

Aging-related magnification of genetic effects on cognitive and brain integrity

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Heritability studies document substantial genetic influences on cognitive performance and decline in old age. Increasing evidence shows that effects of genetic variations on cognition, brain structure, and brain function become stronger as people age. Disproportionate impairments are typically observed for older individuals carrying disadvantageous genotypes of different candidate genes. These data support the resource-modulation hypothesis, which states that genetic effects are magnified in persons with constrained neural resources, such as older adults. However, given that findings are not unequivocal, we discuss the need to address several factors that may resolve inconsistencies in the extant literature (gene–gene and gene–environment interactions, study populations, gene–environment correlations, and epigenetic mechanisms).

Inter-individual differences in cognitive and brain aging

Human aging is characterized by large and increased inter-individual differences in different aspects of cognitive performance, brain structure, and brain function [1–3]. Whereas some older individuals may have cognitive abilities that match those of younger individuals, older persons of the same age may show rapid decline in cognitive and brain integrity [3,4]. Conceivably, multiple factors contribute to individual differences at neural and behavioral levels, including genetic predispositions and lifestyle factors. In recent years evidence has accumulated that the effects of common genetic variations may increase in aging, contributing to inter-individual neural and cognitive differences among older adults.

Heritability estimates of cognitive and brain measures in old age

Heritability studies demonstrate increased genetic influences on different types of cognition in aging [5–7], and also regarding the rate of cognitive decline [8]. Meta-analytic evidence suggests increased heritability from early to late adulthood, especially for episodic memory (see [Glossary](#)), but also for working memory and spatial ability [6]. In addition, it has been shown that one-third of individual

differences in global cognitive changes from 65 to 96 years of age are attributable to genetic factors [8]. Concerning brain measures, available aging data are sparse, although studies generally suggest decreasing heritability estimates across the adult lifespan, followed by increases in late adulthood for global brain volumes [9]. Genetic estimates of ventricular volume, an indirect measure of brain volume, have also revealed increasing heritability in old age [10].

Glossary

Allele: different forms of a gene are termed alleles.

Candidate gene: a gene whose function has been implicated in a particular phenotype of interest, such as brain and cognitive function.

Cognitive dedifferentiation: aging-related increase in correlations between different cognitive domains. A common mechanism or an ensemble of common mechanisms may lead to decline in different cognitive processes, and consequently to a higher degree of dedifferentiation across domains of functioning.

Diffusion tensor imaging (DTI): neuroimaging technique sensitive to the diffusion of water molecules within the architecture of the tissue. It allows the assessment of degree of anisotropy and structural orientation that characterize diffusion tensor imaging. Fractional anisotropy (FA) indicates directionality of diffusion, and mean diffusivity (MD) indicates diffusion, independent of directionality. Higher white-matter integrity is associated with higher FA and lower MD.

Epigenetics: study of how external or environmental factors influence gene expression, for instance through changes in DNA methylation.

Episodic memory: ability to recall specific past events that are localized in time and space.

Executive functioning: complex cognitive process, including different sub-processes such as inhibition of a response, updating of working-memory representations, and ability to flexibly shift between different tasks or cognitive operations.

Functional magnetic resonance imaging (fMRI): neuroimaging method that allows measurement of neural activity by detecting associated changes in blood flow and changes in deoxyhemoglobin levels, which are reflected in the blood-oxygen-level-dependent (BOLD) signal.

Genome-wide association study (GWAS): examination of multiple common genetic variants across the entire genome for their association with a particular trait.

Genotype: the identity of the two alleles at a specific genetic locus.

Global cognitive ability: broad intellectual ability that mainly represents reasoning, but also other cognitive domains, including memory, processing speed, and verbal comprehension.

Heterozygote: a carrier of two different alleles at a specific genetic locus.

Homozygote: a carrier of two identical alleles at a specific genetic locus.

Mild cognitive impairment (MCI): individuals with MCI are characterized by more severe cognitive decline than would be expected in normal aging and are at an increased risk of developing dementia.

Prodromal dementia/Alzheimer disease (AD): stage of dementia or AD before a clinical diagnosis may be rendered that is characterized by mild symptoms typical for the disease.

