normal cognitive function

As memory is particularly badly affected by ageing, genes previously associated with memory phenotypes have been widely studied with regard to cognitive decline. For example, brain-derived neurotrophic factor ($BDNF$) has been implicated in hippocampal-dependent learning and memory in humans and non-human species and there is a steady decline in $BDNF$ expression associated with normal ageing [19]. A single functional common polymorphism has been identified in $BDNF$, a valine to methionine change at amino acid 66. The methionine allele has been implicated in abnormal hippocampal function, lower hippocampal volume and reduced cognitive function. Some, but not all studies have identified an association between $BDNF$ and cognitive function in elderly subjects [18].

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non-demented individuals [21]. By contrast, the ε4 allele of the APOE gene, associated with the more common late-onset AD (LOAD), was shown by a meta-analysis to be associated also with non-impaired cognitive function, particularly in elderly subjects [22]. ε4 carriers performed significantly worse on measures of episodic memory, executive functioning, global cognitive functioning and perceptual speed. In a Scottish sample that was studied for cognitive change from age 11 to age 79 years, and then from age 79 to age 87, individuals with at least one ε4 allele declined more in intelligence and memory functions across these two periods of the life course [23,24] (Figure 1). More recently, a poly-t repeat in the neighbouring translocase of outer mitochondrial membrane 40 (TOMM40) gene has been linked to the age of onset of LOAD [25]. Recent GWAS (Figure 2) identified several more genetic variants that increase an individual’s risk of developing LOAD in the genes bridging integrator 1 (BIN1), complement component (3b/4b) receptor 1 (CR1) and phosphatidylinositol binding clathrin assembly protein (PICALM) [26–28]. However, reports on whether these variants are associated with cognitive function in non-demented elderly subjects are mixed [21,29,30].

**Psychiatric disease**

Cognitive deficits are present in many psychiatric diseases, including schizophrenia and bipolar disorder, and are also found at a higher rate in unaffected family members than in the general population [31]. Therefore, genes previously associated with psychiatric disease are good candidates for cognitive deficits in the absence of psychiatric disease.

The gene Disrupted in Schizophrenia 1 (DISC1) was initially linked to psychiatric illness when it was identified at the breakpoint of a balanced translocation segregating within a large Scottish family suffering from multiple forms of mental illness [32]. There is some evidence implicating variation in DISC1 in cognitive function, in patients, unaffected family members and the general population. Elderly Scottish women homozygous for the cysteine allele of a non-synonymous single nucleotide polymorphism (SNP) in exon 11 had significantly lower cognitive ability scores than men, controlling for their childhood cognitive ability. This study suggests that variation in DISC1 affects cognitive ageing specifically in women [33]. However, the findings were not replicated in a second, younger Scottish cohort [34]. Distinct allelic haplotypes have been associated with psychotic and bipolar spectrum disorders along with cognitive impairments in a Finnish bipolar disorder family study [35].

Dystrobrevin binding protein 1 (DTNBP1), initially associated with schizophrenia, has been associated via meta-analysis with cognitive function in several cohorts of varying ages [36].

**Imaging endophenotypes**

 Associations between genetic variants and brain structure have been investigated, based on the assumption that individual differences in brain structure are good intermediate variables for cognitive function. However, the results have been inconsistent, with some studies reporting associations with LOAD risk variants and others with healthy controls. The limitations of these studies include small sample sizes, lack of replication, and the use of different imaging modalities and clinical phenotypes.

Figure 1. Apolipoprotein E (APOE) ε4 status and ageing of cognition in the Lothian Birth Cohort of 1921: (a) general intelligence from age 11 years to age 79 years; (b) verbal declarative memory from age 79 years to age 87 years. Based on data from [23,24], respectively.

Figure 2. Genome-wide association study design. The exact number of individuals and single nucleotide polymorphisms (SNPs) typed at each stage will differ from study to study and will depend on the availability of subjects, effect size of individual SNPs and funds.
phenotypes (so-called ‘endophenotypes’) for cognitive ability. For example, variation in adrenergic, beta-2, receptor, surface (ADRB2), has been associated both with cognitive ability and white matter integrity (controlling for childhood ability) in a cohort of elderly Scots [37,38]. There was some evidence that white matter integrity mediated the association between ADRB2 and cognitive ability in old age.

Mattay et al. [39] also reviewed genes identified by brain imaging genetic studies and related to systemic disease or cardiovascular function [angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE) and methylenetetrahydrofolate reductase (NAD(P)H), (MTHFR)], or inflammatory processes [ interleukin 1, beta (IL1B); tumor necrosis factor (TNF) and caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase), (CASP1; ICE)]. They concluded that neuroimaging techniques provide a promising way to identify genes associated with cognitive ageing.

Oxidative stress
One mechanism that has been used to identify candidate genes is oxidative stress [40]. Oxidative stress occurs during cellular respiration when the defence mechanisms of the cell fail to remove damaging by-products formed during respiration. These so-called ‘free-radicals’ can damage DNA and protein. Oxidative stress is believed to be responsible for many aspects of ageing, including cognitive decline. Therefore, anti-oxidant defence genes are good candidates for influencing cognitive decline. However, to date, no genetic variants within such genes have been definitively associated with either cognitive ability in old age or cognitive decline [40].

Summary of candidate gene studies
Despite many studies being published, to date only APOE and possibly COMT, BDNF and DTNBPI have repeatedly been associated with either cognitive ability in older people or cognitive decline [18,34]. It should also be noted that even when genetic variants are significantly associated with cognitive phenotypes, effect sizes are typically very small (1–2%).

Genome-wide association studies
As candidate gene studies have failed to identify genetic variants that account for much of the variance in cognitive ability or cognitive ageing, researchers have more recently turned to a hypothesis-free study design. GWAS allow multiple (up to 1 million) SNPs to be investigated in a single study (Figure 2) and have been used to identify genetic variation influencing many common diseases and traits (e.g. http://www.genome.gov/gwastudies; http://www.gwascentral.org).

A small-scale GWAS failed to identify common genetic variants associated with cognitive ability [41,42], although other GWAS have implicated WW and C2 domain containing 1 (WWC1; KIBRA); calmodulin binding transcription activator 1 (CAMTA1) and sodium channel, voltage-gated, type I, alpha subunit (SCN1A) with memory phenotypes [43–45]. A recent GWAS, which included 3500 older individuals, identified no single genetic variant associated with fluid and crystallised intelligence [46]. However, it concluded that approximately 50% of the variation in cognitive ability in later life is accounted for by multiple genetic variants in linkage disequilibrium (LD) with common SNPs, each having a very small effect.

Concluding remarks
In summary, despite behavioural genetic studies consistently showing that the heritability of cognitive ability in old age is high, very few specific genetic variants that influence cognitive ability and cognitive ageing have been identified. To date, the majority of studies have focussed on the identification of relatively common genetic variants that influence these traits. With the introduction of large-scale whole-genome sequencing, it is hoped that multiple rare variants influencing cognitive ability and cognitive ageing will be identified. By investigating gene expression levels, researchers will be also able to identify the effects of multiple genetic variants on gene function. Finally, technological advances now allow epigenetic mechanisms to be investigated on a genome-wide scale. This might lead to new insights into mechanisms that influence variation in cognitive ability and cognitive function (Box 3).

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