Neuropsychol Rev (2009) 19:451–477
DOI 10.1007/s11065-009-9116-z

REVIEW

The Impact of Genetic Research on our Understanding of Normal Cognitive Ageing: 1995 to 2009

Antony Payton

Received: 1 May 2009 / Accepted: 17 August 2009 / Published online: 19 September 2009

Abstract Identifying the risk factors for individual differences in age-related cognitive ability and decline is amongst the greatest challenges facing the healthcare of older people. Cognitive impairment caused by "normal ageing" is a major contributor towards overall cognitive deficit in the elderly and a process that exhibits substantial inter- and intra-individual differences. Both cognitive ability and its decline with age are influenced by genetic variation that may act independently or via epistasis/gene-environment interaction. Over the past fourteen years genetic research has aimed to identify the polymorphisms responsible for high cognitive functioning and successful cognitive ageing. Unfortunately, during this period a bewildering array of contrasting reports have appeared in the literature that have implicated over 50 genes with effect sizes ranging from 0.1 to 21%. This review will provide a comprehensive account of the studies performed on cognitively healthy individuals, from the first study conducted in 1995 to present. Based on current knowledge the strong and weak methodologies will be identified and suggestions for future study design will be presented.

Keywords Cognitive ability · Cognitive decline · Genetic · Polymorphism · Elderly

A. Payton (✉)
Centre for Integrated Genomic Medical Research,
University of Manchester,
Stopford Building, Oxford road,
Manchester M13 9PT, UK
e-mail: tony.payton@manchester.ac.uk

Introduction

Cognition is our ability to reason, understand, learn and adapt. Measures of cognition, such as tests of memory, processing speed, fluid intelligence (novel problem solving) and verbal comprehension, can be extremely diverse and yet the majority of these tests are highly correlated. More than a century ago Charles Spearman used factor analysis to derive a single measurement from different cognitive test scores which he coined "general cognitive ability" (also known as "general intelligence" or simply "g") (Spearman 1904). This factor accounts for approximately half of the observed variation in human intelligence and represents one of the most replicated findings in psychology (Deary 2001). For the majority of our adult lives this ability tends to remains relatively stable. However, after approximately fifty years of age there is a gradual decline, caused by either pre-dementia or the normal ageing process, which eventually results in differing degrees of cognitive impairment (Rabbitt and Lowe 2000). Severe cognitive impairment in the elderly is an increasing problem for developed countries and one that carries with it high personal, social and economic burdens (Tannenbaum et al. 2005; Comas-Herrera et al. 2007). Cognitive genetic research is one of a host of disciplines that include imaging, proteonomics and metabolomics, that eventually hope to converge in elucidating the biological basis of successful cognitive ageing. The role that genetic variation plays in determining cognitive ability and its eventual decline in the elderly is a compelling one with extensive twin studies indicating that heritability accounts for half of the inter-individual variation observed in cognitive functioning and approximately one third of the variance in cognitive decline (Bouchard and McGue 2003; Finkel et al. 2005).

The brain reserve capacity hypothesis predicts higher intelligence to be protective against cognitive impairment in later life (Mori et al. 1997). Certainly to date the majority of cognitive genetic studies have opted for the measurement of intelligence at a single time point which is considerably cheaper, quicker and easier than their longitudinal counterparts. Whilst the genetic contribution towards cognitive decline is equally interesting, extracting meaningful data from longitudinal studies is a much more arduous task. Confounders such as variation in the decline of different cognitive domains, practice effects, selective drop-out and attrition, mean that large cohorts with a substantial follow-up and appropriate analytical adjustments are required to tease out associated polymorphisms (Rabbitt et al. 2004a).

Unfortunately, to date our knowledge of genes involved in cognitive variation has been limited by the discovery of small effect sizes and lack of replication. The purpose of this review is therefore to discuss the findings of cognitive genetic research undertaken on healthy individuals over the past fourteen years, to attempt to gauge the credibility of these studies given current knowledge and to identify appropriate study designs for future research. Discussion regarding the "intelligence" phenotype and its heritability will not be covered in any detail here and those with interest should refer to the recent and excellent review given by Deary and colleagues (Deary et al. 2009). Instead, this review will focus on a selection of cross-sectional and longitudinal genetic findings taken from over 200 published reports and will attempt to identify the more credible information pertaining to cognitive functioning. Due to the extensive number of genes currently investigated they have been divided into broad categories of neurotransmitter, disease/disorder, developmental and metabolic. Genes can have multiple functions and therefore this categorisation will never be perfect but for ease of purpose it is necessary. As well as the importance of single polymorphisms in cognition, it is also becoming apparent that the detection of epistasis/gene-environment interactions and small genetic effect sizes will be essential to increase further knowledge. This introduces new problems relating to study power that will demand new strategies for study design, necessitate collaboration and require focused funding for larger multidisciplinary projects.

Cross-sectional Cognitive Association Studies

Neurotransmitters

Neurotransmitters and their interactions form the basis of cognitive functioning and the close correlation between age-related cognitive decline and the decrease in several neurotransmitters and their receptors are well-documented (Versijpt et al. 2003; Sarter and Bruno 2004; Bäckman et al. 2006). Their potential importance in neurocognitive functioning is reflected by the fact that the investigation of neurotransmitter genes in healthy individuals accounts for two-thirds of all publications in the field of cognitive genetics and has involved the study of over 50 independent cohorts with sample sizes ranging from 50 to over 2000 (Table 1). Of these, particular attention has been given to the research of three genes, partly because previous evidence suggested a strong biological basis for their involvement in cognition and partly because they were amongst the first to be identified as containing a putative functional polymorphism. These genes comprise the dopamine receptor D2 (DRD2), catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF).

Dopamine Receptor D2

Dopaminergic neurones are especially sensitive to the effects of an age-related increase in oxidative stress. Free radical production by monoamine oxidase (major metabolic enzyme for dopamine breakdown), the high metabolic rates of dopaminergic neurones coupled with the relatively low production of antioxidants in the brain, all contribute towards increased sensitivity to damage in later life (Luo and Roth 2000). Multiple proteins within the dopaminergic system exhibit a marked decrease in expression with increasing age including the dopamine transporter, tyrosine hydroxylase and dopamine receptors (D1 and D2) that decrease approximately 4% per decade from early to late adulthood (Rinne et al. 1990; Bäckman et al. 2006). Whilst the trajectory of decline for these dopaminergic proteins have been reported as linear by many studies (Reeves et al. 2002), there are some reports that suggest the dopamine receptor D2 and the dopamine transporter show an accelerated decline beyond middle age that closely corresponds to the trajectory of cognitive decline observed in the elderly (Rinne et al. 1990; Antonini et al. 1993; Bannon and Whitty 1997; Ma et al. 1999). The reasons for the inconsistencies in determining the trajectory of loss remain unclear, although studies of this kind tend to use relatively small sample sizes and do not always use a sufficiently wide age range.

Age-related loss of dopamine receptor D2 occurs in multiple brain regions including the frontal cortex and hippocampus (Kaasinen et al. 2000) and this has been shown to have an impact on cognitive performance particularly for tests that tap into frontal brain regions such as the Wisconsin Card Sorting Test and Stroop Color-Word Test (Volkow et al. 1998). In 1995 Berman and Noble were the first to report an association between a genetic polymorphism and human intelligence when they observed an association between a functional polymorphism (TAQ1)

Table 1 Neurotransmitter related genes associated with cognition

Gene	Investigated polymorphism	Cohorts	Observation	Author
ADRB2	rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu)	Dutch family members (n=800) and Scottish elderly (n=1063)	Associated with IQ in Dutch cohort and Matrix Reasoning and Moray House test in Scottish cohort. Age specific effects observed.	Bochdanovits et al. 2009
BDNF	rs6265 (Val66Met)	11 independent studies (mean n=382)	Association reported by 9 independent studies	Miyajima et al. 2008a, b (summary of studies)
CCKAR	rs179973 (A-81G) rs1800908 (G-128 T)	Community-dwelling Japenese age 40–79 years (n=2251)	Association with IQ for both SNPs	Shimokata et al. 2005
CHRM2	rs8191992 (3'UTR)	USA Caucasian parents (n=828)	Association with IQ in Dutch and USA studies	Comings et al. 2003
	rs324650 (intron) and rs2061174 (intron)	Dutch family members (n=667)		Gosso et al. 2006a
	rs324650 and rs2061174	Dutch family members (n=762)		Gosso et al. 2007
	8 SNPS including: rs8191992 and rs2061174	USA family members (n=2158)		Dick et al. 2007
	rs8191992 and 29 additional SNPs	Three independent cohorts from UK and Australia (total n=4386)	No association with diverse measures of ability	Lind et al. (2009)
CHRNA7	2 base pair deletion exon 6	Schizophrenics (n=2158), unaffected relatives (n=116) and healthy controls (n=39)	Association with episodic memory for both schizophrenics and healthy controls that accounted for 2–3% of variance.	Dempster et al. 2006
COMT	rs4680 (Val158/108Met)	Meta-analysis of 46 studies (including 40 healthy cohorts) IQ (n=9115), verbal fluency (n=1808), verbal recall (n=2538), N-Back task (n=2104), Trail Making task (n=896), Wisconsin card sorting (n=2829)	Weak association observed with IQ that accounted for 0.1% of variance.	Barnett et al. 2008
DBH	rs1108580 (G444A)	Healthy adults (61 women, n=103)	Associated with working memory	Parasuraman et al. 2005
	19 base pair ins/del	Postmenopausal women (n=1371)	Homozygous del associated with reduced scores on the six-item orientation-memory-concentration test	Togsverd et al. 2007
DRD2/ ANKK1	rs1800497 (TAQ1)	Boys with alcoholic or non-alcoholic fathers (n=182)	A1 allele associated with reduced visuospatial ability	Berman and Noble, 1995
		High IQ (n=51), average IQ (n=51) and low IQ (n=31) children	Non-significant trend for A1 allele and increased IQ	Petrill et al. 1997
		High IQ (n=51) and average IQ (n=51) children	No association with IQ	Ball et al. 1998
		High IQ n=71 and average IQ (n=78)	No association with IQ	Moises et al. 2001
		Memory impaired elderly (n=49)	A1 allele associated with increased MMSE score	Bartrés-Faz et al. 2002
		Healthy Chinese girls (n=112)	A1 allele associated with increased IQ	Tsai et al. 2002
		Traumatic brain injury patients (n=141)	TAQ1 haplotype associated with cognitive recovery	McAllister et al. 2008
		Psychosis patients (n=84) and healthy controls (n=85)	No association with executive function, memory or working memory in either patients or controls	Bombin et al. 2008

Table 1 (continued)

Gene	Investigated polymorphism	Cohorts	Observation	Author
DRD3	rs6280 (Ser9Gly)	High IQ (n=51) and average IQ (n=51) children	No association with IQ	Ball et al. 1998
		Psychosis patients (n=84) and healthy controls (n=85)	Association with executive functioning in patients and controls	Bombin et al. 2008
HTR2A	rs6314 (H452Y)	349 healthy young volunteers	21% poorer memory associated with minor allele	de Quervain et al. 2003
		Healthy volunteers (n=622)	Association with episodic memory in younger but not older volunteers	Papassotiropoulos et al. 2005
MAOA	MAOA-uVNTR	Healthy Chinese girls (n=191)	VNTR associated with IQ before Bonferroni correction	Yu et al. 2005
PPP1R1B	17 SNPs investigated including 7 SNP haplotype comprised of: rs4795390, rs879606, rs11651497, rs907094, rs3764353, rs3764352, rs3794712	Families of European ancestry (n =257)	Association with IQ and working memory	Meyer-Lindenberg et al. 2007
SLC6A4	5-HTTLPR (s and l alleles)	Swedish Caucasian controls (n=54)	S allele associated with improved Wisconsin Card Sorting Test results	Borg et al. 2009
SNAP25	rs363050 and rs363039 (intron 1)	Dutch family members (n=667)	Association with IQ	Gosso et al. 2006b
	rs363043 and rs353016 (intron 1)	Dutch family members (n=762)	Association with IQ	Gosso et al. 2008

Adrenergic, beta-2-, receptor (ADRB2); brain-derived neurotrophic factor (BDNF); cholecystokinin A receptor (CCKAR); cholinergic receptor, muscarinic 2 (CHRM2); cholinergic receptor, nicotinic, alpha 7 (CHRNA7); catechol-O-methyltransferase (COMT); dopamine beta-hydroxylase (DBH); ankyrin repeat and kinase domain containing 1 (ANKK1 (formally referred to as DRD2 TAQ1)); dopamine receptor D3 (DRD3); 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A); monoamine oxidase A (MAOA); protein phosphatase 1, regulatory subunit 1B (PPP1R1B); solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4); synaptosomal-associated protein, 25 kDa (SNAP25)

(Comings et al. 1991) within the DRD2 gene and a test of visuospatial performance (Berman and Noble 1995). They found that participants (n=182) carrying one or two copies of the minor A1 allele scored significantly lower on the Benton's Judgment of Line Orientation Test than those who were homozygous for the common A2 allele.

The first attempts at replication compared TAQ1 allele frequencies of high, average and low IQ individuals (n= 50–80 in each group) (Petrill et al. 1997, Ball et al. 1998; Moises et al. 2001). Whilst all three studies observed no significant differences between genotype frequency and IQ, the Petrill study found a non-significant decrease in the A1 allele frequency for the low IQ group (17.1%) compared against the average (25.5%) and high IQ (26.5%) groups, which was an effect that went in the opposite direction to that reported by Berman and Noble. The Petrill observation was later supported by a study of Chinese girls (n=112) where those homozygous for the A1 allele had significantly higher IQ than those homozygous for the A2 allele (Tsai et al. 2002) although the numbers of individuals in the A1/A1 (n=15) and A2/A2 (n=48) genotype groups were small and the significance was borderline (p-value, 0.036). However, further evidence that the TAQ1 A1 allele may be correlated with enhanced cognitive performance came in the same year when Bartrez-Faz and colleagues reported that it was associated with higher scores for both the Mini Mental State Examination (MMSE) and long term verbal memory, and a decrease in left caudate nucleus volume in an elderly population (mean age 66 years, n=49) (Bartrés-Faz et al. 2002).

The reasons for the discrepancies between the original TAQ1 study and subsequent IQ studies may partially be explained by the moderate correlation between IQ and visuospatial ability (0.4), although this would not account the differences between the IQ studies which may be a consequence of inadequate sample size. However, in 2004 the evidence that genetic variation within the DRD2 gene influences cognitive ability disappeared when it was found that the TAQ1 polymorphism was not located in the DRD2 gene but 10 kilobases downstream in a gene called ankyrin repeat and kinase domain containing 1 (ANKK1) (Neville et al. 2004), which is believed to be involved in the activation of the transcription factor nuclear factor-kappaB (NF-κB) (Huang et al. 2009a). TAQ1 is in fact an SNP (rs1800497) located within a coding region of the gene where it causes a change in amino acid (glutamic acid to

lysine) that prevents the translation of the gene into protein. The Huang study also identified an additional non-synonymous SNP within the ANKK1 gene (rs2734849) that altered the expression of NF-κB-regulated genes. NF-κB has recently been shown to contribute towards vascular endothelial dysfunction in the elderly, and therefore this pathway may be of interest for the study of cognitive decline in the elderly where vascular dysfunction is closely correlated with cognitive performance and white matter hyperintensities (Pierce et al. 2009; Kearney-Schwartz et al. 2009).

More recent genetic studies have examined haplotypes within a series of closely linked genes called the "NTAD cluster" that comprise NCAM1, TTC12, ANKK1, and DRD2 (Gelernter et al. 2006; Yang et al. 2008). One such study reported that cognitive outcome measures after traumatic brain injury was associated with a 3 SNP haplotype block within the ANKK1 gene that included the TAQ1 polymorphism (McAllister et al. 2008). The latest study to investigate the TAQ1 SNP in relation to cognition, and one incidentally that was incorrectly reporting a study of DRD2 rather than ANKK1, found no association with cognitive abilities (attention, working memory, learning and memory and executive function) in 84 psychosis patients and 85 healthy controls (Bombin et al. 2008). Despite the mixed findings, the TAQ1 polymorphism warrants further study. However, future research should include the entire NTAD cluster, NF-κB and related genes and consider the possibility of age-specific effects.

Catechol-O-methyltransferase

Interest in the dopaminergic pathway continued with studies of the dopamine receptors (DRD3 and DRD4), dopamine beta-hydroxylase and dopamine transporter (SLC6A3) genes. Generally, these produced a small number of mixed findings that are yet to be replicated (Table 1). By contrast, the COMT gene, which codes for the main enzyme responsible for the breakdown of dopamine, has become one of the most extensively researched in the field of cognitive genetics. A common functional polymorphism within this gene (Val158Met) has been shown to increase activity three-to-four-fold (activity increase associated with the Valine allele) (Lachman et al. 1996). This polymorphism has been investigated by over 60 cognitive genetic studies.