Single-nucleotide polymorphism (SNP): a variation at a single position in a deoxyribonucleic acid (DNA) sequence.

Working memory: ability to consciously maintain and manipulate information in mind.

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Although effects of common genetic variations are small (<1% of explained variance), overall they still account for a considerable amount of phenotypic variance. Heritability estimates based on single-nucleotide polymorphisms (SNPs) for cognitive measures range between 31% and 51%, indicating substantial heritability for behavioral measures [11,12].

SNP-based heritability is typically lower than heritability estimates based on twin studies [6], the latter reflecting both general effects of specific genes and gene–gene interactions. By contrast, estimations based on SNPs alone do not capture gene–gene interactions, likely resulting in this discrepancy. Interestingly, heritability for cognition seems to decrease once individuals reach dementia or terminal decline. Genetic contributions to different forms of memory are smaller in samples of individuals with Alzheimer's disease (AD) and their unaffected family members than for unaffected family members alone [13], suggesting that genes account less for individual differences in AD patients.

The resource-modulation hypothesis

The resource-modulation hypothesis, introduced by Lindenberger and colleagues, posits that losses of anatomical and neurochemical brain resources in normal aging modulate the effects of common genetic variations on cognitive functioning [14]. This notion is based on the assumption that the function relating brain resources to cognition is non-linear, and that genetic differences therefore exert increasingly larger effects on performance as resources recede from high to medium levels (Figure 1). Given that neural measures of brain structure and function may be closer to the molecular effects of a gene than cognitive measures, they are expected to be more sensitive to genetic effects [15]. Thus, older adults may benefit more from beneficial genetic predispositions relative to younger adults, and thereby be able to maintain brain and cognitive functioning in senescence.

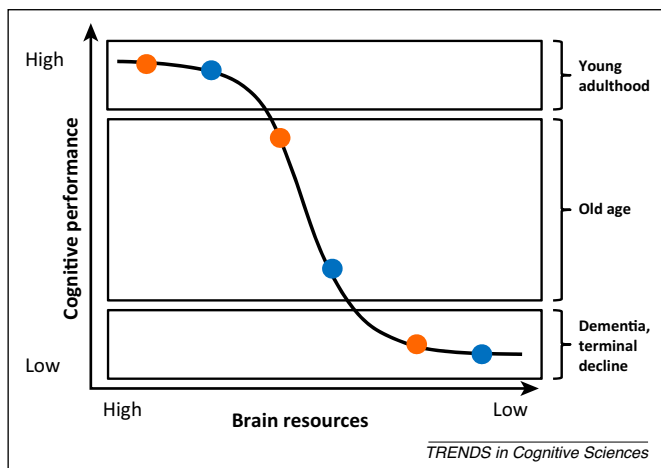


Figure 1. The resource-modulation hypothesis assumes that the function relating brain resources to cognition is non-linear and predicts magnified genetic effects on cognitive performance in old age. In healthy aging, associated with decline in anatomical and chemical brain resources, constant amounts of genetic variation translate into increasingly large performance differences. With resources further depleted, genetic effects are expected to diminish. The colored circles represent two hypothetical individuals with different genetic predispositions as they move from early adulthood through old age to dementia or terminal decline. Adapted from [14] with permission from Frontiers Research Foundation.

Support for aging-related magnification of genetic effects on brain and behavior

Increasing evidence from behavioral, structural, and functional imaging studies supports the resource-modulation hypothesis. The bulk of studies suggest that effects of genetic variations are either small or not detectable in younger adults, but become magnified in old age, with older carriers of disadvantageous genotypes declining disproportionately with respect to brain and cognition. We next review these effects with examples involving different candidate genes.