It has been hypothesised that an age-related loss of neurochemical and anatomical brain resources will amplify the genetic effects of polymorphisms on cognition (Lindenberger et al. 2008). In support of this hypothesis a study of young adults (mean age 25 years, n=164) and elderly non-demented individuals (mean age 65 years, n=154) found that the COMT Val158 allele was associated with poorer performance on executive function and working memory tasks and that the effect increased with age (Nagel et al. 2008). This work also supports the "inverted-U" hypothesis, which proposes that either hypodopaminergic (observed in ageing) or hyperdopaminergic function (observed in amphetamine stimulation) results in a shift from optimal levels required for cognitive performance (Goldman-Rakic et al. 2000). The Nagel publication also reported that "the few cognitive studies with older adults have invariably reported COMT effects in the expected direction." Upon closer inspection the results of these studies are not particularly invariable. The first investigated episodic and semantic memory, executive function and visuospatial ability in men (n=286, age range 35–85 years) (de Frias et al. 2004; de Frias et al. 2005). Although they found that the Val158 allele was associated with low cognitive performance, this association was observed for all age ranges and not just the elderly. In addition, the COMT/age interaction was observed for the test of visuospatial ability in middle-aged men (mean age 41 years) but not "young-old" (mean age 53 years) or "old-old" (mean age 72 years). The next cited study was by Harris and colleagues using Scottish participants (n=460) from the Lothian region who underwent cognitive testing at 11 and again at 79 years of age. Here a significant association between the Val158Met polymorphism and cognitive ability was reported at age 79 but not at age 11. However, the heterozygous group scored higher than the homozygous groups on a test of executive function, which the authors attributed to the inverted-U hypothesis. This is in contrast to the Nagel study which observed no association with executive function. In fact, the only report that could be described as "invariable" (at least in relation to the Nagel study) was another study of Scottish elderly (Aberdeen birth cohort, n=473) (Starr et al. 2007). Those homozygous for the Val158 allele did score lower on a measure of general cognitive ability (mean score=33.0) compared against heterozygous (34.9) and homozygous Met158 individuals (34.9). The effect was only significant for the tests taken between the ages of 64 and 68 years but not at age 11. However, unlike the Harris study higher scores were not observed for heterozygous individuals.

The literature concerning the COMT Val158Met polymorphism and cognition is extensive, as is the breadth of differing methods, results and conclusions. Fortunately, a meta-analysis has been performed on the majority of published work up to the end of August 2007 (Barnett et al. 2008). This analysis grouped together data from 67 independent cohorts that mainly consisted of healthy individuals but also included schizophrenic and bipolar disorder patients. They then compared the genotype frequencies against measures of cognitive ability that

included IQ score (21 cohorts, n=9115), verbal fluency (12 cohorts, n=1808), verbal recall (18 cohorts, n=2538), Trail Making task (10 cohorts, n=896), Wisconsin Card Sorting Test (25 cohorts, n=2829) and n-Back Task accuracy (7 cohorts, n=2104). The results were largely disappointing with only a suggestive indication that individuals homozygous for the Met allele scored slightly higher on IQ tests (p=0.026; contribution of the polymorphism towards the variance in cognition observed within the cohort (effect size)=0.1%). The IQ result was a robust one with no changes to significance when adjustments were made for sex, disease status and interestingly age. The authors concluded that the role of the Val158Met polymorphism in cognition was "little if any." However, it should be emphasised that the advantage of an increased sample size via meta-analysis is often accompanied by problems of between-study heterogeneity and publication bias (Kavvoura and Ioannidis 2008). Meta-analysis techniques are therefore not as effective at detecting association as a suitably powered primary study.

Brain-derived Neurotrophic Factor

BDNF is a protein with several functions and is involved in neuronal differentiation (Ahmed et al. 1995), neuronal plasticity and survival (Poo 2001) and oxidative stress (Mattson et al. 2002; Wang et al. 2006, Harris et al. 2007). Similar to DRD2 there is a steady decline in BDNF expression associated with normal ageing (Hattiangady et al. 2005) and BDNF plasma concentrations have been reported as a biomarker for impaired memory and general intelligence in community-dwelling elderly (Komulainen et al. 2008). An epistasis interaction between the COMT and BDNF genes has been documented where older homozygous COMT Val66 individuals performed worse on cognitive tasks if they also possessed at least one copy of the BDNF Met66 allele (Nagel et al. 2008). Unfortunately, as with most interaction analysis this study was relatively underpowered and remains to be replicated.

An influence between the BDNF Val66Met polymorphism and cognitive abilities does at first glance appear to be reassuring given that of the twelve publications, eleven have found significant findings (Miyajima et al. 2008a). Of these, correlations with working memory have been the most inconsistent with a large study of adolescents (n=785) failing to find any association (Hansell et al. 2007). However, the prefrontal cortex, which is involved in working memory, does not fully develop structurally or functionally until early adulthood (Fuster 2001) and BDNF mRNA are found at lower levels in the dorsolateral prefrontal cortex of adolescents compared to that found in adults (Webster et al. 2002). Despite this, the majority of studies have found that the Met66 allele is associated with low cognitive performance, which complements the findings of functional studies that have shown that the Met66 allele inhibits intracellular trafficking of BDNF (Egan et al. 2003; Chen et al. 2004) and is associated with hippocampal and frontal lobe grey matter volume (Bueller et al. 2006; Frodl et al. 2007; Pezawas et al. 2004).

Conversely, a study of two independent Scottish elderly cohorts (n=471, mean age 79 years and n=433, mean age 65 years) observed that the Met66 allele was associated with high cognitive performance on a test of executive function (Harris et al. 2006). The authors argued that whilst the Met66 allele may be damping cognition for the young and middle aged it may have a protective effect in old age. Unfortunately, these results were not replicated in a study of elderly non-demented English (mean age 63 years, n=722) that found the Met66 allele was associated with poorer performance on several tests of cognitive ability including a test of general intelligence than in those without this gene. (Miyajima et al. 2008a). The reasons for the differences in findings are unknown although one explanation may be that the switch to a protective effect of the Val66 allele may occur between the ages of 65 and 79. Indeed, a recent study of healthy older adults (mean age 65 years, n=53) found that at the initial point of testing the Met66 allele was associated with reduced cognitive performance (Erickson et al. 2008). A subsequent testing 10 years later of the same subjects showed a significant decrease in the trajectory of the scores for those who were homozygous for the Val66 allele. This suggests that age-related cognitive decline may be the determining factor for an apparent change in allelic susceptibility and this may be reflected by the Scottish cohorts being older than the English cohort. However, even though the mean age of one of the Scottish cohorts was 16 years older than the English volunteers the second Scottish cohort was only 2 years older and yet both Scottish cohorts showed similar results.

Another contributing factor towards contrasting results may be the complexity of the gene itself. Containing eleven exons and nine functional promoter regions BDNF is expressed in a tissue and brain region specific manner (Pruunsild et al. 2007). Expression is also regulated by a number of transcription factors and interaction between haplotypes within the RE1-silencing transcription (REST) gene and Val66Met have been reported which effect cognition (Miyajima et al. 2008b). A second functional polymorphism ((GC)n, (CA)n, dinucleotide repeat) located 1 kb upstream of the first transcription initiation site has been identified (Okada et al. 2006). Finally, BDNF mRNA forms double stranded RNA duplexes with mRNA of the antiBDNF gene (BDNFOS) which may represent another regulatory mechanism (Pruunsild et al. 2007). Overall, BDNF is a more complex gene than originally anticipated and a number of factors may have to be analysed in

combination in order to untangle its true influence on cognition.

Neurological Disorders/Disease

Neurological conditions such as Alzheimer's disease (AD), schizophrenia and the various forms of mental retardation have a genetic aetiology and cognitive impairment phenotype that makes the study of their susceptibility genes of interest for normal cognitive ageing research. The AD gene apolipoprotein E (APOE) has been intensively studied in relation to its effect on both cross-sectional and longitudinal cognition of non-demented people. A recent meta-analysis of 77 APOE studies (Jan 1993 to Aug 2008) involving 40,942 cognitively healthy subjects found that the presence of the APOEε4 allele was associated with a small but significant effect sizes (measured as mean weighted effect size (d)) of executive functioning (−.06), episodic memory (−.14), processing speed (−.07) and a global measure of cognitive ability (−.05) (Wisdom et al. 2009). An age-related increase in effect size of the APOEε4 allele on episodic memory and general cognitive ability was also observed.

Of the eleven other disease/disorder associated genes reported in normal cognition ageing (Table 2), the majority have either yet to be replicated or have produced a small number of inconsistent results. Of these, two of the more interesting associations with cognition involve the schizophrenia associated gene (dysbindin) and a progeria gene (Werner syndrome).

Werner Syndrome Gene

Werner syndrome is a rare progeroid condition, which has a prevalence of 1:200,000 in Caucasians and 1:30,000 in Japanese (Kudlow et al. 2007). The Werner syndrome gene (WRN) codes for a helicase protein which under normal circumstances proofreads DNA for errors and prevents genomic instability by unwinding complex DNA structures (triplexes, tetraplexes and RNA-DNA hybrids) (Brosh et al. 2006). Several mutations within the WRN gene result in loss of gene function which manifests as symptoms of premature ageing, including susceptibility to osteoarthritis and cancer, grey hair and skin wrinkling (Epstein et al. 1966; Goto et al. 1996; Goto 1997). Although cognitive deficit is not a typical disease manifestation of Werner syndrome the relationship between polymorphisms and cognitive functioning in non-demented elderly individuals has been explored as part of a broader study looking at the effects of WRN and normal ageing (Bendixen et al. 2004). Researchers found that an intron 1 SNP (rs2725335) was associated with general cognitive ability in elderly dizygotic twins (n=426, aged 70–80 years). A follow-up study by the same group found that two additional WRN SNPs (rs2251621 and rs2725338) also reached significance (Sild et al. 2006). The SNPs identified by the Sild study were described as being in the 5′ untranslated region and flanking region of the WRN gene. Despite being close to the WRN gene, rs2251621 is located in the first intron of the gene purine-rich element binding protein G isoform A (PURG). The function of PURG is unknown, although its expressed protein is very similar in structure to purine-rich element binding protein A, which regulates DNA replication and transcription. A large independent elderly Dutch study (n=1245, aged 85 years and over) found no association between three WRN SNPs (including rs2725335) and tests of processing speed and immediate and delayed memory (Kuningas et al. 2006) although this study did not investigate rs2251621 or rs2725338. They did, however, observe a marginal association between an exon 34 SNP (rs1346004) and a test of attention (p-value, 0.04). More recently, SNP rs2725335 has been associated with a test of logical memory in a sample of elderly Scottish people (n=1063, 70 years of age) (Houlihan et al. 2009). Unfortunately, the SNP did not reach significance with other cognitive phenotypes, including attention, processing speed and memory, and the significance with logical memory disappeared after correction for multiple testing.

Despite the limited publications and borderline associations the WRN gene should still be regarded as a viable candidate for normal cognitive ageing. Future research should acknowledge that WRN is a large gene (140 kb) that requires 14 haplotype tagging SNPs (assuming a MAF≥0.1 and r2≥0.8) to cover sequence spanning the first to last exons. Neighbouring genes may also be of interest, depending how far linkage disequilibrium extends, and include the upstream contrapodal PURG gene and the downstream gene Neuregulin 1 (NRG1). Interestingly, a polymorphism within the NRG1 gene (SNP8NRG243177) has been associated with decreased activation of the frontal and temporal lobes and a reduced premorbid IQ in schizophrenia patients (Hall et al. 2006) but has yet to be examined at in healthy individuals.

Dystrobrevin Binding Protein 1

The dystrobrevin binding protein 1 (DTNBP1) gene encodes a coiled-coil protein called dysbindin that forms part of a larger protein complex which conducts organelle assembly and protein trafficking (Benson et al. 2001). DTNBP1 small interfering RNA (siRNA) has been shown to increase cell surface DRD2 and block dopamine induced internalisation in human neuroblastoma and rat primary cortical neurones (Iizuka et al. 2007). Iizuka and colleagues

Table 2 Neurological disease/disorder genes associated with cognition

Gene	Investigated polymorphism	Cohorts	Observation	Author
AKT1	rs1130214 (3'UTR)	Finnish twins: schizophrenics (n=61), bipolar (n=31) and controls (n=65)	Association with verbal learning and memory in cases and controls	Pietiläinen et al. 2009
	rs2494732, rs1130233, rs3730358 and rs1130214	Healthy individuals of European Ancestry (n=319)	Haplotype associated with IQ, processing speed and executive function. Interaction with BDNF also reported.	Tan et al. 2008
APOE	APOEε2-4	Community dwelling Italian elderly (n=620)	APOEe4 associated with reduced episodic memory and recall	de Blasi et al. 2009
		Scottish seventy-year-olds (n=1013)	No association with memory abilities	Luciano et al. 2009a
		Meta-analysis of 77 studies (40,942 cognitively healthy individuals)	APOEe4 has small effect on episodic memory, executive functioning, processing speed and general cognitive ability. This effect increases with age.	Wisdom et al. 2009
CTSD	rs17571 (Ala58Val)	Healthy elderly, UK (n=767, mean age 62 years)	Associated with fluid intelligence	Payton et al. 2003
DAOA	GCGGC haplotype: rs1570709, rs9586848, rs7324448, rs1575633, rs7329966	Schizophrenics (n=178) and controls (n=144)	Association with semantic fluency in both patients and controls	Opgen-Rhein et al. 2008
DISC1	rs821616 (exon 11)	Scottish seventy-year-olds (n=462)	Associated with lower Moray House Test scores in elderly women compared to elderly men	Thomson et al. 2005
DTNBP1	CTCTAC haplotype	Schizophrenics (n=213) and controls (n=126)	Association with general cognitive ability in both cohorts	Burdick et al. 2006
	7 SNPs previously associated with schizophrenia	Schizophrenics (n=76), unaffected sibs (n=31) and healthy controls (n=31)	Association between rs760761 and IQ in all three groups	Zinkstok et al. 2007
	6 SNPs previously associated with schizophrenia	Greek male military conscripts (n=2243)	Association with non-verbal IQ and attention	Stefanis et al. 2007
	39 tagSNPs	Schizophrenics (n=336) and controls (n=172)	No association with IQ, executive function or processing speed	Peters et al. 2008
	12 SNPs	Scottish (n=1054), Australian (n=1806) and English (n=745) healthy individuals	Associations observed with several cognitive abilities	Luciano et al. 2009b
FMR1	CGG repeat	Healthy individuals from various ethnic groups (n=283)	Explains 4% of verbal IQ variance in women	Allen et al. 2005
HLA-DRB1	HLA-DRB1*01	The Sydney Older Persons Study, Australia.	HLA-DRB1*01 is a positive predictors of verbal fluency and logical memory. HLA-DRB1*05 associated with poorer performance on Boston naming test.	Shepherd et al. 2004
	HLA-DRB1*05	Non-demented elderly (n=151).		
IGF2R	TG repeat sequence	High IQ (n=51), average IQ (n=51) and very high IQ (n=52)	Association with general intelligence	Chorney et al. 1998
		Similar powered cohort to that described above	Failure to replicate Chorney study	Hill et al. 2002
IL1B	rs16944 (−551 promoter)	Community dwelling elderly (n=369)	Associated with memory	Baune et al. 2008
		Non-demented elderly males (n=161)	Association with the Cognitive Abilities Screening Instruments (CASI) test	Tsai et al. 2008
NCSTN	rs12239747, rs2274185, rs7528638 and IVS16-119G→C	Scottish elderly (n=462)	Association with 4 SNP haplotype and Moray House Test scores at age 11 and 79 years	Deary et al. 2005
SORL1	GWA study	Dementia free elderly (n=705)	Association with rs1131497 and abstract reasoning	Seshadri et al. 2007

Table 2 (continued)

Gene	Investigated polymorphism	Cohorts	Observation	Author
	rs3824968	Scottish elderly (n=1078)	Association with spatial span before Bonferroni correction	Houlihan et al. 2009
TNFA	rs1800629	369 community dwelling elderly	Associated with processing speed	Baune et al. 2008
WRN	rs2725335, rs2725349, rs1800391, rs1346066	Elderly (n=426, 70–90 years)	Association with cognitive composite score	Bendixen et al. 2004
	rs2251621, rs2725335, and rs2725338	Elderly (n=426, 70–90 years)	Association with cognitive composite score	Sild et al. 2006
	rs2725335, rs1346044, rs2725362	Elderly (n=1245, >85 years)	No association with memory, processing speed or global cognitive function	Kuningas et al. 2006
	rs2725335	Scottish elderly (n=1078)	Association with logical memory	Houlihan et al. 2009

V-akt murine thymoma viral oncogene homolog 1 (AKT1); apolipoprotein E (APOE); cathepsin D (CTSD); D-amino acid oxidase activator (DAOA); disrupted in schizophrenia 1 (DISC1); dystrobrevin binding protein 1 (DTNBP1); fragile X mental retardation 1 (FMR1); major histocompatibility complex, class II, DR beta 1 (HLA-DRB1); insulin-like growth factor 2 receptor (IGF2R); interleukin 1, beta (IL1B); nicastrin (NCSTN); sortilin-related receptor, L(DLR class) A repeats-containing (SORL1); tumor necrosis factor (TNF); Werner syndrome (WRN)

hypothesised that polymorphisms within DTNBP1 may downregulate dysbindin and have a similar action to that caused by siRNA thus resulting in a disturbance of dopaminergic transmission and impaired cognitive performance.

DTNBP1 has been a major focus in schizophrenia research and of the 45 DTNBP1 studies listed on the schizophrenia research forum there have been 19 associations, 2 non-significant trends and 24 negative findings with meta-analysis showing significance for several SNPs (www.schizophreniaforum.org, update 27.03.2009). Varying degrees of cognitive impairment are observed in schizophrenia, and this has promoted researchers to investigate the role of DTNBP1 on this symptom domain in both schizophrenics and healthy controls. Burdick and colleagues were the first to report a correlation between DTNBP1 and a measure of general cognitive ability in both patients (n=213) and controls (n=126) where they found that a six locus haplotype (rs909706, rs1018381, rs2619522, rs760761, rs2619528 and rs1011313) accounted for 3% of cognitive variance in both groups (Burdick et al. 2006). A smaller study of 76 schizophrenics, 31 unaffected sibs and 31 healthy controls found an association between rs760761 and rs2619522 (both intronic and in strong linkage disequilibrium) and IQ (Zinkstok et al. 2007), which was later replicated by a larger independent study of healthy men (n=2243) (Stefanis et al. 2007). The latest study to investigate DTNBP1 and cognition used three independent Caucasian cohorts from Scotland (n=1054, measures at 11 and 70 years), Australia (n=1808, mean age 16–19 years dependent upon test) and England (n=745, mean age 63 years), all of whom had undergone a broad array of tests (Luciano et al. 2009a). Analysis of the haplotype tagSNP rs1018381 reported by Burdick showed association with a measure of general cognitive ability in the Australian cohort, a non-significant trend for logical memory in the Scottish cohort (p-value, 0.06) and reduced scores for the majority of tests taken by the English volunteers (although these failed to reach significance). Analysis of rs760761 and rs2619522 that were associated with IQ in both the Zinkstok and Stefanis reports also showed association with tests of executive function in the English and Scottish cohorts with all groups showing an effect in the same direction. Additional associations were observed in the Scottish and English cohorts for several SNPs with both memory and executive function tests that were not observed in the other cohorts and which may be due to age-specific effects. The English study also genotyped several SNPs located in the 3′ end of the gene which had not previously been investigated. Of these rs742105 was significantly associated with three separate tests memory recall (immediate, delayed and cumulative). To date one publication has found no association between polymorphisms in the DTNBP1 gene and cognitive ability (Peters et al. 2008). This study of Anglo-Irish schizophrenics (n=336) and controls (n=172) found no evidence that any of the 39 tagSNPs used (covering the DTNBP1 gene and 10 kb on either side) influenced cognitive measures of either patients or controls.

The results published so far are indicative that DTNBP1 may influence cognitive functioning. The approach used by the Peters study, which used tagSNPs to cover the entire gene and substantial flanking sequence should be adopted for future studies although this should be combined with the use of several large independent cohorts which was the approach used by Luciano and colleagues. In addition, the potential interaction between DTNBP1 and DRD2 is an intriguing one which remains to be explored.

Developmental

Twin studies have revealed that not only is brain volume highly heritable (0.90–0.95, frontal lobe volumes; 0.40–0.70, hippocampus) but it is also moderately correlated with working memory (r=0.27) and processing speed (r_g=0.39) (Pfefferbaum et al. 2000; Sullivan et al. 2001; Posthuma et al. 2003; Peper et al. 2007). Although genes have been shown to influence brain volume and brain volume is correlated with intelligence, it is still unclear whether the effect is directly causal, such that genes influence volume which influences intelligence, or has an indirect effect, such that genes influence intelligence which determines volume. There also appears to be little correlation between atrophy of brain regions and cognitive ability in community-dwelling elderly once the analysis has been adjusted for whole brain volume (Shenkin et al. 2009). In the Shenkin study, intracranial area (estimator of maximum cranial volume) accounted for over six per cent of the variance in general intelligence in the elderly compared to atrophy which accounted for less than one per cent. These results indicate that developmental genes that determine brain volume may be important predictors of mental health and cognitive status in later life.

Prior to 2006 the msh homeobox 1 gene (MSX1), which acts as a transcriptional repressor during embryogenesis, was the only developmental gene associated with cognition (Fisher et al. 1999). Since then four additional genes have been reported in the literature: neuregulin1 receptor (ERBB4), which induces cellular differentiation (Nicodemus et al. 2006); kallikrein-related peptidase 8 (KLK8), which promotes neurite outgrowth (Izumi et al. 2008); S100 calcium binding protein B (S100B), which is involved in neurite extension and axonal proliferation (Lambert et al. 2007) and the neuronal scaffold protein WW and C2 domain containing 1 (WWC1) (Papassotiropoulos et al. 2006) (Table 3). Of these WWC1 (formally known as KIBRA) has been the only developmental gene to be studied by multiple independent groups.

WW and C2 Domain Containing 1

WWC1 codes for a postsynaptic scaffold protein called KIBRA that connects cytoskeletal and signalling molecules. KIBRA is mainly expressed in the hippocampus, cortex, cerebellum and hypothalamus and its expression is upregulated during early brain development suggesting it plays a role in neurogenesis and synaptogenesis (Johannsen et al. 2008). High levels of KIBRA expression are observed in the cerebellar Purkinje cells which have been implicated in learning (Thompson and Kim 1996). KIBRA has also been shown to be the substrate of protein kinase C zeta which itself is involved in long-term potentiation in the adult brain (Büther et al. 2004).

A genome wide association study (GWAS) of over 500,000 SNPs, using a pooled DNA method (n=341, median age 22 years) followed by replication in two independent cohorts (n=256, median age 55 years and n=424, median age 21 years), first identified KIBRA as a regulator of memory performance (Papassotiropoulos et al.

Table 3 Developmental genes associated with cognition

Gene	Investigated polymorphism	Cohorts	Observation	Author
ERBB4	rs3791709-rs4673628–rs2272024 haplotype	Healthy controls (n=370)	Association with verbal memory and digit span factor	Nicodemus et al. 2006
KLK8	28 SNPs	Healthy controls (n=166)	rs1612902 associated with memory and IQ	Izumi et al. 2008
MSX1	Microsatellite marker	Low IQ (n=51), average IQ (n=51) and high IQ (n=50)	Association with IQ	Fisher et al. 1999
S100B	25 SNPs	Elderly with MMSE>25 (n=1162) compared against elderly with MMSE ≤ 25 (n=1215)	Association between with rs2300403 and cognitive ability	Lambert et al. 2007
WWC1 (KIBRA)	rs17070145	Three independent healthy cohorts (n=341, 256 and 427)	Association with episodic memory	Papassotiropoulos et al. 2006
		Healthy elderly (n=64)	Association with episodic memory	Schaper et al. 2008
		Healthy elderly (n=312)	Association with episodic memory	Almeida et al. 2008
		Elderly with subjective memory complaints (n=70)	Association with episodic memory	Nacmias et al. 2008
	39 tagSNPs and rs17070145	Two independent cohorts (n=319 and 365)	No association with several verbal memory tasks	Need et al. 2008

V-erb-a erythroblastic leukemia viral oncogene homolog 4 (ERBB4); kallikrein-related peptidase 8 (KLK8); msh homeobox 1 (MSX1); S100 calcium binding protein B (S100B); WW and C2 domain containing 1 (WWC1)

2006). Associations between episodic memory and a T > C substitution (rs17070145) in intron 9 of the gene were observed in all three cohorts where the presence of the T allele was correlated with improved episodic memory. No association was observed for the cognitive domains of attention, concentration or working memory. This finding was later replicated by a study of healthy elderly (n=64) (Schaper et al. 2008) and another study that included elderly volunteers (n=312, 50–89 years) with and without mild cognitive impairment (MCI) (Almeida et al. 2008). The Almeida study also reported no difference in allele frequencies between participants with or without MCI. Nacmias and colleagues also observed the association with episodic memory in an elderly population with subjective memory complaints (n=70, mean age 60.7 years), but they found the T allele was associated with lower episodic memory scores (Nacmias et al. 2008). The T allele has been reported as a susceptibility allele for late-onset AD (Corneveaux et al. 2009; Rodríguez-Rodríguez et al. 2009) and this may have account for the opposing findings. However, if this were the case then a difference in allele frequencies may have been expected between the MCI and non-MCI volunteers in the Almeida study and yet none was. There were also no significant differences between the genotype frequencies (CC and CT/TT) or the MMSE scores either within or between these two studies indicating that the polymorphism would not predispose towards AD in these cohorts. Finally, a comprehensive study of 39 tagSNPs within the WWC1 gene (including rs17070145) and additional SNPs extending 20 kb upstream found no association with any tests of memory in two independent cohorts (319 and 365 individuals of European origin) (Need et al. 2008). The Pappassotiropoulos study identified genetic effect sizes of up to 6.2% and both the cohorts used in the Need study had approximately 90% power to detect a 3% effect size and they included exactly the same phenotypes into their regression model as those used by Pappassotiropoulos. The reasons for the discrepancies therefore remain unclear, and larger studies with better characterised cohorts will be required to determine whether WWC1 is truly associated with cognition.

Metabolic Related Genes

Stereological studies have shown that within a healthy ageing brain there is a minimal loss of neurones in hippocampal and cortical regions (West et al. 1994; Morrison and Hof 1997). Instead, more subtle changes occur during normal ageing including shrinkage and loss of dendrites and dendritic spines, reduction in soma volume (Dickstein et al. 2007), an age-related increase in oxidative damage to lipids, proteins and DNA, a decrease in antioxidants (Dröge and Schipper 2007) and the accumulation of neurotoxic proteins (Gibson 2005). The field of ageing research has particularly focused on a number of metabolic and antioxidant genes including those in the insulin signalling pathway, sirtuins (regulators of fat and glucose metabolism in mammals), superoxide dismutase and catalase (Rodgers et al. 2005; Broughton and Partridge 2009; Harman 1956; Dröge and Schipper et al. 2007). Mutations within these "ageing genes" have been shown to dramatically increase the life-span of yeasts, nematodes, fruit flies and mice and may be expected to effect cognitive performance particularly in the elderly where oxidative damage to neurones and vasculature has had time to accumulate (Sanderson et al. 2008). However, a comprehensive study of 109 genes mainly implicated in oxidative stress (sample size 420–437) identified only a single intronic SNP (APP, rs2830102) associated with cognitive functioning in the elderly, and this remains to be replicated by independent groups (Harris et al. 2007). To date only a handful of metabolic related genes have been implicated in cognitive functioning in healthy individuals (Table 4).

Aldehyde Dehydrogenase 5 Family, Member A1

Aldehyde dehydrogenase 5 family, member A1 (ALDH5A1) (formally known as SSADH) encodes the mitochondrial enzyme succinate semialdehyde dehydrogenase that is involved in the metabolism of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). ALDH5A1 is located on chromosome 6p22 which has been identified as a region associated with dyslexia, reading ability and spelling ability (Francks et al. 2004; Cope et al. 2005; Luciano et al. 2007; Platko et al. 2008) although the finding with dyslexia has been challenged (Petryshen et al. 2000). Very rare mutations within ALDH5A1 lower expression of the enzyme and increase accumulation of GABA and 4-hydroxybutyrate which result in a range of clinical phenotypes including mild mental retardation, seizures and behavioural problems (Akaboshi et al. 2003). Several mechanisms of action have been proposed to explain the effects of ALDH5A1 on cognition, including the neurotoxicity of GABA and 4-hydroybutyrate and the influence of GABA on long-term potentiation (LTP) and synaptic inhibition (Gibson 2005; Sgaravatti et al. 2007; Marshall 2008).

An association between a functional ALDH5A1 SNP (exon 3, C358T, rs2760118), where the T allele has 18% less enzymatic activity (V_{Max}) (Blasi et al. 2002), and IQ has been reported in high IQ children (n=197) and their families (trio n=104) (Plomin et al. 2004). Individuals with one or two copies of the T allele had significantly lower IQ compared to those carrying the C allele (1.5 IQ points). A later study hypothesised that the potential neurotoxicity

Table 4 Metabolic genes associated with cognition

Gene	Investigated polymorphism	Cohorts	Observation	Author
ALDH5A1 (SSADH)	rs2760118 (H538Y)	High IQ (n=197), average IQ (n=201) and parents of high IQ offspring trios (n=196)	Association with IQ	Plomin et al. 2004
	rs2760118 (C538T)	Volunteers aged 18–107 years (n=514)	Associated with MMSE	de Rango et al. 2008
APP	rs2830102	Scottish mental survey 1932 (n=437) and 1947 (n=485)	Associated with cognitive ageing	Harris et al. 2007
CBS	68 bp insertion exon 8 (844ins68)	High IQ (n=101) and average IQ (n=101)	Association with IQ	Barbaux et al. 2000
		Non-demented elderly aged 60–90 years (n=1011)	No association with memory, psychomotor speed or global cognitive function	de Lau et al. 2009
CETP	rs1800776, rs1800775, rs2303790 and rs5882	Two elderly cohorts (n=158 and 173)	Association with rs5882 and MMSE	Barzilai et al. 2006
	rs5882	Scottish mental survey 1932. IQ scores at age 11 and 79 years (n=525)	No association with IQ, memory or processing speed	Johnson et al. 2007
KL	rs9536314	1078 elderly volunteers	Association with reaction time	Houlihan et al. 2009
MTHFR	rs1801133 (C677T)	Scottish mental survey 1932. IQ scores at age 11 and 80 years (n=536)	No association with IQ	Visscher et al. 2003
	rs1801133 (C677T) and rs1801131 (A1298C)	Healthy controls (n=122), cognitively impaired (not demented) (n=24) and AD patients (n=48)	No association with cognitive function	Ravaglia et al. 2004
	rs1801133	Elderly men and post-menopausal women (n=818, 50–70 years)	Association with sensorimotor speed and non-significant trend with other cognitive tasks	Durga et al. 2006
	rs1801133	Nonagenarians (n=1581)	No association with cognitive ability (MMSE and five other brief tests), decline or survival	Bathum et al. 2007
	rs1801133 and rs1801131	Non-demented elderly (n=1011)	No association with memory, psychomotor speed or global cognitive function	de Lau et al. 2009
PPARG	rs1805192 (Pro12Ala)	Elderly volunteers (mean age, 74.1; 41% Black; 52% women) (n=2961)	Association with Digit Symbol Substitution Test and MMSE	Yaffe et al. 2008
PRNP	rs1799990 (M129V)	Healthy volunteers (n=335)	Association with IQ	Rujescu et al. 2003
		Scottish mental survey 1947 (n=1078)	Association with letter number sequencing, spatial span and matrix reasoning	Houlihan et al. 2009

Aldehyde dehydrogenase 5 family, member A1 (ALDH5A1); amyloid beta (A4) precursor protein (APP); cystathionine-beta-synthase (CBS); cholesteryl ester transfer protein (CETP); klotho (KL); 5,10-methylenetetrahydrofolate reductase (MTHFR); peroxisome proliferator-activated receptor gamma (PPARG); prion protein (PRNP)

caused by reduced ALDH5A1 may have a greater adverse effect on cognition and even survival of elderly individuals (de Rango et al. 2008). The study of 264 elderly (65–85 years) found that the distribution of the T allele was greater in those with lower cognitive functioning (MMSE ≤ 23) compared with higher functioning individuals (MMSE> 23) (p-value, 0.05) and that survival was lower for individuals with the TT genotype.

Whilst the role that metabolic and antioxidant genes play in ageing and longevity is a convincing one, there is no compelling evidence thus far that they have a substantial impact on cognition either in the young or elderly. However, current investigations of these genes have been too few, poorly powered and the majority lack replication. These issues need addressing before further conclusions can be drawn.