Apolipoprotein E (APOE) polymorphism

APOE is a lipoprotein involved in many steps of lipid homeostasis and injury repair in the brain [16]. The e4 allele of APOE is a strong risk factor for AD [17,18], and is associated with accelerated cognitive decline in normal aging [19,20]. A meta-analysis showed that e4 carriers have lower performance on several cognitive measures [21]. Crucially, APOE-related effects were more pronounced in older than younger individuals with respect to global cognitive ability and episodic memory. In line with this pattern, longitudinal studies have documented interactions between age and APOE, with increasing negative effects of e4 in persons older than 50 years on learning and episodic memory (Figure 2) [22]. In another study, e4 carriers showed exacerbated decline in verbal memory and reasoning between 79 and 87 years of age [23]. So far, most genome-wide association studies (GWAS) with healthy adults have not used cognitive decline as the outcome or stratified the data across age groups. However, two GWAS demonstrated effects of APOE on rate of cognitive decline [24,25], thus supporting the magnification view.

Stronger effects of APOE in old age are also seen at the neural level. An fMRI study reported an interaction between age and APOE status during encoding of episodic memories, with e4 carriers showing decreased activation in multiple brain regions including the hippocampus, an area crucial for successful episodic memory [26]. Notably, these findings were independent of individual differences in

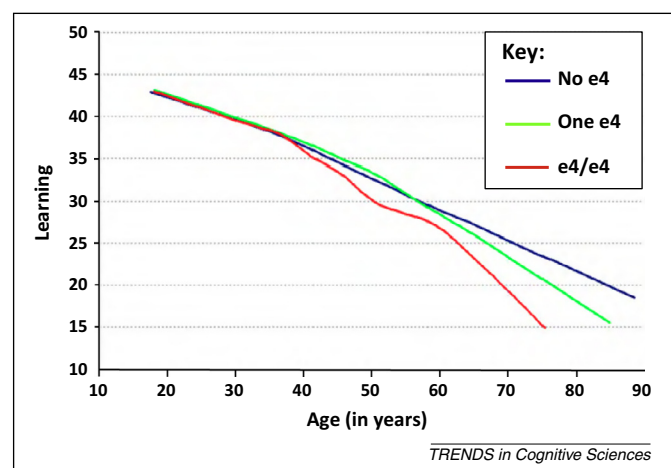


Figure 2. Effects of the apolipoprotein E (APOE) polymorphism on learning, with increased negative dose–response effects of the e4 allele across adult age. Learning reflects the number of correctly recalled words in the Rey Auditory Verbal Learning Test. Adapted from [22] with permission from Elsevier.

gray-matter volumes. However, data from another lifespan fMRI study suggested an opposite pattern for hippocampal activation in older adults [27]. In this study there was decreased hippocampal activity during encoding and retrieval of neutral pictures with increasing age, and these decreases were weaker for e4 carriers than for non-carriers. These two studies provide evidence in line with the resource-modulation hypothesis, although they document opposing genetic effects on neural functioning in old age. One source of variation that may account for this discrepancy between studies is task difficulty. Older adults at higher risk for cognitive decline typically show more brain activity during relatively simple tasks than individuals at lower risk. However, during more difficult tasks, the pattern may be reversed [28]. In line with this notion, participants were instructed to remember images in the study where older e4 carriers had lower brain activity at encoding [26]. This task is clearly more cognitively challenging than judging the contents of images during study, a task for which greater brain activity in older e4 carriers was observed [27]. Concerning structural brain-imaging markers, longitudinal studies demonstrate more hippocampal atrophy for e4 carriers [29,30] that may contribute to the effects of *APOE* on functional brain activity. Consistent with the assumption that genetic effects diminish once individuals reach very low cognitive-performance levels (Figure 1), evidence indicates that *APOE* does not affect progression rate in clinical AD [31], or even the rate of decline from preclinical to clinical dementia [32].

Brain-derived neurotrophic factor (*BDNF*) polymorphism
BDNF promotes synaptic plasticity and is crucial for hippocampus-dependent learning and memory [33]. Variation in the *BDNF* gene is associated with individual differences in secretion of this protein, which is greater in Val homozygotes than in Met carriers [34]. Meta-analytic evidence confirms negative, albeit small, effects of the *BDNF* Met allele on human episodic memory [35]. Importantly, age-comparative studies have reported magnified effects of *BDNF* in old age, with older Val homozygotes showing better episodic memory compared with older Met carriers [36]. In addition, in line with the resource-modulation hypothesis, longitudinal data from a sample of older adults aged 70 to 103 years demonstrate exacerbated decline in perceptual speed across 13 years for Met carriers [37], an effect that remained after excluding prodromal dementia cases (Figure 3A). Similarly, pilots carrying the Met allele (aged 40–69 years) declined disproportionately across 2 years in flight-simulator performance, presumably reflecting executive functioning [38]. At the neural level, *BDNF* Met carriers exhibited lower hippocampal activity during encoding and retrieval of episodic memories [35]. A study with persons across the entire adult lifespan documented larger decreases in hippocampal activity with advancing age for Met carriers than for Val homozygotes during both encoding and retrieval of episodic memories (Figure 3B) [39], which was independent of inter-individual differences in hippocampal volume. Age magnification of the effects of *BDNF* has also been reported for other measures of brain integrity, emphasizing the role of *BDNF* in modulating myelin expression [40] and survival of neurons in the adult brain [41]. Specifically, Met carriers

had lower hippocampal volumes than Val homozygotes after age 65, whereas no such differences were apparent at younger ages (Figure 3C) [38]. Crucially, age was unrelated to hippocampal volume in Val homozygotes, supporting the idea that brain maintenance in old age may partly reflect genetic factors [4]. Another study with individuals in the prodromal phase of AD reported that the Met allele was associated with increased memory decline across 3 years, paralleled by more hippocampal atrophy [42]. Similarly, age-related decline in white-matter microstructure, as measured with diffusion tensor imaging, was found for Met carriers, although no such decline was evident for Val homozygotes (Figure 3D) [43].

Taken together, accumulating evidence suggests increased effects of *BDNF* on brain and cognition in aging, with greater decline in performance for older Met carriers.

Catechol-O-methyltransferase (*COMT*) polymorphism
COMT is involved in extracellular degradation of dopamine (DA) in prefrontal cortex (PFC) [44,45]. DA concentrations modulate neuronal signal-to-noise ratio in the PFC that is crucial for efficient cognitive processing [46]. *COMT* Val homozygotes have 3–4-fold higher DA-degrading activity than Met homozygotes [47], resulting in lower prefrontal DA availability and presumably less efficient cognitive processing. Cross-sectional studies demonstrate faster response times [48] and higher accuracy during working memory [49] for older Met homozygotes than for Val carriers, whereas no difference was found between genotype groups among younger individuals. Another study found that older *COMT* Val homozygotes had a strong correlation between episodic and working memory, indicating cognitive dedifferentiation. By contrast, older Met carriers and younger *COMT* genotype groups had identical and considerably weaker correlations between the two types of memory [50]. Most importantly, longitudinal data reveal less decline of executive functions over a 5-year interval [51], and less decline of episodic memory across 15 years [52], for older Met carriers than for Val homozygotes. Results from an fMRI study further suggest that older Val homozygotes are characterized by less efficient processing during a working memory task with low demands, as indicated by increased communication between distal brain regions, compared with Met homozygotes, potentially reflecting a compensatory response [53]. Again, these group differences were not present in younger adults. Relatedly, a structural imaging study in a population-based sample found that *COMT* Val status was associated with reduced white-matter integrity in several prefrontal white-matter tracts in old age, although there were no reliable associations between *COMT* and white-matter integrity in younger age groups [54].

Kidney and brain expressed protein (*KIBRA*) polymorphism

Genetic variation in the *KIBRA* gene has been associated with episodic memory, with T-allele carriers exhibiting better performance than C-allele homozygotes [55]. In the human brain, *KIBRA* is mainly expressed in hippocampus and interacts with proteins involved in long-term potentiation, a cellular mechanism necessary for successful memory