Longitudinal Association Studies

Determining the proportion of cognitive decline in the elderly that can be attributed to genetic variation has proved

a challenge for several reasons. Firstly, cognitive abilities in healthy elderly individuals show substantial intra- and interindividual differences in decline that are caused by a number of factors including genetic and environment influences, stochastic events and disease. A study that followed over 6000 non-demented elderly volunteers for changes in cognitive ability over a twenty year period found that tests of executive functioning decline at an accelerated rate, whilst the decline of memory abilities tended to be linear and verbal abilities remained stable over time (Rabbitt et al. 2004b). The same group also found that cognitive decline is fairly gradual with executive functioning declining at an average of 6% per decade between the ages of 50 and 80 years (Rabbitt and Lowe 2000). Extensive periods of time and regular cognitive measurements are therefore required to be able to accurately estimate heritability or detect genetic effects. Consequently, a large proportion of elderly subjects tend to be lost between subsequent testing due to attrition and therefore the power of longitudinal studies tends to taper quite dramatically over time. In addition, bias can be introduced by differential survival (Glymour et al. 2008). For example high premorbid IQ scores are correlated with a reduced rate of mortality from factors such as coronary heart disease, suicide and accidents (Batty et al. 2009). Therefore, the greater the mean age of the cohort the less they will be representative of the general population and for longitudinal studies the survivors tend to be comprised of an increasingly elite and able group. Indeed, volunteers for cognitive studies in the UK are far from a randomised selection of individuals and tend to be of higher than average IQ, middle class and predominantly women (Rabbitt et al. 2004b). A further consideration is analytical adjustment for practice effects. Even though several years may have passed between testing periods volunteers have been shown to remember the questions or task strategies and therefore show an artificial improvement that varies depending upon the type of cognitive test, the participants educational background and how well they performed on a previous examination (Rabbitt et al. 2004a).

The initial twin studies investigating cognitive decline produced varied findings with heritability estimates ranging from 0.0–0.7 for fluid and 0.0–0.3 for crystallised intelligence (McArdle et al. 1998; Reynolds et al. 2002; McGue and Christensen 2002). Much of this discrepancy could be attributed to the reasons described above. Indeed, the first heritability studies were either relatively large but had a short follow-up (5–8 years) (Reynolds et al. 2002; McGue and Christensen 2002) or had a long follow-up but had only a modest sample size (134 twin pairs) (McArdle et al. 1998). Substantial attrition was also evident with an 80% loss of sample size for the McGue study between the first and last assessment which spanned just 8 years (McGue and Christensen 2002). Further variation may have been caused by the differences in cognitive tests, analytical models and population stratification effects.

A subsequent study of 778 twins (aged 50 years and over) with a follow-up of 13 years investigated the genetic and environmental affects on verbal, spatial, memory and processing speed with analysis performed on the initial ability score (intercept), the rate of decline (slope) and the acceleration of decline (quadratic) (Finkel et al. 2005). As expected a substantial genetic influence was observed on the intercept and yet it was found that the genetic contribution towards the slopes of all cognitive abilities and on the quadratic for verbal ability were "negligible". However, the genetic effect on the quadratic for fluid abilities and processing speed accounted for approximately one third of the variance. It was also observed that the quadratic for memory and spatial abilities (but not verbal ability) was slowed by a faster mean processing speed and later work suggested that changes in processing speed preempt the changes in memory and spatial ability (Finkel et al. 2007). The most recent work by Finkel and colleagues used data collected at up to five measurement points over a 16 year period (Finkel et al. 2009). They found that when the processing speed factor was removed from the model a substantial proportion of the genetic variance for the spatial and memory factors also disappeared. This suggests that the genetic variance in processing speed "drives" the age-related changes in fluid abilities. Taken together these data support the processing speed theory of cognitive ageing which postulates that processing speed is integral to the performance of fluid abilities and that the constraints of processing become more evident with age (Salthouse 1996).

Genes Associated with Cognitive Decline in Healthy Individuals

Due to the difficulties of establishing adequately powered longitudinal studies with sufficient follow-up, publications tend to be fewer in number and are more prone to Type 1 and Type 2 error compared with cross-sectional studies. The handful of investigated genes include apolipoprotein E (APOE), serotonin transporter (SLC6A4), serotonin receptor 2A (HTR2A), estrogen receptors 1 and 2 (ESR1-2) and peroxisome proliferator-activated receptor-gamma (PPARG). Of these only the APOE alleles ε2-ε4 have been looked at by multiple independent groups with ten out of sixteen studies reporting that APOE ε4 increased the rate of decline in non-demented elderly (Savitz et al. 2006). However, fifteen of these studies had a follow-up period ranging from 2 to 8 years with a mean follow-up of just 4.7 years and the majority had not adjusted for practice

effects or investigated the quadratic independently of the slope. Assuming an average decline of 6% per decade in a sample of non-demented elderly (Rabbitt and Lowe 2000) these studies were essentially trying to determine the effect of APOE alleles on an average trajectory variance of just 2.8%.

Of the remaining associations made between polymorphisms and cognitive decline three of them (PPARG and ESR 1 and 2) were reported by the Health, Aging and Body Composition study (Health ABC study, USA) who tested elderly volunteers biannually over a four year period using the Modified Mini-Mental State Examination (3MS) and the Digit Symbol Substitution Test (DSST) (a measure of processing speed, attention and executive function) (Yaffe et al. 2008; Yaffe et al. 2009). The PPARG SNP rs1805192 (Pro12Ala) was selected due to its association with diabetes and obesity, both of which correlate with cognitive decline. In a large but ethnically mixed sample (n=2961; 41% black, 52% women, age range 70–79 years), they found that the Ala polymorphism was associated with higher test scores for both the 3MS and DSST at baseline and that 17.5% of Ala carriers exhibited cognitive decline (defined as a loss of ≥5 3MS points over 4 years) compared to 25% of non-carriers (Yaffe et al. 2008). Estrogen receptor 1 and 2 polymorphisms have previously been associated with AD (Brandi et al. 1999). Therefore Yaffe and colleagues hypothesised that the same SNPs may influence cognitive decline in non-demented individuals. Again using volunteers (n=2527; 1343 women, mean age 73 years) from the health ABC study they identified several associations with cognitive decline (Yaffe et al. 2009). Out of eight SNPs five were associated with cognitive decline in a sex specific manner, and one (ESR2, rs1256030) was associated with decline in both men and women. All except one of the SNPs were located within an intron although two SNPs (rs8179176 and rs9340799, both ESR1, intron 1) are within a region (intron 1/exon 2 boundary) that has been reported to regulate expression (Maruyama et al. 2000). However, ESR1, ESR2 and PPARG are large genes that require between 13 and 45 tagSNPs to cover the coding regions (assuming a MAF>10%, r^2>0.8, Caucasian population). The studies are therefore limited in both their follow-up and depth of SNP coverage.

The Swedish Adoption Twin Study of Ageing (SATSA) and the Dyne Steel cohort for cognitive genetic studies have both reported that serotonergic genes regulate the rate of cognitive decline (Reynolds et al. 2006; Payton et al. 2005). Serotonin is involved in both brain development and cognitive functioning and there is an age-related decrease in serotonin levels that may predispose to depression, cognitive impairment and dementia (van Kesteren and Spencer 2003; Meneses 1999; Rehman and Masson 2001). Reynolds and colleagues studied the longitudinal effects of a promoter polymorphism within the HTR2A gene (rs6311; −1438 G/A) on the longitudinal decline over a 13 year period using 595 elderly individuals (517 at final testing occasion, mean age 65 years at baseline testing). They found that individuals homozygous for the G allele declined slower for a test of episodic memory than those carrying the A allele which accounted for a difference in trajectory of between 2–6% per year. A non-synonymous HTR2A SNP (rs6313; H452Y), which has been shown to blunt receptor response (Göthert et al. 1998), has also been associated with variation in episodic memory that accounted for 21% of the variation of test scores measured at a single time-point (de Quervain et al. 2003). Further evidence that the serotonergic pathway is involved in cognition has come from our Manchester group where we reported that a functional VNTR within the intron 2 (MacKenzie and Quinn 1999) of the serotonin transporter also regulates the rate of cognitive decline in elderly non-demented volunteers (n=758) all of whom had been followed for changes in cognitive performance over a 15 year period (Payton et al. 2005). We found that those who carried VNTR12 allele, that was associated with an increase in transporter transcription, declined significantly faster than those carrying the VNTR10 allele. This accounted for a 2.9% faster decline in general intelligence per decade for heterozygous individuals and 4.4% faster decline for homozygous VNTR12 individuals when compared against those homozygous for VNTR10. To date no attempts have been made to replicate the serotonin transporter or HTR2A results or to test for an interaction between these two genes.

Study Considerations

The overview of cognitive genetic research given above is one largely bereft of consensus and adequate research design. This is not necessarily a reflection upon the overall quality of research. Many previous studies were limited in scope but given the early discovery of low hanging fruit, such as the association between APOE and AD, there was no reason to believe that such large effect polymorphisms would not exist for cognition particularly when the heritability is so high. Neither is the lack of inconsistency limited to cognitive genetic studies. Indeed, a failure to replicate an initial positive finding is a common characteristic of the majority of association studies investigating complex diseases and traits (Hattersley and McCarthy 2005). Inadequate sample size, population stratification, environmental exposure, publication bias, variation in classification and measurements are all examples that may make one groups findings different from those of another. Combined with the development of high throughput techniques, and hence a dramatic increase in the number of original publications in human genetic epidemiology, the reader is now faced with a frustrating variety of results and

conclusions (Lin et al. 2006). Meta-analysis goes some way to provide a solution to this problem by detecting and adjusting for inconsistency between data sets, although even this technique has several pitfalls (Kavvoura and Ioannidis 2008). Sadly however, if the question were to be asked "after 14 years of cognitive genetic research what genes can we conclusively say are responsible for the variation in cognition or its decline with age in healthy individuals?" the answer would have to be "none." This doesn't imply that we have not already identified intelligence genes but merely that better designed studies are required to confirm or refute which of them actually play a role in cognition and which of them do not. Listed below are a number of confounders that can result in type I and type II errors. However, a good association study should always include an independent replication cohort in its design, which would dramatically reduce the numbers of false positive publications.

MMSE as a Cognitive Screening Tool

Amidst the extensive array of cognitive measures there exist tests that are not suitable for purpose for the study of healthy people. One commonly used test for measuring cognition in the elderly is the Mini-Mental State Examination (MMSE). The MMSE was designed over 30 years ago as a screening tool for dementia and it remains a widely used method (Folstein et al. 1975). Unfortunately, it has limitations as a measure of cognitive outcome. Primarily, it has a substantial ceiling effect which makes it impossible to differentiate between medium and high performing individuals (Tombaugh and McIntyre 1992). Studies that rely solely on the MMSE as a measure of cognitive function therefore possess a lack of sensitivity that would make the accurate detection of small effect polymorphisms much more unlikely. To help counter the shortcomings of the MMSE an extended version of the test has been developed. The Modified Mini-Mental State Examination (3MS) increases the maximum score from 30 to 100 and extends the number of questions aimed at measuring memory and executive function. Comparison of the MMSE and 3MS in a population of over 12000 elderly participants (65 years and over) in the MRC Cognitive Function and Ageing Study found that ceiling effects were reduced from almost a quarter of the volunteers (scoring 29 or 30) for the MMSE test to 9% for the 3MS test (Huppert et al. 2005). However, even a ceiling effect of 9% would ultimately influence power and may be considered to high.

Sex-specific Effects

Sex-specific differences in the prevalence of mental retardation and neuronal efficiency are well documented (Ropers and Hamel 2005; Neubauer et al. 2005). Whether differences exist for general cognitive ability remain a contentious issue (Irwing and Lynn 2005; Blinkhorn 2005; Irwing and Lynn 2006) although there appears to be no gender differences in the patterns of cognitive ageing (Finkel et al. 2006). The uncertainty for the existence of sex specific effects is reflected by the fact that only a small number of other genes in addition to ESR1 and ESR2 have been shown to exhibit a sex specific influence on cognition. The fragile X mental retardation 1 gene (FMR1; Xq27.3) contains a CGG repeat in the 5′ untranslated region which can silence the gene and cause mental retardation if the number of repeats exceeds 200 (Crawford et al. 2001). A study using 66 men and 217 women, who were divided according to their CGG repeat number, observed that women, but not men, with >50 repeats scored significantly lower (4% difference in score) on a test of verbal IQ when compared against females with less than 50 repeats (Allen et al. 2005). A sex specific effect has also been observed with the disrupted in schizophrenia 1 (DISC1) gene (Thomson et al. 2005). The study of 171 men and 254 women who had taken the Moray House IQ Test at age 11 and again at age 79 found that a non-synonymous exon 11 SNP was weakly associated with reduced scores in elderly women only (p-value, 0.043; after adjustment for ability at age 11). Whilst current evidence is not particularly strong for the existence of sex specific effects it is something that researchers should be aware of when conducting analysis.

Interactions

A common misconception about genes is that they are rigid entities that serve single functions throughout our lives. On the contrary, a single gene can perform multiple tasks at various stages of development, alter the function of other genes, act in a tissue specific manner and respond to changes in the environment. The nature versus nurture debate became so polarised during the last century that the possibility of gene-environment interaction was largely overlooked (Ridley 2003). Reports of interactions are now increasing exponentially for a wide variety of diseases and traits including cancer (Thorgeirsson et al. 2008), asthma (Kim et al. 2009) and obesity (Qi and Cho 2008). One of the first high quality publications demonstrating interaction was by Caspi and colleagues who tested why some people were susceptible to depression caused by stressful life events whilst others were not (Caspi et al. 2003). The study divided 847 participants, who had been assessed for depression and stressful life events on ten occasions between the ages of 3 and 26, into three groups according to whether they carried the short (s) or long (l) form of a serotonin transporter (5-HTTLPR) polymorphism (homozygous s/s, heterozygous

s/l and homozygous l/l). They observed that individuals carrying at least one copy of the short allele (associated with reduced transcriptional efficiency) were more prone to depression and suicidality compared to those who carried two copies of the long allele, and this effect was dependent upon the number of stressful life events they had experienced. A potentially important conclusion from the authors was that multifactorial disorders may not necessarily result from many genetic variations of small effect but may be attributed to a smaller number of variations whose effects are mediated via their exposure to the environment.

To date eight studies have identified gene-environment interactions that effect cognition (Table 5). One of these studies reported that the minor alleles of two SNPs (rs1800562 and rs1799945) within the hemochromatosis gene influenced lead-related cognitive decline in non-demented elderly men (n=358) (Wang et al. 2007). Unfortunately, this study had several limitations including the use of the MMSE as a measure of ability, a relatively small population size for interaction analysis and an inadequate time period between the two testing sessions (mean=3.2 years). Three other gene-environment studies also had a severe lack of power due to small sample size particularly once the subjects were sub grouped (Froehlich et al. 2007; Morales et al. 2008; Johnson et al. 2008). A more convincing study found that the positive effect of breastfeeding on IQ was regulated by a common polymorphism (rs174575; CG) within the fatty acid desaturase 2 (FADS2) gene (Caspi et al. 2007). Caspi and colleagues used two independent cohorts from New Zealand (n=1037) and the UK (n=2232) and found that breastfed children had a significantly higher IQ (approximately 6.0 IQ points). In addition, genotype showed significant interaction with breastfeeding in both populations (New Zealand, p-value, 0.035; UK, p-value, 0.018) with the presence of the C allele increasing IQ in those who were breastfed, whilst those homozygous for the G allele showed no difference in IQ whether they were breastfed or not.

Five epistasis (gene-gene) interactions have also been reported (Table 5). BDNF as already discussed is the most consistently associated gene in cognition and yet there still exists contrasting reports regarding its function in cognition. Whilst population differences, testing methods and sample size may be contributing factors it is also necessary to consider that single polymorphisms are unlikely to act independently. An example of this is the serotonin transporter gene that has at least two functional polymorphisms and where it has been demonstrated that analysing these polymorphisms in combination is a more powerful approach than analysing them independently (Hranilovic et al. 2004). This study highlights the need for research groups to adopt a haplotype tagging approach where genetic variations are selected that capture the majority of diversity for the entire gene and surrounding regions. Of more than 200 publications in the field of cognitive genetics only 8 have adopted this method and even fewer have analysed haplotype findings in combination with other genes. One such study was performed by Miyajima and colleagues who investigated the epistatic interaction between BDNF and the REST gene which is a regulator of BDNF expression (Miyajima et al. 2008b). A haplotype within the REST gene, that contained an exon 4 hexadecapeptide variable number tandem repeat (VNTR) with either four or five copies and a non-synonymous SNP, was weakly associated with general intelligence (p-value, 0.05) in an elderly non-demented cohort (n=746). When the REST haplotypes were analysed with BDNF haplotypes an interaction was observed (global p-value, 0.0003) that was more significant than when either gene was analysed independently. However, investigating polymorphisms in combination is a considerable drain on power and only 45 people (6%) possessed the haplotype combination associated with improved performance.