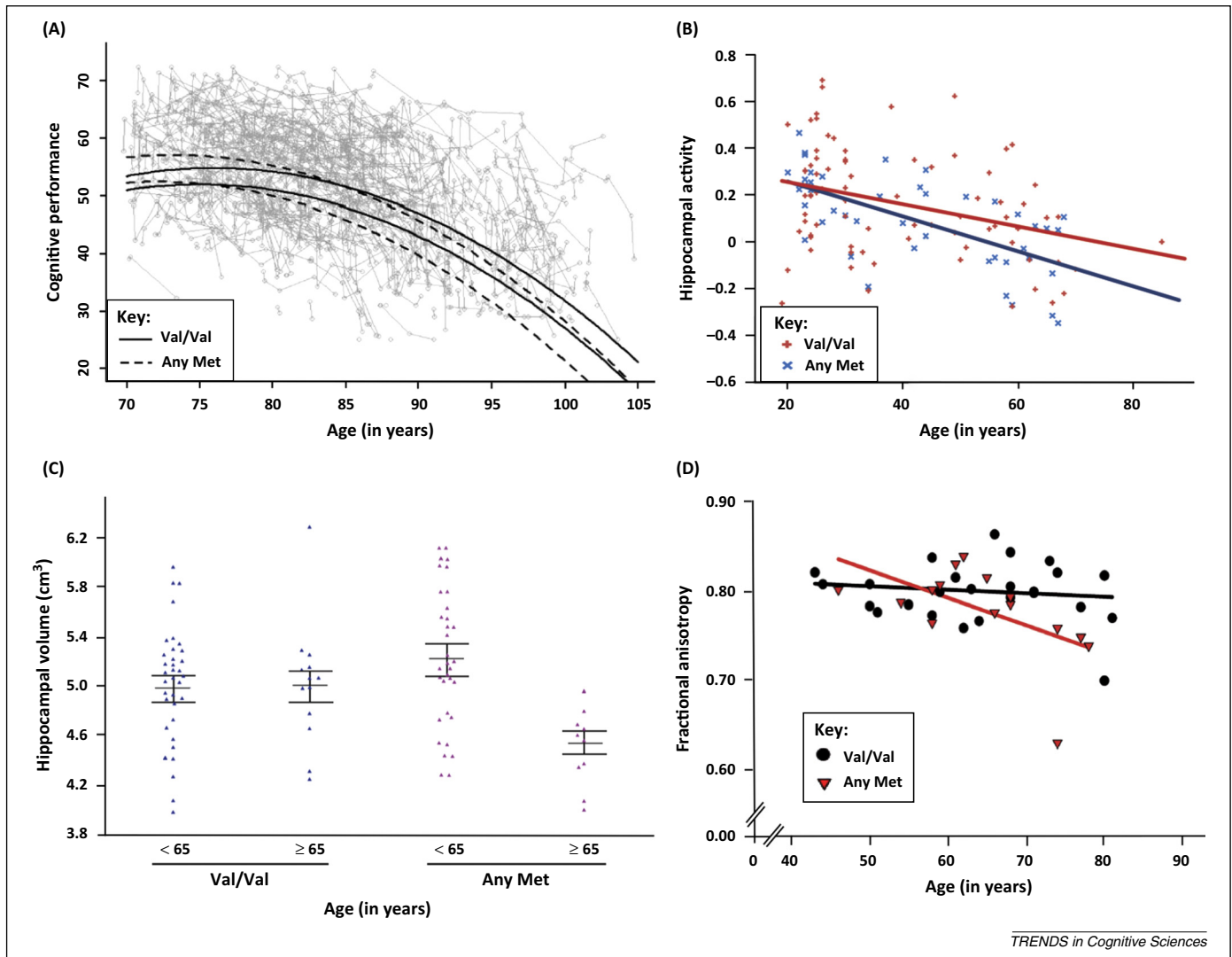


Figure 3. Effects of the brain-derived neurotrophic factor (*BDNF*) polymorphism on (A) longitudinal decline in perceptual speed across 13 years, with steeper decline for *BDNF* Met carriers. Perceptual speed is measured using the digit-letter task, which requires participants to name letters associated with a digit, according to a template. The y-axis indicates the total number of correct responses after 3 minutes. Adapted from [37] with permission from American Psychological Association. Interaction between age and *BDNF*, reflecting (B) lower hippocampal activity during retrieval of episodic memories, (C) smaller hippocampal volumes, and (D) lower white-matter integrity in the splenium for older *BDNF* Met carriers. Hippocampal activity in (B) indicates parameter estimates of the blood-oxygen-level-dependent (BOLD) response measured in arbitrary units in left hippocampus, which is greater during retrieval relative to a baseline condition. White-matter integrity is indicated by fractional anisotropy. Adapted from [39] and [38] with permission from Nature Publishing Group, and from [43] with permission from Frontiers Research Foundation.

formation and consolidation [56]. In agreement with the resource-modulation hypothesis, a recent study reported that older adults carrying the *KIBRA* T allele showed better spatial learning compared with C-allele homozygotes, although no genotype effects were found in younger adults [57]. Another study also documented better episodic memory in older *KIBRA* T carriers than in C-allele homozygotes, but there was no effect of this polymorphism in a sample of older adults with mild cognitive impairment [58]. This pattern is consistent with the resource-modulation hypothesis and the prediction that genetic effects diminish once individuals approach dementia or death (Figure 1).

Larger effects of *KIBRA* on episodic memory in old age were replicated in a lifespan sample aged 35–85 years, documenting an advantageous effect of the T allele on immediate free recall with advancing age [59]. In an fMRI subsample, T-allele carriers also exhibited increased hippocampal activity compared with C homozygotes during retrieval of episodic memories. However, *KIBRA*

modulated episodic memory and hippocampal activation only in relatively younger elderly persons (aged 55–60 years). Despite age magnification of *KIBRA* effects on behavior in the larger sample, there was no genetic modulation of brain activity and memory in the scanner task in the older age group (aged 65–75 years). The authors speculated that older adults carrying the disadvantageous genotype may have increased hippocampal activation associated with pathological aging that overshadows genetic effects. This underscores the importance to screen for participants with dementia or prodromal dementia in this type of research.

Another lifespan study reported further evidence in favor of the resource-modulation hypothesis [60], both with respect to brain function and behavior. First, increasing age was associated with larger genetic effects on immediate and delayed free recall (Figure 4A,B). During an fMRI task, older C homozygotes had lower hippocampal activation during encoding and retrieval compared with younger