Interaction analysis is providing information that should have been obvious from the start, in that genetic variants are unlikely to act independently. Biological pathways are regulated by multiple genes, that themselves are influenced by other genes and possibly multiple genetic variants. In addition, genes act on cues from the environment. Perhaps by considering these factors in combination rather than independently a clearer picture will emerge. Interactions and sex specific effects may provide a stronger association and hence not necessarily demand an increase in sample size. However, if the effect sizes prove to be small and/or the allele of interest has a low frequency then particularly for interaction analysis this could dramatically increase cost.

Sample Size

Sample size is a clear constricting factor for many of the studies described above. What constitutes an adequate sample size is open to interpretation as the calculation requires an estimate of effect size and this is yet unknown. It has been recommended that researchers should be aiming to break the "1% quantitative trait loci barrier" which requires between 800 and 1000 samples to detect a polymorphism which accounts for at least 1% of the variance in cognitive ability within the general population with 80% power (Plomin 2003; Craig and Plomin 2006). Unfortunately, as can be seen in Tables 1, 2, 3, 4 and 5 only a small proportion of cognitive genetic research groups reach or break this threshold and even some recent studies still seem content to use sample sizes of a few hundred or less (Bombin et al. 2008; Tsai et al. 2008; Izumi et al. 2008;

Table 5 Epistasis and gene-environment interactions that influence cognition

Interaction	Investigated polymorphism	Cohorts	Observation	Author
Epistasis				
BDNF/REST	BDNF rs6265 REST rs2227902, rs3796530 48 base pair repeat at codons 735–768	Dyne Steel cohort, Manchester, UK. Community-dwelling elderly (n=746)	BDNF Val66 and a REST haplotype was associated with an increase in g.	Miyajima et al. 2008b
CTSD/APOE	CTSD rs17571 (C/T)	Dyne Steel cohort, Manchester, UK.	CTSD T allele and APOEε4 associated with reduced processing speed, memory and fluid intelligence	Payton et al. 2006
CTSD/HLA	HLA-DRB1 APOEε2-4	Community-dwelling elderly (n=766)	CTSD T allele and HLA-DR2 associated with reduced processing speed and memory	
PRNP/KL	PRNP rs1799990 KL rs9536314	Scottish mental survey 1932 (n=550)	PRNP associated with cognitive change (Moray House Test IQ) that was dependent upon the KL allele status	Kachiwala et al. 2005
CHRNA4/ APOE	rs1044396 and APOEε4	Middle aged (53–64 years, n=110) and older adults (65–75 years, n=120).	Interaction between APOE and CHRNA4 polymorphisms that influenced attention and white matter volume	Espeseth et al. 2006
CHRNA4/ CHRM2	rs1044396 and rs8191992	Recruited from Washington DC, age range 18–90 years (n=406)	Interaction between SNPs within nicotinic and muscarinic receptors that effected visual attention but not working memory	Greenwood et al. 2009
Gene-environment				
BDNF/ Hypertension	BDNF rs6265	Caucasian volunteers (mean age 54 years, n=189, hypertensive n=49)	Association between homozygous Val66 and associative memory and processing speed that was more pronounced in women and those with hypertension	Raz et al. 2009
BDNF/ Glucose	BDNF rs6265		Elevated blood glucose levels were associated with reduced memory performance in BDNF Met66 carriers	Raz et al. 2008
DRD4/Lead	DRD4 exon 3 48 bp repeat	US children (n=174)	Association with spatial working memory and interaction of the 7 allele repeat and lead that was also showed gender differences	Froehlich et al. 2007
FADS2/Breast feeding	rs174575 (C/G)	Dunedin Multidisciplinary Health and Development Study, New Zealand (n=1037) Environmental Risk (E-risk) Longitudinal Twin Study, England and Wales (n=2232)	Breastfed children carrying the C allele had a 6–7 IQ point advantage over non-breastfed children	Caspi et al. 2007
GSTP1/ p,p'-DDT	rs1695 (Ile105Val)	Asthma Multicenter Infants Cohort study, Menorca, Spain (n=326)	Val allele associated with reduced memory, executive function and verbal skills that was indirectly proportional to levels of p,p'-DDT	Morales et al. 2008
HFE/Lead	rs1800562 (C282Y) rs1799945 (H63D)	Normative Aging Study, Boston, USA (n=358)	Association between minor alleles and lead-related cognitive decline	Wang et al. 2007
MTHFR/ Hypertension	rs1801133 (C677T)	Caucasian volunteers (age range 18–80 years, n=160)	Hypertensive carriers of the T allele scored significantly lower on a test of spatial navigation	Deshmukh et al. 2009
PPARG/ Diabetes	rs1801282 (Pro12Ala)	Scottish mental survey 1932 (n=519)	Association between Ala carriers and Moray House Test of IQ at age 79 in diabetics	Johnson et al. 2008

Brain-derived neurotrophic factor (BDNF); RE1-silencing transcription factor (REST); cathepsin D (CTSD); apolipoprotein E (APOE); major histocompatibility complex, class II, DR beta 1 (HLA-DRB1); prion protein (PRPN); klotho (KL); cholinergic receptor, nicotinic, alpha 4 (CHRNA4); cholinergic receptor, muscarinic 2 (CHRM2); dopamine receptor D4 (DRD4); fatty acid desaturase 2 (FADS2); glutathione S-transferase pi 1 (GSTP1); hemochromatosis (HFE); 5,10-methylenetetrahydrofolate reductase (MTHFR); peroxisome proliferator-activated receptor gamma (PPARG)

Schaper et al. 2008; Nacmias et al. 2008). A further emphasis for the need of adequate sample size comes from the GWAS studies of general intelligence (Butcher et al. 2005; Meaburn et al. 2008; Butcher et al. 2008). All of these studies were performed by the same group using an increase in microarray density of 10 k, 100 k and 500 k SNPs. Using a DNA pooling technique on sample of low and high IQ individuals (n=approximately 400 for each group) followed by genotyping of between 4000 and 6000 additional samples the group identified a small number (between 5 and 10) of associated SNPs on each platform. Each SNP only accounted for between 0.15 to 0.2% of the cognitive variance and this magnitude of effect would require a sample number exceeding 4000 to achieve 80% power. The group also created composite SNP sets from the associated SNPs that accounted for between 0.76 and 1% of the variance and which would require smaller numbers for replication (sample sizes of 700 to 800 for 80% power). However, a collaboration of four independent groups (total n=3539) failed to replicate the 5 SNP set or the composite set results derived from the 10 K platform (Luciano et al. 2008). Hence, we can only conclude that the 10 k microarray/pooling technique may be inadequate to find polymorphisms associated with cognition and that replication of the 100 and 500 k findings is required to confirm the small effect sizes.

Population Stratification

Whilst inadequate statistical power is the most commonly cited cause of non-replication, population stratification effects should also be considered. Unless they are family based, association studies generally require that subjects are from the same population. Variation in disease prevalence, including diabetes, hypertension and dementia, and differences in allele frequencies are common amongst different populations. If analysed together, particularly if the populations are not equally represented throughout the normal distribution, they may distort results leading to a false association, an effect known as population stratification. Although generally, acknowledged as a source of bias, some believe the magnitude of effect is not problematic especially when studying different ethnic groups of non-Hispanic European decent (Wacholder et al. 2002). By contrast, others have shown that even in moderate sample sizes consisting of a few hundred individuals, combinations in disease prevalence and differences in allele frequencies can result in false positive results (Heiman et al. 2004).

Although there are methods for dealing with potential population stratification, including "genomic control," principal components analysis and "structure methods" (Rodriguez-Murillo and Greenberg 2008) the first step for any study should be the collection of adequate information on ethnic background.

Vascular Risk Factors

Despite age being the main risk factor for cognitive impairment, vascular risk factors such as hypertension, diabetes mellitus, obesity, smoking, hypercholesterolemia, metabolic syndrome and dyslipidemia have also been shown to play a role in both cognitive decline and dementia (Duron and Hanon 2008). The relative risk for dementia in association with hypertension, obesity, diabetes and dyslipidemia is approximately 1.5 for each factor (Kloppenborg et al. 2008; Whitmer et al. 2007; Gustafson et al. 2003). However, dementia can be considered the end stage of an accumulation of damage and therefore may not be representative of the relative risk caused by vascular factors at much earlier stages of cognitive decline. Indeed, a recent comparison of cross-sectional and longitudinal studies that investigated these four vascular risk factors on cognitive decline in non-demented individuals found variations in effect sizes (van den Berg et al. 2009). Both hypertension (comparison of 24 studies) and diabetes (comparison of 27 studies) were associated with the decline of multiple cognitive abilities over time. However, the association with obesity (comparison of 6 studies) was less clear with domain and age specific effects being reported that were largely inconsistent between studies. Associations with Dyslipidemia (comparison of 7 studies) were equally inconsistent.

Unfortunately, very few cognitive genetic studies have adjusted for vascular risk factors in their analysis even though the evidence suggests that diabetes and hypertension are likely to influence cognitive decline. This information would be particularly relevant to the study of elderly populations where vascular effects are most pronounced.

Summary

Given the wealth of data and lack of total consensus for even a single gene we can assume that either cognitive genetic research has missed the large to moderate effect polymorphisms or that small effect sizes and interactions will predominate. The latter seems an increasingly likely prospect and one which will demand an overhaul of study design, more concentrated funding and the knowledge that gathering detailed environmental data may prove as important as the collection of high quality psychometric and genetic information. At present, the increasing numbers of underpowered and poorly designed studies is making the field difficult to follow, evaluate and interpret and the cost

effectiveness of small scale studies is questionable. To ensure optimum use of technology, such as microarrays and the next generation of sequencing, thousands if not tens of thousands of samples will be required, and this will necessitate collaboration and recruitment on a grander scale. The use of principal component analysis and genotype-imputation (Huang et al. 2009b) means that research groups with diverse cognitive measures and genotypes from different microarrays can combine data. These collaborations are beginning to emerge for the study of individual genes (Luciano et al. 2008; Luciano et al. 2009a), and several large cognitive groups in the UK will soon be combining their microarray data for joint analysis. Whether this proves sufficient remains to be seen and a global call for collaboration should be encouraged in order to increase power and provide additional conformation. However, smaller studies will continue to be published and a strategy used by the schizophrenia research community where all studies are recorded on the schizophrenia forum website (www.schizophreniaforum.org) along with the meta-analysis would be an excellent approach for cognitive genetic research groups to follow.

In addition, to the study of SNPs, VNTRs and micro-satellites there are other variations both genetic and epigenetic that will begin to appear in the cognitive genetic literature in the near future. Copy Number Variants (CNVs) are large regions of DNA (1 kilobase to several megabases) that can be duplications, insertions, deletions or complex rearrangements which can alter gene function. CNVs have already been associated with several neuropsychiatric conditions including schizophrenia, autism and mental retardation (Cook and Scherer 2008; Kirov et al. 2009; Kumar and Christian 2009). Given their current affect on psychiatric conditions that are associated with a loss of cognitive function it is highly likely that we will see similar associations with cognitive function in cognitively healthy individuals in the near future. Epigenetic regulation of gene expression is another area of potential interest but one that has yet to be explored in the field of cognition. A recent study using a rat model of infant maltreatment showed that early-life adversity altered the methylation patterns of the BDNF gene in the prefrontal cortex of the abused rats which in turn caused a persistent change in BDNF expression (Roth et al. 2009). Changes to methylation patterns were also found to be passed down to the offspring of maltreated women. As discussed earlier, BDNF has been a central focus of cognitive genetic studies and epigenetic modulation of expression of this and other genes may help strengthen future associations. This may entail the gathering of data on stressful life events and the establishment of cognitive brain banks. However, ventures such as this are already underway by projects such as the Research into Ageing funded Dyne Steel cohort for cognitive genetic research which is an ongoing longitudinal study based at the University of Manchester (www.medicine.manchester.ac.uk/genomicepidemiology/research/geneticepidemiology/neurologicalgenetics/behaviouraltraits/cognitiveimpairment/). The point at which variation within a gene has sufficient impact to be realistically useful for diagnosis and treatment for cognitive impairment is still open to speculation. Certainly, nothing approaching a substantial effect size has yet been reported and the conclusion of some scientists that effect sizes under 1% will be the norm does not bode well for future drug development. This, however, assumes that polymorphisms act independently and in my discussion of genes such as BDNF and DRD2 I hope to have dispelled this assumption. As already mentioned genes are fluid entities and their variation in function is rarely due to the effects of a single SNP. Broadening our investigations to include other potential contributing factors that may include CNVs, methylation and environment and then analysing them in combination may tease out those elusive large effects.

Identifying the genetic risk factors for susceptibility to cognitive deficit caused by normal cognitive ageing will be one of a number of important breakthroughs needed to ameliorate cognitive impairment in the elderly. This is a research priority with care costs for those with severe cognitive impairment set to triple in the UK from £5.4 billion in 2002 to £16.7 billion in 2031 in real terms (Comas-Herrera et al. 2007). Whilst there are some tentatively interesting findings in the field of cognitive genetics, there is still clearly a lot of work to do that would benefit from more stringent methodologies, a broadening of the types of variation that gets investigated and the aggregation of current resources.

Disclosures I have no conflicts of interest to report.

Genetic glossary

Allele	One of a number of different polymorphic states. For example for an SNP where a T is replaced by a G, the T and G are the two alleles
Epigenetic	Describes something which influences the behaviour of a cell without directly affecting its DNA or other genetic machinery, such as an environmental effect
Exon	Coding regions of DNA that are transcribed and translated into protein
Genotype	The specific allele makeup of a polymorphism. For example, an SNP where an A is the common allele and

	a T is the minor allele can have three potential genotypes: homozygous AA or TT, or heterozygous AT
Haplotype	A set of polymorphisms from the same region which are usually inherited as a unit
Heterozygous	Occurs when alleles at the same chromosomal position are different. For example if a T is inherited from a specific genetic location from the mother and an A is inherited at the same position from the father then the genotype will be heterozygous (AT)
Homozygous	Occurs when alleles at the same chromosomal position are the same
Intron	Regions of DNA located between exons which do not translate into protein
Mutation	DNA variations that occur at a frequency of less than 1% within a population
Non-synonymous	A substitution of one nucleotide for another nucleotide within an exon of a gene that results in the production of a different amino acid
Polymorphism	DNA variations that occur at a frequency of greater than 1% within a population
Promoter site	Region of DNA that regulates the amount of protein produced
Single nucleotide polymorphism (SNP)	DNA sequence variation occurring at a single nucleotide. They are identified by an individual reference sequence (rs) number. For example rs6265 (an SNP within the BDNF gene)
Stochastic	Random or probabilistic event
TagSNP	Multiple SNPs can be inherited together on a single block of DNA (these SNPs are said to be in linkage disequilibrium). Therefore, it is possible to genotype a small number of SNPs on a block in order to identify a haplotype. The selected SNPs are called tagSNPs and they are a way of reducing genotyping costs while maintaining power to detect association.
Transcription	Transfer of genetic information from DNA to RNA

References

Ahmed, S., Reynolds, B. A., & Weiss, S. (1995). BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronalprecursors. *Journal of Neuroscience, 15*, 5765–5778.

Akaboshi, S., Hogema, B. M., Novelletto, A., Malaspina, P., Salomons, G. S., Maropoulos, G. D., et al. (2003). Mutational spectrum of the succinate semialdehyde dehydrogenase (ALDH5A1) gene and functional analysis of 27 novel disease-causing mutations in patients with SSADH deficiency. *Human Mutation, 22*, 442–450.

Allen, E. G., Sherman, S., Abramowitz, A., Leslie, M., Novak, G., Rusin, M., et al. (2005). Examination of the effect of the polymorphic CGG repeat in the FMR1 gene on cognitive performance. *Behavior Genetics, 35*, 435–445.

Almeida, O. P., Schwab, S. G., Lautenschlager, N. T., Morar, B., Greenop, K. R., Flicker, L., et al. (2008). KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. *Journal of Cellular and Molecular Medicine, 12*, 1672–1676.

Antonini, A., Leenders, K. L., Reist, H., Thomann, R., Beer, H. F., & Locher, J. (1993). Effect of age on D2 dopamine receptors in normal human brain measured by positron emission tomography and [11C] raclopride. *Archives of Neurology, 50*, 474–480.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S. C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience and Biobehavioral Reviews, 30*, 791–807.

Ball, D., Hill, L., Eley, T. C., Chorney, M. J., Chorney, K., Thompson, L. A., et al. (1998). Dopamine markers and general cognitive ability. *NeuroReport, 9*, 347–349.

Bannon, M. J., & Whitty, C. J. (1997). Age-related and regional differences in dopamine mRNA expression in human midbrain. *Neurology, 48*, 969–977.

Barbaux, S., Plomin, R., & Whitehead, A. S. (2000). Polymorphisms of genes controlling homocysteine/folate metabolism and cognitive function. *NeuroReport, 11*, 1133–1136.