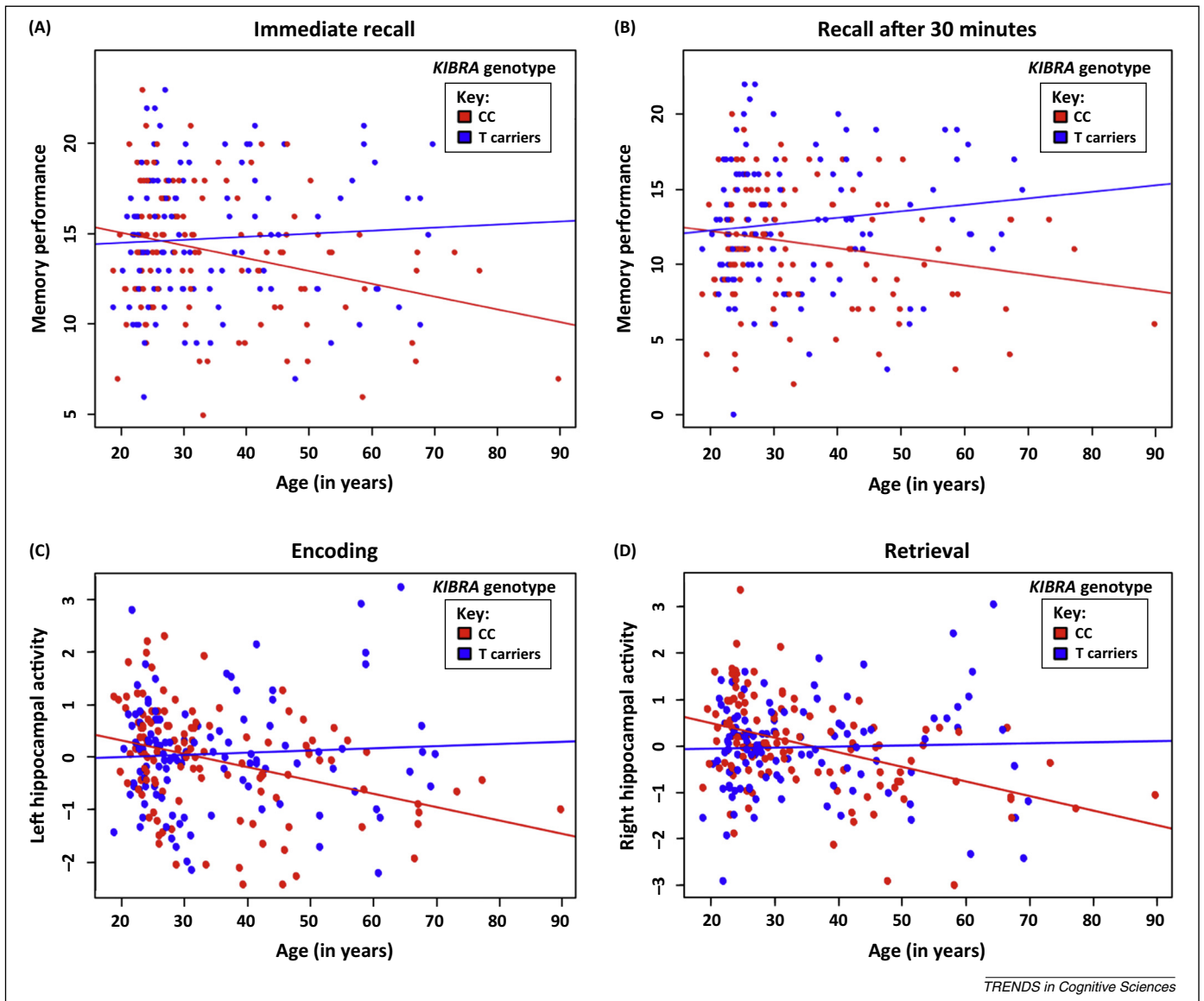


Figure 4. Groups with different kidney and brain expressed protein (*KIBRA*) genotypes show different correlations between increasing age and performance on (A) immediate and (B) 30 minute delayed recall of a story, as measured with the Wechsler Memory Scale. (C,D) *KIBRA* genotype group differences in the correlation between age and brain activation during an episodic memory task. (C) The *KIBRA* CC group (red) exhibits a negative correlation between age and activity in left hippocampus during encoding, which is not observed for T-allele carriers (blue). (D) The *KIBRA* CC group (red) exhibits a negative correlation between age and activity in right hippocampus during retrieval, which is not observed for T-allele carriers (blue). Hippocampal activity indicates parameter estimates of the BOLD response measured in arbitrary units, which is greater during encoding and retrieval relative to a baseline condition. Adapted from [60] with permission from Elsevier.

C homozygotes, demonstrating stronger genetic effects with advancing age (Figure 4C,D).

Dopamine D2 receptor (*DRD2*) polymorphisms

A behavioral study investigated the effect of genetic variation in the *DRD2* gene on the ability to inhibit an action. Genetic predisposition for higher density of extrastriatal D2 receptors (*DRD2* CC) was associated with better inhibition of unwanted action tendencies, an effect that was more pronounced in older than in younger adults (Figure 5) [61]. With respect to brain functioning, another variation in the *DRD2* gene showed a similar pattern of age magnification, both on brain and behavior: lower performance in long-term memory updating was found for older carriers of the allele associated with fewer D2 receptors, as compared with non-carriers [62]. In addition, older risk carriers had lower brain activity in left caudate nucleus, a region crucial

for updating [63]. Although there are relatively few studies investigating the effects of *DRD2*, the available data suggest that this gene influences brain and cognition more strongly in older than in younger adults.

Factors affecting age magnification of genetic effects

As reviewed above, studies have often observed genetic effects in older, but not younger, adults. This may partly account for inconsistent findings in the extant literature because many studies have included younger participants only or collapsed the data across different age-cohorts. However, in age-comparative work, the available evidence is not unequivocal either, and a few studies have failed to find magnification of genetic effects on brain and cognition in aging (e.g., [64,65]). In the following we highlight factors that may limit or enhance the likelihood of observing magnified genetic effects in aging.