Barnett, J. H., Scoriels, L., & Munafò, M. R. (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biological Psychiatry, 64*, 137–144.

Bartrés-Faz, D., Junqué, C., Serra-Grabulosa, J. M., López-Alomar, A., Moya, A., Bargalló, N., et al. (2002). Dopamine DRD2 Taq I polymorphism associates with caudate nucleus volume and cognitive performance in memory impaired subjects. *NeuroReport, 13*, 1121–1125.

Barzilai, N., Atzmon, G., Derby, C. A., Bauman, J. M., & Lipton, R. B. (2006). A genotype of exceptional longevity is associated with preservation of cognitive function. *Neurology, 67*, 2170–2175.

Bathum, L., von Bornemann Hjelmborg, J., Christiansen, L., McGue, M., Jeune, B., & Christensen, K. (2007). Methylenetetrahydrofolate reductase 677C>T and methionine synthase 2756A>G mutations: no impact on survival, cognitive functioning, or cognitive decline in nonagenarians. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62*, 196–201.

Batty, G. D., Wennerstad, K. M., Smith, G. D., Gunnell, D., Deary, I. J., & Tynelius, P. (2009). IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men. *Epidemiology, 20*, 100–109.

Baune, B. T., Ponath, G., Rothermundt, M., Riess, O., Funke, H., & Berger, K. (2008). Association between genetic variants of IL-1beta, IL-6 and TNF-alpha cytokines and cognitive performance in the elderly general population of the MEMO-study. *Psychoneuroendocrinology, 33*, 68–76.

Bendixen, M. H., Nexø, B. A., Bohr, V. A., Frederiksen, H., McGue, M., Kølvraa, S., et al. (2004). A polymorphic marker in the first intron of the Werner gene associates with cognitive function in aged Danish twins. *Experimental Gerontology, 39*, 1101–1107.

Benson, M. A., Newey, S. E., Martin-Rendon, E., Hawkes, R., & Blake, D. J. (2001). Dysbindin, a novel coiled-coil-containing

protein that interacts with the dystrobrevins in muscle and brain. *Journal of Biological Chemistry, 276*, 24232–24241.

Berman, S. M., & Noble, E. P. (1995). Reduced visuospatial performance in children with the D2 dopamine receptor A1 allele. *Behavior Genetics, 25*, 45–58.

Blasi, P., Boyl, P. P., Ledda, M., Novelletto, A., Gibson, K. M., Jakobs, C., et al. (2002). Structure of human succinic semialdehyde dehydrogenase gene: identification of promoter region and alternatively processed isoforms. *Molecular Genetics and Metabolism, 76*, 348–362.

Blinkhorn, S. (2005). Intelligence: a gender bender. *Nature, 438*, 31–32.

Bochdanovits, Z., Gosso, F. M., van den Berg, L., Rizzu, P., Polderman, T. J., Pardo, L. M., et al. (2009). A Functional polymorphism under positive evolutionary selection in ADRB2 is associated with human intelligence with opposite effects in the young and the elderly. *Behavior Genetics, 39*, 15–23.

Bombin, I., Arango, C., Mayoral, M., Castro-Fornieles, J., Gonzalez-Pinto, A., Gonzalez-Gomez, C., et al. (2008). DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. *Am J Med Genet B Neuropsychiatr Genet, 147B*, 873–879.

Borg, J., Henningsson, S., Saijo, T., Inoue, M., Bah, J., Westberg, L., et al. (2009). Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *Int J Neuropsychopharmacol*, 1-10, (in press) PMID: 19500776.

Bouchard, T. J., Jr., & McGue, M. (2003). Genetic and environmental influences on human psychological differences. *Journal of Neurobiology, 54*, 4–45.

Brandi, M. L., Becherini, L., Gennari, L., Racchi, M., Bianchetti, A., Nacmias, B., et al. (1999). Association of the estrogen receptor alpha gene polymorphisms with sporadic Alzheimer's disease. *Biochemical and Biophysical Research Communications, 265*, 335–338.

Brosh, R. M., Jr., Opresko, P. L., & Bohr, V. A. (2006). Enzymatic mechanism of the WRN helicase/nuclease. *Methods in Enzymology, 409*, 52–85.

Broughton, S., & Partridge, L. (2009). Insulin/IGF-like signalling, the central nervous system and aging. *Biochemical Journal, 418*, 1–12.

Bueller, J. A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J. K. (2006). BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biological Psychiatry, 59*, 812–815.

Burdick, K. E., Lencz, T., Funke, B., Finn, C. T., Szeszko, P. R., Kane, J. M., et al. (2006). Genetic variation in DTNBP1 influences general cognitive ability. *Human Molecular Genetics, 15*, 1563–1568.

Butcher, L. M., Meaburn, E., Knight, J., Sham, P. C., Schalkwyk, L. C., Craig, I. W., et al. (2005). SNPs, microarrays and pooled DNA: identification of four loci associated with mild mental impairment in a sample of 6000 children. *Human Molecular Genetics, 14*, 1315–1325.

Butcher, L. M., Davis, O. S., Craig, I. W., & Plomin, R. (2008). Genome-wide quantitative trait locus association scan of general cognitive ability using pooled DNA and 500 K single nucleotide polymorphism microarrays. *Genes Brain and Behavior, 7*, 435–446.

Büther, K., Plaas, C., Barnekow, A., & Kremerskothen, J. (2004). KIBRA is a novel substrate for protein kinase Czeta. *Biochemical and Biophysical Research Communications, 317*, 703–707.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Caspi, A., Williams, B., Kim-Cohen, J., Craig, I. W., Milne, B. J., Poulton, R., et al. (2007). Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proceedings of the National Academy of Sciences of the United States of America, 104*, 18860–18865.

Chen, Z. Y., Patel, P. D., Sant, G., Meng, C. X., Teng, K. K., Hempstead, B. L., et al. (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *Journal of Neuroscience, 24*, 4401–4411.

Chorney, M. J., Chorney, K., Seese, N., Owen, M. J., Daniels, J., McGuffin, P., et al. (1998). A quantitative trait locus associated with cognitive ability in children. *Psychological Science, 9*, 159–166.

Comas-Herrera, A., Wittenberg, R., Pickard, L., & Knapp, M. (2007). Cognitive impairment in older people: future demand for long-term care services and the associated costs. *International Journal of Geriatric Psychiatry, 22*, 1037–1045.

Comings, D. E., Comings, B. G., Muhleman, D., Dietz, G., Shahbahrami, B., Tast, D., et al. (1991). The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *JAMA, 266*, 1793–1800.

Comings, D. E., Wu, S., Rostamkhani, M., McGue, M., Lacono, W. G., Cheng, L. S., et al. (2003). Role of the cholinergic muscarinic 2 receptor (CHRM2) gene in cognition. *Molecular Psychiatry, 8*, 10–11.

Cook, E. H., Jr., & Scherer, S. W. (2008). Copy-number variations associated with neuropsychiatric conditions. *Nature, 455*, 919–923.

Cope, N., Harold, D., Hill, G., Moskvina, V., Stevenson, J., Holmans, P., et al. (2005). Strong evidence that KIAA0319 on chromosome 6p is a susceptibility gene for developmental dyslexia. *American Journal of Human Genetics, 76*, 581–591.

Corneveaux, J. J., Liang, W. S., Reiman, E. M., Webster, J. A., Myers, A. J., Zismann, V. L., et al. (2009). Evidence for an association between KIBRA and late-onset Alzheimer's disease. *Neurobiol Aging*, (in press) PMID: 18789830.

Craig, I., & Plomin, R. (2006). Quantitative trait loci for IQ and other complex traits: single-nucleotide polymorphism genotyping using pooled DNA and microarrays. *Genes Brain Behav, 5*(Suppl 1), 32–37.

Crawford, D. C., Acuna, J. M., & Sherman, S. L. (2001). FMR1 and the fragile X syndrome: human genome epidemiology review. *Genetics in Medicine, 3*, 359–371.

Deary, I. J. (2001). Human intelligence differences: a recent history. *Trends in Cognitive Sciences, 5*, 127–130.

Deary, I. J., Hamilton, G., Hayward, C., Whalley, L. J., Powell, J., Starr, J. M., et al. (2005). Nicastrin gene polymorphisms, cognitive ability level and cognitive ageing. *Neuroscience Letters, 373*, 110–114.

Deary, I. J., Johnson, W., & Houlihan, L. M. (2009). Genetic foundations of human intelligence. *Hum Genet*, (in press) PMID: 19294424.

Dempster, E. L., Toulopoulou, T., McDonald, C., Bramon, E., Walshe, M., Wickham, H., et al. (2006). Episodic memory performance predicted by the 2 bp deletion in exon 6 of the "alpha 7-like" nicotinic receptor subunit gene. *American Journal of Psychiatry, 163*, 1832–1834.

Deshmukh, A., Rodrigue, K. M., Kennedy, K. M., Land, S., Jacobs, B. S., & Raz, N. (2009). Synergistic effects of the MTHFR C677T polymorphism and hypertension on spatial navigation. *Biological Psychology, 80*, 240–245.

de Blasi, S., Montesanto, A., Martino, C., Dato, S., De Rango, F., Bruni, A. C., et al. (2009). APOE polymorphism affects episodic memory among non demented elderly subjects. *Experimental Gerontology, 44*, 224–227.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2004). COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behavior Genetics, 34*, 533–539.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2005). Catechol O-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. *Journal of Cognitive Neuroscience, 17*, 1018–1025.

de Lau, L. M., van Meurs, J. B., Uitterlinden, A. G., Smith, A. D., Refsum, H., Johnston, C.,et al. (2009). Genetic variation in homocysteine metabolism, cognition, and white matter lesions. *Neurobiol Aging*, 2009, (in press) PMID: 19019492.

de Quervain, D. J., Henke, K., Aerni, A., Coluccia, D., Wollmer, M. A., Hock, C., et al. (2003). A functional genetic variation of the 5-HT2a receptor affects human memory. *Nature Neuroscience, 6*, 1141–1142.

de Rango, F., Leone, O., Dato, S., Novelletto, A., Bruni, A. C., Berardelli, M., et al. (2008). Cognitive functioning and survival in the elderly: the SSADH C538T polymorphism. *Annals of Human Genetics, 72*, 630–635.

Dick, D. M., Aliev, F., Kramer, J., Wang, J. C., Hinrichs, A., Bertelsen, S., et al. (2007). Association of CHRM2 with IQ: converging evidence for a gene influencing intelligence. *Behavior Genetics, 37*, 265–272.

Dickstein, D. L., Kabaso, D., Rocher, A. B., Luebke, J. I., Wearne, S. L., & Hof, P. R. (2007). Changes in the structural complexity of the aged brain. *Aging Cell, 6*, 275–284.

Dröge, W., & Schipper, H. M. (2007). Oxidative stress and aberrant signaling in aging and cognitive decline. *Aging Cell, 6*, 361–370.

Durga, J., van Boxtel, M. P., Schouten, E. G., Bots, M. L., Kok, F. J., & Verhoef, P. (2006). Folate and the methylenetetrahydrofolate reductase 677C−>T mutation correlate with cognitive performance. *Neurobiology of Aging, 27*, 334–343.

Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. *Vascular Health and Risk Management, 4*, 363–381.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*, 257–269.

Epstein, C. J., Martin, G. M., Schultz, A. L., & Motulsky, A. G. (1966). Werner's syndrome a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. *Medicine, 45*, 177–221.

Erickson, K. I., Kim, J. S., Suever, B. L., Voss, M. W., Francis, B. M., & Kramer, A. F. (2008). Genetic Contributions to Age-Related Decline in Executive Function: A 10-Year Longitudinal Study of COMT and BDNF Polymorphisms. *Frontiers in Human Neuroscience, 2*, 11.

Espeseth, T., Greenwood, P. M., Reinvang, I., Fjell, A. M., Walhovd, K. B., Westlye, L. T., et al. (2006). Interactive effects of APOE and CHRNA4 on attention and white matter volume in healthy middle-aged and older adults. *Cognitive Affective & Behavioral Neuroscience, 6*, 31–43.

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2005). The longitudinal relationship between processing speed and cognitive ability: genetic and environmental influences. *Behavior Genetics, 35*, 535–549.

Finkel, D., Reynolds, C. A., Berg, S., & Pedersen, N. L. (2006). Surprising lack of sex differences in normal cognitive aging in twins. *International Journal of Aging and Human Development, 62*, 335–357.

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2007). Age changes in processing speed as a leading indicator of cognitive aging. *Psychology and Aging, 22*, 558–568.

Finkel, D., Reynolds, C. A., McArdle, J. J., Hamagami, F., & Pedersen, N. L. (2009). Genetic Variance in Processing Speed Drives Variation in Aging of Spatial and Memory Abilities. *Developmental Psychology, 45*, 820–834.

Fisher, P. J., Turic, D., Williams, N. M., McGuffin, P., Asherson, P., Ball, D., et al. (1999). DNA pooling identifies QTLs on chromosome 4 for general cognitive ability in children. *Human Molecular Genetics, 8*, 915–922.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 313*, 1419–1420.

Francks, C., Paracchini, S., Smith, S. D., Richardson, A. J., Scerri, T. S., Cardon, L. R., et al. (2004). A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United Kingdom and from the United States. *Am J Hum Genet*, 75, 1046 –1058.

Frodl, T., Schule, C., Schmitt, G., Born, C., Baghai, T., Zill, P., et al. (2007). Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Archives of General Psychiatry, 64*, 410–416.

Froehlich, T. E., Lanphear, B. P., Dietrich, K. N., Cory-Slechta, D. A., Wang, N., & Kahn, R. S. (2007). Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. *Biological Psychiatry, 62*, 243–249.

Fuster, J. M. (2001). The prefrontal cortex - an update: Time is of the essence. *Neuron, 30*, 319–333.

Gelernter, J., Yu, Y., Weiss, R., Brady, K., Panhuysen, C., Yang, B. Z., et al. (2006). Haplotype spanning TTC12 and ANKK1, flanked by the DRD2 and NCAM1 loci, is strongly associated to nicotine dependence in two distinct American populations. *Human Molecular Genetics, 15*, 3498–3507.

Gibson, K. M. (2005). Gamma-hydroxybutyric aciduria: a biochemist's education from a heritable disorder of GABA metabolism. *Journal of Inherited Metabolic Disease, 28*, 247–265.

Glymour, M. M., Weuve, J., & Chen, J. T. (2008). Methodological challenges in causal research on racial and ethnic patterns of cognitive trajectories: measurement, selection, and bias. *Neuropsychology Review, 18*, 194–213.

Goldman-Rakic, P. S., Muly, E. C., & Williams, G. V. (2000). D(1) receptors in prefrontal cells and circuits. *Brain Research Brain Research Reviews, 31*, 295–301.

Gosso, M. F., van Belzen, M., de Geus, E. J., Polderman, J. C., Heutink, P., Boomsma, D. I., et al. (2006a). Association between the CHRM2 gene and intelligence in a sample of 304 Dutch families. *Genes Brain and Behavior, 5*, 577–584.

Gosso, M. F., de Geus, E. J., van Belzen, M. J., Polderman, T. J., Heutink, P., Boomsma, D. I., et al. (2006b). The SNAP-25 gene is associated with cognitive ability: evidence from a family-based study in two independent Dutch cohorts. *Molecular Psychiatry, 11*, 878–886.

Gosso, F. M., de Geus, E. J., Polderman, T. J., Boomsma, D. I., Posthuma, D., & Heutink, P. (2007). Exploring the functional role of the CHRM2 gene in human cognition: results from a dense genotyping and brain expression study. *BMC Medical Genetics, 8*, 66.

Gosso, M. F., de Geus, E. J., Polderman, T. J., Boomsma, D. I., Heutink, P., & Posthuma, D. (2008). Common variants underlying cognitive ability: further evidence for association between the SNAP-25 gene and cognition using a family-based study in two independent Dutch cohorts. *Genes Brain and Behavior, 7*, 355–364.

Göthert, M., Propping, P., Bönisch, H., Brüss, M., & Nöthen, M. M. (1998). Genetic variation in human 5-HT receptors: potential pathogenetic and pharmacological role. *Annals of the New York Academy of Sciences, 861*, 26–30.

Goto, M. (1997). Hierarchical deterioration of body systems in Werner's syndrome: implications for normal aging. *Mechanisms of Ageing and Development, 98*, 239–254.

Goto, M., Miller, R. W., Ishikawa, Y., & Sugano, H. (1996). Excess of rare cancers in Werner syndrome (adult progeria). *Cancer Epidemiology, Biomarkers and Prevention, 5*, 239–246.

Greenwood, P. M., Lin, M. K., Sundararajan, R., Fryxell, K. J., & Parasuraman, R. (2009). Synergistic effects of genetic variation in nicotinic and muscarinic receptors on visual attention but not working memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 3633–3638.

Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Archives of Internal Medicine, 163*, 1524–1528.

Hall, J., Whalley, H. C., Job, D. E., Baig, B. J., McIntosh, A. M., Evans, K. L., et al. (2006). A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. *Nature Neuroscience, 9*, 1477–1478.

Hansell, N. K., James, M. R., Duffy, D. L., Birley, A. J., Luciano, M., Geffen, G. M., et al. (2007). Effect of the BDNF V166M polymorphism on working memory in healthy adolescents. *Genes Brain and Behavior, 6*, 260–268.

Harman, D. (1956). Aging: a theory based on free radical and radiation chemistry. *Journal of Gerontology, 11*, 298–300.

Harris, S. E., Fox, H., Wright, A. F., Hayward, C., Starr, J. M., Whalley, L. J., et al. (2006). The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. *Molecular Psychiatry, 11*, 505–513.

Harris, S. E., Fox, H., Wright, A. F., Hayward, C., Starr, J. M., Whalley, L. J., et al. (2007). A genetic association analysis of cognitive ability and cognitive ageing using 325 markers for 109 genes associated with oxidative stress or cognition. *BMC Genetics, 8*, 43.

Hattersley, A. T., & McCarthy, M. I. (2005). What makes a good genetic association study? *Lancet, 366*, 1315–1323.

Hattiangady, B., Rao, M. S., Shetty, G. A., & Shetty, A. K. (2005). Brain-derived neurotrophic factor, phosphorylated cyclic AMP response element binding protein and neuropeptide Y decline as early as middle age in the dentate gyrus and CA1 and CA3 subfields of the hippocampus. *Experimental Neurology, 195*, 353–371.

Heiman, G. A., Hodge, S. E., Gorroochurn, P., Zhang, J., & Greenberg, D. A. (2004). Effect of population stratification on case-control association studies. I. Elevation in false positive rates and comparison to confounding risk ratios (a simulation study). *Human Heredity, 58*, 30–39.

Hill, L., Chorney, M. J., Lubinski, D., Thompson, L. A., & Plomin, R. (2002). A quantitative trait locus not associated with cognitive ability in children: a failure to replicate. *Psychological Science, 13*, 561–562.

Houlihan, L. M., Harris, S. E., Luciano, M., Gow, A. J., Starr, J. M., Visscher, P. M., et al. (2009). Replication study of candidate genes for cognitive abilities: the Lothian Birth Cohort 1936. *Genes Brain and Behavior, 8*, 238–247.

Hranilovic, D., Stefulj, J., Schwab, S., Borrmann-Hassenbach, M., Albus, M., Jernej, B., et al. (2004). Serotonin transporter promoter and intron 2 polymorphisms: relationship between allelic variants and gene expression. *Biological Psychiatry, 55*, 1090–1094.

Huang, W., Payne, T. J., Ma, J. Z., Beuten, J., Dupont, R. T., Inohara, N., et al. (2009a). Significant association of ANKK1 and detection of a functional polymorphism with nicotine dependence in an African-American sample. *Neuropsychopharmacology, 34*, 319–330.

Huang, L., Li, Y., Singleton, A. B., Hardy, J. A., Abecasis, G., Rosenberg, N. A., et al. (2009b). Genotype-imputation accuracy across worldwide human populations. *American Journal of Human Genetics, 84*, 235–250.

Huppert, F. A., Cabelli, S. T., & Matthews, F. E. (2005). MRC Cognitive Function and Ageing Study. Brief cognitive assessment in a UK population sample — distributional properties and the relationship between the MMSE and an extended mental state examination. *BMC Geriatric, 5*, 7.

Iizuka, Y., Sei, Y., Weinberger, D. R., & Straub, R. E. (2007). Evidence that the BLOC-1 protein dysbindin modulates dopamine D2 receptor internalization and signaling but not D1 internalization. *Journal Neuroscience, 27*, 12390–12395.

Irwing, P., & Lynn, R. (2005). Sex differences in means and variability on the progressive matrices in university students: a meta-analysis. *British Journal of Psychology, 96*, 505–524.

Irwing, P., & Lynn, R. (2006). Intelligence: is there a sex difference in IQ scores? *Nature, 442*, E1–E2.

Izumi, A., Iijima, Y., Noguchi, H., Numakawa, T., Okada, T., Hori, H., et al. (2008). Genetic variations of human neuropsin gene and psychiatric disorders: polymorphism screening and possible association with bipolar disorder and cognitive functions. *Neuropsychopharmacology, 33*, 3237–3245.

Johannsen, S., Duning, K., Pavenstädt, H., Kremerskothen, J., & Boeckers, T. M. (2008). Temporal-spatial expression and novel biochemical properties of the memory-related protein KIBRA. *Neuroscience, 155*, 1165–1173.

Johnson, W., Harris, S. E., Collins, P., Starr, J. M., Whalley, L. J., & Deary, I. J. (2007). No association of CETP genotype with cognitive function or age-related cognitive change. *Neuroscience Letters, 420*, 189–192.

Johnson, W., Harris, S. E., Starr, J. M., Whalley, L. J., & Deary, I. J. (2008). PPARG Pro12Ala genotype and risk of cognitive decline in elders? Maybe with diabetes. *Neuroscience Letters, 434*, 50–55.

Kaasinen, V., Vilkman, H., Hietala, J., Nagren, K., Helenius, H., Olsson, H., et al. (2000). Age-related D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiology of Aging, 21*, 683–688.

Kachiwala, S. J., Harris, S. E., Wright, A. F., Hayward, C., Starr, J. M., Whalley, L. J., et al. (2005). Genetic influences on oxidative stress and their association with normal cognitive ageing. *Neuroscience Letters, 386*, 116–120.

Kavvoura, F. K., & Ioannidis, J. P. (2008). Methods for meta-analysis in genetic association studies: a review of their potential and pitfalls. *Human Genetics, 123*, 1–14.

Kearney-Schwartz, A., Rossignol, P., Bracard, S., Felblinger, J., Fay, R., Boivin, J. M., et al. (2009). Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke, 40*, 1229–1236.

Kim, J. H., Ellwood, P. E., & Asher, M. I. (2009). Diet and asthma: looking back, moving forward. *Respiratory Research, 10*, 49.

Kirov, G., Grozeva, D., Norton, N., Ivanov, D., Mantripragada, K. K., Holmans, P., et al. (2009). Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. *Human Molecular Genetics, 18*, 1497–1503.

Kloppenborg, R. P., van den Berg, E., Kappelle, L. J., & Biessels, G. J. (2008). Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *European Journal of Pharmacology, 585*, 97–108.

Komulainen, P., Pedersen, M., Hänninen, T., Bruunsgaard, H., Lakka, T. A., Kivipelto, M., et al. (2008). BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA Study. *Neurobiology of Learning and Memory, 90*, 596–603.

Kudlow, B. A., Kennedy, B. K., & Monnat, R. J., Jr. (2007). Werner and Hutchinson-Gilford progeria syndromes: mechanistic basis of human progeroid diseases. *Nature Reviews Molecular Cell Biology, 8*, 394–404.

Kumar, R. A., & Christian, S. L. (2009). Genetics of autism spectrum disorders. *Current Neurology and Neuroscience Reports, 9*, 188–197.

Kuningas, M., Slagboom, P. E., Westendorp, R. G., & van Heemst, D. (2006). Impact of genetic variations in the WRN gene on age related pathologies and mortality. *Mechanisms of Ageing and Development, 127*, 307–313.

Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics, 6*, 243–250.

Lambert, J. C., Ferreira, S., Gussekloo, J., Christiansen, L., Brysbaert, G., Slagboom, E., et al. (2007). Evidence for the association of the S100beta gene with low cognitive performance and dementia in the elderly. *Molecular Psychiatry, 12*, 870–880.

Lin, B. K., Clyne, M., Walsh, M., Gomez, O., Yu, W., Gwinn, M., et al. (2006). Tracking the epidemiology of human genes in the literature: the HuGE Published Literature database. *American Journal of Epidemiology, 164*, 1–4.

Lind, P. A., Luciano, M., Horan, M., Marioni, R. E., Wright, M. J., Montgomery, G. W., et al. (2009). No association between cholinergic muscarinic receptor 2 (*CHRM2*) genetic variation and cognitive abilities in three independent samples. *Beh Genet*, (in press) PMID: 19418213.

Lindenberger, U., Nagel, I. E., Chicherio, C., Li, S. C., Heekeren, H. R., & Bäckman, L. (2008). Age-related decline in brain resources modulates genetic effects on cognitive functioning. *Frontiers in Neuroscience, 2*, 234–244.

Luciano, M., Lind, P. A., Duffy, D. L., Castles, A., Wright, M. J., Montgomery, G. W., et al. (2007). A haplotype spanning KIAA0319 and TTRAP is associated with normal variation in reading and spelling ability. *Biological Psychiatry, 62*, 811–817.

Luciano, M., Lind, P. A., Deary, I. J., Payton, A., Posthuma, D., Butcher, L. M., et al. (2008). Testing replication of a 5-SNP set for general cognitive ability in six population samples. *European Journal of Human Genetics, 16*, 1388–1395.

Luciano, M., Miyajima, F., Lind, P. A., Bates, T. C., Horan, M., Harris, S. E., et al. (2009a). Variation in the Dysbindin gene and normal cognitive function in three independent population samples. *Genes Brain and Behavior, 8*, 218–227.

Luciano, M., Gow, A. J., Taylor, M. D., Hayward, C., Harris, S. E., Campbell, H., et al. (2009b). Apolipoprotein E is not related to memory abilities at 70 years of age. *Behavior Genetics, 39*, 6–14.

Luo, Y., & Roth, G. S. (2000). The roles of dopamine oxidative stress and dopamine receptor signaling in aging and age-related neurodegeneration. *Antiox Redox Signal, 2*, 449–460.

Ma, S. Y., Ciliax, B. J., Stebbins, G., Jaffar, S., Joyce, J. N., Cochran, E. J., et al. (1999). Dopamine transporter-immunoreactive neurons decrease with age in the human substantia nigra. *Journal of Comparative Neurology, 409*, 25–37.

Marshall, F. H. (2008). The role of GABA(B) receptors in the regulation of excitatory neurotransmission. *Results and Problems in Cell Differentiation, 44*, 87–98.

Maruyama, H., Toji, H., Harrington, C. R., Sasaki, K., Izumi, Y., Ohnuma, T., et al. (2000). Lack of an association of estrogen receptor alpha gene polymorphisms and transcriptional activity with Alzheimer disease. *Archives of Neurology, 57*, 236–240.

Mattson, M. P., Chan, S. L., & Duan, W. (2002). Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. *Physiological Reviews, 82*, 637–672.

McAllister, T. W., Flashman, L. A., Harker-Rhodes, C., Tyler, A. L., Moore, J. H., Saykin, A. J., et al. (2008). Single nucleotide polymorphisms in ANKK1 and the dopamine D2 receptor gene affect cognitive outcome shortly after traumatic brain injury: a replication and extension study. *Brain Injury, 22*, 705–714.

McArdle, J. J., Prescott, C. A., Hamagami, F., & Horn, J. L. (1998). A contempory method for developmental-genetic analysis of age changes in intellectual abilities. *Developmental Neuropsychology, 14*, 69–114.

McGue, M., & Christensen, K. (2002). The heritability of level and rate-of-change in cognitive functioning in Danish twins aged 70 years and older. *Experimental Aging Research, 28*, 435–451.

MacKenzie, A., & Quinn, J. (1999). A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 15251–15255.

Meaburn, E. L., Harlaar, N., Craig, I. W., Schalkwyk, L. C., & Plomin, R. (2008). Quantitative trait locus association scan of early reading disability and ability using pooled DNA and 100 K SNP microarrays in a sample of 5760 children. *Molecular Psychiatry, 13*, 729–740.

Meneses, A. (1999). 5-HT system and cognition. *Neuroscience and Biobehavioral Reviews, 23*, 1111–1125.

Meyer-Lindenberg, A., Straub, R. E., Lipska, B. K., Verchinski, B. A., Goldberg, T., Callicott, J. H., et al. (2007). Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *Journal of Clinical Investigation, 117*, 672–682.

Miyajima, F., Ollier, W., Mayes, A., Jackson, A., Thacker, N., Rabbitt, P., et al. (2008a). Brain-derived neurotrophic factor polymorphism Val66Met influences cognitive abilities in the elderly. *Genes Brain Behav, 7*, 411–417.

Miyajima, F., Quinn, J. P., Horan, M., Pickles, A., Ollier, W. E., Pendleton, N., et al. (2008b). Additive effect of BDNF and REST polymorphisms is associated with improved general cognitive ability. *Genes Brain and Behavior, 7*, 714–719.

Moises, H. W., Frieboes, R. M., Spelzhaus, P., Yang, L., Köhnke, M., Herden-Kirchhoff, O., et al. (2001). No association between dopamine D2 receptor gene (DRD2) and human intelligence. *Journal of Neural Transmission, 108*, 115–121.

Morales, E., Sunyer, J., Castro-Giner, F., Estivill, X., Julvez, J., Ribas-Fitó, N., et al. (2008). Influence of glutathione S-transferase polymorphisms on cognitive functioning effects induced by p, p'-DDT among preschoolers. *Environmental Health Perspectives, 116*, 1581–1585.

Mori, E., Hirono, N., Yamashita, H., Imamura, T., Ikejiri, Y., Ikeda, M., et al. (1997). Premorbid brain size as a determinant of reserve capacity against intellectual decline in Alzheimer's disease. *American Journal of Psychiatry, 154*, 18–24.

Morrison, J. H., & Hof, P. R. (1997). Life and death of neurons in the aging brain. *Science, 278*, 412–419.

Nacmias, B., Bessi, V., Bagnoli, S., Tedde, A., Cellini, E., Piccini, C., et al. (2008). KIBRA gene variants are associated with episodic memory performance in subjective memory complaints. *Neuroscience Letters, 436*, 145–147.

Nagel, I. E., Chicherio, C., Li, S. C., von Oertzen, T., Sander, T., Villringer, A., et al. (2008). Human aging magnifies genetic effects on executive functioning and working memory. *Frontiers in Human Neuroscience, 2*, 1.

Need, A. C., Attix, D. K., McEvoy, J. M., Cirulli, E. T., Linney, K. N., Wagoner, A. P., et al. (2008). Failure to replicate effect of Kibra on human memory in two large cohorts of European origin. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*, 667–668.

Neubauer, A. C., Grabner, R. H., Fink, A., & Neuper, C. (2005). Intelligence and neural efficiency: further evidence of the influence of task content and sex on the brain-IQ relationship. *Brain Research Cognitive Brain Research, 25*, 217–225.

Neville, M. J., Johnstone, E. C., & Walton, R. T. (2004). Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation, 23*, 540–545.

Nicodemus, K. K., Luna, A., Vakkalanka, R., Goldberg, T., Egan, M., Straub, R. E., et al. (2006). Further evidence for association between ErbB4 and schizophrenia and influence on cognitive intermediate phenotypes in healthy controls. *Molecular Psychiatry, 11*, 1062–1065.

Okada, T., Hashimoto, R., Numakawa, T., Iijima, Y., Kosuga, A., Tatsumi, M., et al. (2006). A complex polymorphic region in the brain-derived neurotrophic factor (BDNF) gene confers susceptibility to bipolar disorder and affects transcriptional activity. *Molecular Psychiatry, 11*, 695–703.

Opgen-Rhein, C., Lencz, T., Burdick, K. E., Neuhaus, A. H., DeRosse, P., Goldberg, T. E., et al. (2008). Genetic variation in the DAOA gene complex: impact on susceptibility for schizophrenia and on cognitive performance. *Schizophrenia Research, 103*, 169–177.

Papassotiropoulos, A., Henke, K., Aerni, A., Coluccia, D., Garcia, E., Wollmer, M. A., et al. (2005). Age-dependent effects of the 5-hydroxytryptamine-2a-receptor polymorphism (His452Tyr) on human memory. *NeuroReport, 16*, 839–842.

Papassotiropoulos, A., Stephan, D. A., Huentelman, M. J., Hoerndli, F. J., Craig, D. W., Pearson, J. V., et al. (2006). Common Kibra alleles are associated with human memory performance. *Science, 314*, 475–478.

Parasuraman, R., Greenwood, P. M., Kumar, R., & Fossella, J. (2005). Beyond heritability: neurotransmitter genes differentially modulate visuospatial attention and working memory. *Psychological Science, 16*, 200–207.

Payton, A., Holland, F., Diggle, P., Rabbitt, P., Horan, M., Davidson, Y., et al. (2003). Cathepsin D exon 2 polymorphism associated with general intelligence in a healthy older population. *Molecular Psychiatry, 8*, 14–18.

Payton, A., Gibbons, L., Davidson, Y., Ollier, W., Rabbitt, P., Worthington, J., et al. (2005). Influence of serotonin transporter gene polymorphisms on cognitive decline and cognitive abilities in a non-demented elderly population. *Molecular Psychiatry, 10*, 1133–1139.

Payton, A., Horan, M., Davidson, Y., Gibbons, L., Ollier, W., Rabbitt, P., et al. (2006). Influence and interactions of cathepsin D, HLA-DRB1 and APOE on cognitive abilities in an older non-demented population. *Genes Brain and Behavior, 5*, 23–31.

Peper, J. S., Brouwer, R. M., Boomsma, D. I., Kahn, R. S., & Hulshoff, H. E. (2007). Genetic influences on human brain structure: a review of brain imaging studies in twins. *Human Brain Mapping, 28*, 464–473.

Peters, K., Wiltshire, S., Henders, A. K., Dragović, M., Badcock, J. C., Chandler, D., et al. (2008). Comprehensive analysis of tagging sequence variants in DTNBP1 shows no association with schizophrenia or with its composite neurocognitive endophenotypes. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics , 147B*, 1159–1166.

Petrill, S. A., Plomin, R., McClearn, G. E., Smith, D. L., Vignetti, S., Chorney, M. J., et al. (1997). No association between general cognitive ability and the A1 allele of the D2 dopamine receptor gene. *Behavior Genetics, 27*, 29–31.

Petryshen, T. L., Kaplan, B. J., Liu, M. F., & Field, L. L. (2000). Absence of significant linkage between phonological coding dyslexia and chromosome 6p23-21.3, as determined by use of quantitative-trait methods: confirmation of qualitative analyses. *American Journal of Human Genetics, 66*, 708–714.

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., et al. (2004). The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *Journal of Neuroscience, 24*, 10099–10102.

Pfefferbaum, A., Sullivan, E. V., Swan, G. E., & Carmelli, D. (2000). Brain structure in men remains highly heritable in the seventh and eighth decades of life. *Neurobiology of Aging, 21*, 63–74.

Pierce, G. L., Lesniewski, L. A., Lawson, B. R., Beske, S. D., & Seals, D. R. (2009). Nuclear factor-{kappa}B activation contributes to vascular endothelial dysfunction via oxidative stress in overweight/obese middle-aged and older humans. *Circulation, 119*, 1284–1292.

Pietiläinen, O. P., Paunio, T., Loukola, A., Tuulio-Henriksson, A., Kieseppä, T., Thompson, P., et al. (2009). Association of AKT1 with verbal learning, verbal memory, and regional cortical gray matter density in twins. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B*, 683–692.

Platko, J. V., Wood, F. B., Pelser, I., Meyer, M., Gericke, G. S., O'Rourke, J., et al. (2008). Association of reading disability on chromosome 6p22 in the Afrikaner population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*, 1278–1287.

Plomin, R. (2003). Genetics, genes, genomics and g. *Molecular Psychiatry, 8*, 1–5.

Plomin, R., Turic, D. M., Hill, L., Turic, D. E., Stephens, M., Williams, J., et al. (2004). A functional polymorphism in the succinate-semialdehyde dehydrogenase (aldehyde dehydrogenase 5 family, member A1) gene is associated with cognitive ability. *Molecular Psychiatry, 9*, 582–586.

Poo, M. M. (2001). Neurotrophins as synaptic modulators. *Nature Reviews Neuroscience, 2*, 24–32.

Posthuma, D., Baaré, W. F., Hulshoff Pol, H. E., Kahn, R. S., Boomsma, D. I., & De Geus, E. J. (2003). Genetic correlations between brain volumes and the WAIS-III dimensions of verbal comprehension, working memory, perceptual organization, and processing speed. *Twin Research, 6*, 131–139.

Pruunsild, P., Kazantseva, A., Aid, T., Palm, K., & Timmusk, T. (2007). Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics, 90*, 397–406.

Qi, L., & Cho, Y. A. (2008). Gene-environment interaction and obesity. *Nutrition Reviews, 66*, 684–694.

Rabbitt, P., & Lowe, C. (2000). Patterns of cognitive ageing. *Psychological Research, 63*, 308–316.

Rabbitt, P., Diggle, P., Holland, F., & McInnes, L. (2004a). Practice and drop-out effects during a 17-year longitudinal study of cognitive aging. *Journal of Gerontology B Psychological Sciences Social Sciences, 59*, 84–97.

Rabbitt, P. M. A., Diggle, P., Holland, F., McInnes, L., Bent, N., Abson, V., et al. (2004b). The University of Manchester longitudinal study of cognition in normal healthy old age, 1983 through 2003. *Aging, Neuropsychology and Cognition, 11*, 245–279.

Ravaglia, G., Forti, P., Maioli, F., Scali, R. C., Arnone, G., Talerico, T., et al. (2004). Common polymorphisms in methylenetetrahydrofolate reductase (MTHFR): relationships with plasma homocysteine concentrations and cognitive status in elderly northern italian subjects. *Archives Gerontology and Geriatrics Supplement, 9*, 339–348.

Raz, N., Dahle, C. L., Rodrigue, K. M., Kennedy, K. M., Land, S. J., & Jacobs, B. S. (2008). Brain-derived neurotrophic factor Val66Met and blood glucose: a synergistic effect on memory. *Frontiers in Human Neuroscience, 2*, 12.

Raz, N., Rodrigue, K. M., Kennedy, K. M., & Land, S. (2009). Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. *Neuropsychology, 23*, 105–116.

Reeves, S., Bench, C., & Howard, R. (2002). Aging and the nigrostriatal dopamine system. *International Journal of Geriatric Psychiatry, 17*, 359–370.

Rehman, H. U., & Masson, E. A. (2001). Neuroendocrinology of ageing. *Age and Ageing, 30*, 279–287.

Reynolds, C. A., Finkel, D., Gatz, M., & Pedersen, N. L. (2002). Sources of influence on rate of cognitive change over time in Swedish twins: an application of latent growth models. *Experimental Aging Research, 28*, 407–433.

Reynolds, C. A., Jansson, M., Gatz, M., & Pedersen, N. L. (2006). Longitudinal change in memory performance associated with HTR2A polymorphism. *Neurobiology of Aging, 27*, 150–154.

Ridley, M. (2003). *Nature via nurture*. New York: Harper Collins.

Rinne, J. O., Lonnberg, P., & Marjamaki, P. (1990). Age-dependent decline of dopamine-D1 and dopamine-D2 receptor. *Brain Research, 508*, 349–352.

Rodgers, J. T., Lerin, C., Haas, W., Cygi, S. P., Spiegelman, B. M., & Puigserver, P. (2005). Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1. *Nature, 434*, 113–118.

Rodriguez-Murillo, L., & Greenberg, D. A. (2008). Genetic association analysis: a primer on how it works, its strengths and its weaknesses. *International Journal of Andrology, 31*, 546–556.

Rodríguez-Rodríguez, E., Infante, J., Llorca, J., Mateo, I., Sánchez-Quintana, C., García-Gorostiaga, I., et al. (2009). Age-dependent association of KIBRA genetic variation and Alzheimer's disease risk. *Neurobiology of Aging, 30*, 322–324.

Ropers, H. H., & Hamel, B. C. (2005). X-linked mental retardation. *Nature Reviews Genetics, 6*, 46–57.

Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry, 65*, 760–769.

Rujescu, D., Hartmann, A. M., Gonnermann, C., Möller, H. J., & Giegling, I. (2003). M129V variation in the prion protein may influence cognitive performance. *Molecular Psychiatry, 8*, 937–941.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*, 403–428.

Sanderson, T. H., Kumar, R., Sullivan, J. M., & Krause, G. S. (2008). Insulin blocks cytochrome c release in the reperfused brain through PI3-K signaling and by promoting Bax/Bcl-XL binding. *Journal of Neurochemistry, 106*, 1248–1258.

Sarter, M., & Bruno, J. P. (2004). Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities. *Neurobiology of Aging, 25*, 1127–1139.

Savitz, J., Solms, M., & Ramesar, R. (2006). Apolipoprotein E variants and cognition in healthy individuals: a critical opinion. *Brain Research Reviews, 51*, 125–135.

Schaper, K., Kolsch, H., Popp, J., Wagner, M., & Jessen, F. (2008). KIBRA gene variants are associated with episodic memory in healthy elderly. *Neurobiology of Aging, 29*, 1123–1125.

Seshadri, S., DeStefano, A. L., Au, R., Massaro, J. M., Beiser, A. S., Kelly-Hayes, M., et al. (2007). Genetic correlates of brain aging on MRI and cognitive test measures: a genome-wide association and linkage analysis in the Framingham Study. *BMC Medical Genetics, 8*, S15.

Sgaravatti, A. M., Sgarbi, M. B., Testa, C. G., Durigon, K., Pederzolli, C. D., Prestes, C. C., et al. (2007). Gamma-hydroxybutyric acid induces oxidative stress in cerebral cortex of young rats. *Neurochemistry International, 50*, 564–570.

Shenkin, S. D., Rivers, C. S., Deary, I. J., Starr, J. M., & Wardlaw, J. M. (2009). Maximum (prior) brain size, not atrophy, correlates with cognition in community-dwelling older people: a cross-sectional neuroimaging study. *BMC Geriatric, 9*, 12.

Shepherd, C. E., Piguet, O., Broe, G. A., Creasey, H., Waite, L. M., Brooks, W. S., et al. (2004). Histocompatibility antigens, aspirin use and cognitive performance in non-demented elderly subjects. *Journal of Neuroimmunology, 148*, 178–182.

Shimokata, H., Ando, F., Niino, N., Miyasaka, K., & Funakoshi, A. (2005). Cholecystokinin A receptor gene promoter polymorphism and intelligence. *Annals of Epidemiology, 15*, 196–201.

Sild, M., Koca, C., Bendixen, M. H., Frederiksen, H., McGue, M., Kølvraa, S., et al. (2006). Possible associations between successful aging and polymorphic markers in the Werner gene region. *Annals of the New York Academy of Sciences, 1067*, 309–310.

Spearman, C. (1904). 'General Intelligence' objectively determined and measured. *American Journal of Psychology, 15*, 201–293.

Starr, J. M., Fox, H., Harris, S. E., Deary, I. J., & Whalley, L. J. (2007). COMT genotype and cognitive ability: a longitudinal aging study. *Neuroscience Letters, 421*, 57–61.

Stefanis, N. C., Trikalinos, T. A., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Ntzani, E. E., et al. (2007). Impact of schizophrenia candidate genes on schizotypy and cognitive endophenotypes at the population level. *Biological Psychiatry, 62*, 784–792.

Sullivan, E. V., Pfefferbaum, A., Swan, G. E., & Carmelli, D. (2001). Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. *Hippocampus, 11*, 754–762.

Tan, H. Y., Nicodemus, K. K., Chen, Q., Li, Z., Brooke, J. K., Honea, R., et al. (2008). Genetic variation in AKT1 is linked to dopamine-associated prefrontal cortical structure and function in humans. *Journal of Clinical Investigation, 118*, 2200–2208.

Tannenbaum, C., Mayo, N., & Ducharme, F. (2005). Older women's health priorities and perceptions of care delivery: results of the WOW health survey. *Canadian Medical Association Journal, 173*, 153–159.

Thompson, R. F., & Kim, J. J. (1996). Memory systems in the brain and localization of a memory. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 13438–13444.

Thomson, P. A., Harris, S. E., Starr, J. M., Whalley, L. J., Porteous, D. J., & Deary, I. J. (2005). Association between genotype at an exonic SNP in DISC1 and normal cognitive aging. *Neuroscience Letters, 389*, 41–45.

Thorgeirsson, T. E., Geller, F., Sulem, P., Rafnar, T., Wiste, A., Magnusson, K. P., et al. (2008). A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature, 452*, 638–642.

Togsverd, M., Werge, T. M., Tankó, L. B., Bagger, Y. Z., Qin, G. G., Hansen, T., et al. (2007). Cognitive performance in elderly women: significance of the 19 bp insertion/deletion polymorphism in the 5' flank of the dopamine beta-hydroxylase gene, educational level, body fat measures, serum triglyceride, alcohol consumption and age. *International Journal of Geriatric Psychiatry, 22*, 883–889.

Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: a comprehensive review. *Journal of the American Geriatrics Society, 40*, 922–935.

Tsai, S. J., Yu, Y. W., Lin, C. H., Chen, T. J., Chen, S. P., & Hong, C. J. (2002). Dopamine D2 receptor and N-methyl-D-aspartate receptor 2B subunit genetic variants and intelligence. *Neuropsychobiology, 45*, 128–130.

Tsai, S. J., Gau, Y. T., Liu, M. E., Hsieh, C. H., Liou, Y. J., & Hong, C. J. (2008). Association study of brain-derived neurotrophic factor and apolipoprotein E polymorphisms and cognitive function in aged males without dementia. *Neuroscience Letters, 433*, 158–162.

van den Berg, E., Kloppenborg, R. P., Kessels, R. P., Kappelle, L. J., & Biessels, G. J. (2009). Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochimica et Biophysica Acta, 1792*, 470–481.

van Kesteren, R. E., & Spencer, G. E. (2003). The role of neurotransmitters in neurite outgrowth and synapse formation. *Reviews in the Neurosciences, 14*, 217–231.

Versijpt, J., Van Laere, K. J., Dumont, F., Decoo, D., Vandecapelle, M., Santens, P., et al. (2003). Imaging of the 5-HT2A system: age-, gender-, and Alzheimer's disease-related findings. *Neurobiology of Aging, 24*, 553–561.

Visscher, P. M., Tynan, M., Whiteman, M. C., Pattie, A., White, I., Hayward, C., et al. (2003). Lack of association between polymorphisms in angiotensin-converting-enzyme and methylenetetrahydrofolate reductase genes and normal cognitive ageing in humans. *Neuroscience Letters, 347*, 175–178.

Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., et al. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *American Journal of Psychiatry, 155*, 344–349.

Wacholder, S., Rothman, N., & Caporaso, N. (2002). Counterpoint: bias from population stratification is not a major threat to the validity of conclusions from epidemiological studies of common polymorphisms and cancer. *Cancer Epidemiology Biomarkers Prevention, 11*, 513–520.

Wang, H., Yuan, G., Prabhakar, N. R., Boswell, M., & Katz, D. M. (2006). Secretion of brain-derived neurotrophic factor from PC12 cells in response to oxidative stress requires autocrine dopamine signaling. *Journal of Neurochemistry, 96*, 694–705.

Wang, F. T., Hu, H., Schwartz, J., Weuve, J., Spiro, A. S., Sparrow, D., et al. (2007). Modifying effects of the HFE polymorphisms on the association between lead burden and cognitive decline. *Environmental Health Perspectives, 115*, 1210–1215.

Webster, M. J., Weickert, C. S., Herman, M., & Kleinman, J. E. (2002). BDNF mRNA expression during postnatal development, maturation and aging of the human prefrontal cortex. *Developmental Brain Research, 139*, 139–150.

West, M. J., Coleman, P. D., Flood, D. G., & Troncoso, J. C. (1994). Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet, 344*, 769–772.

Whitmer, R. A., Gunderson, E. P., Quesenberry, C. P., Jr., Zhou, J., & Yaffe, K. (2007). Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Current Alzheimer Research, 4*, 103–109.

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2009). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiol Aging*, (in press) PMID: 19285755.

Yaffe, K., Kanaya, A. M., Lindquist, K., Hsueh, W. C., Cummings, S. R., Beamer, B., et al. (2008). Health ABC Study. PPAR-gamma Pro12Ala genotype and risk of cognitive decline in elders. *Neurobiology of Aging, 29*(1), 78–83.

Yaffe, K., Lindquist, K., Sen, S., Cauley, J., Ferrell, R., Penninx, B., et al. (2009). Estrogen receptor genotype and risk of cognitive impairment in elders: Findings from the Health ABC study. *Neurobiology of Aging, 30*, 607–614.

Yang, B. Z., Kranzler, H. R., Zhao, H., Gruen, J. R., Luo, X., & Gelernter, J. (2008). Haplotypic variants in DRD2, ANKK1, TTC12, and NCAM1 are associated with comorbid alcohol and drug dependence. *Alcoholism, Clinical and Experimental Research, 32*, 2117–2127.

Yu, Y. W., Tsai, S. J., Hong, C. J., Chen, M. C., Yang, C. W., & Chen, T. J. (2005). Association study of a functional MAOA-uVNTR gene polymorphism and cognitive function in healthy females. *Neuropsychobiology, 52*, 77–82.

Zinkstok, J. R., de Wilde, O., van Amelsvoort, T. A., Tanck, M. W., Baas, F., & Linszen, D. H. (2007). Association between the DTNBP1 gene and intelligence: a case-control study in young patients with schizophrenia and related disorders and unaffected siblings. *Behavioral and Brain Functions, 3*, 19.