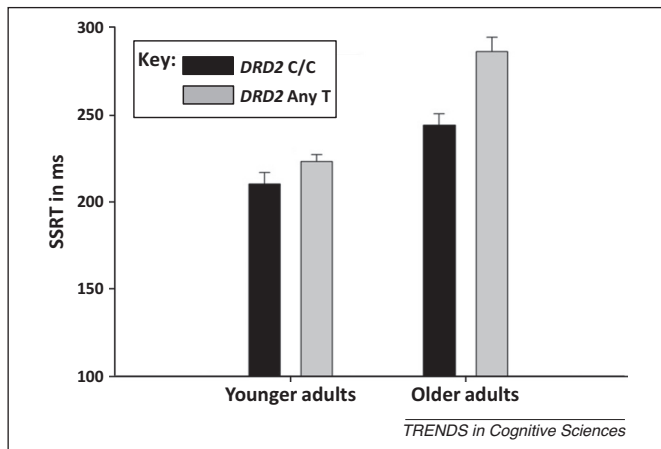


Figure 5. Age magnification of the effects of the dopamine receptor D2 (*DRD2*) polymorphism on inhibitory control (in ms) measured by the stop-signal reaction time task (SSRT), with older T carriers (fewer dopamine D2 receptors) showing disproportionate slowing. Adapted from [61] with permission from Elsevier.

Gene–gene interactions

Most studies focus on the effects of single genes. However, genetic effects on cognition and brain may be particularly strong when carrying two or more disadvantageous genotypes. This could result in both additive and interactive effects, emphasizing the importance of investigating the effects of multiple genes.

Several studies have investigated the joint effects of DA-related genes on executive functioning, working memory, and episodic memory in old age [66–68]. For example, a *DRD2* polymorphism interacted with a DA transporter gene in an episodic memory task requiring recall of words in backward order [68]: carriers of genetic predispositions for more D2 receptors and higher synaptic DA levels had higher recall accuracy. The main effects of each gene and the gene–gene interaction were larger in older than in younger adults. Because both the dopaminergic and glutamatergic systems modulate consolidation of episodic memories, one study investigated whether *DRD2* and glutamate receptor genes interactively affect episodic memory [69]. A gene–gene interaction was observed in older adults only, with individuals carrying genotypes associated with greater DA and glutamate receptor efficacy showing the highest episodic memory performance. Adverse additive effects of *COMT* Val/Val, *BDNF* Met, and age have been reported for executive functioning, such that older adults with a high-risk combination performed particularly poorly. These effects were strengthened by the presence of the *APOE* e4 allele [70]. Regarding neuroimaging data, studies investigating additive or interactive genetic effects in old age are rare. However, data suggest that considering more than one gene may help to explain variance in brain activity: hippocampal activity during episodic encoding decreased as a function of the number of *APOE* e4 and *BDNF* Met alleles (none, one, or both), yielding stronger effects than those of the individual genes [71].

Study population characteristics

Another factor that may contribute to inconsistent findings across studies concerns participant characteristics. Although some studies include population-based samples

or even individuals with different diseases, other studies screen their subjects carefully, which may result in greater participant selectivity. Crucially, most genetic studies on brain and cognition did not control for incident dementia. This is a serious omission, given that the prodromal phase of dementia might start several years, if not decades, before a clinical diagnosis is rendered [72]. As predicted by the resource-modulation model, genetic effects may diminish once individuals reach very low resource levels, as in dementia or terminal decline (Figure 1).

In general, genetic effects may be easier to detect when stratifying individuals according to different characteristics. For instance, interactive effects between two memory-related genes, *KIBRA* and calyntenin 2 (*CLSTN2*), were observed for episodic memory in older adults having relatively mild depression, with individuals carrying both risk alleles performing the worst [73]. By contrast, no genetic effects were observed in non-depressed individuals, suggesting that such effects are most easily detected at suboptimal levels of brain integrity, in this case among older persons with mild depression. Relatedly, imaging studies report stronger effects of *COMT* in populations with reduced brain resources [74–76] compared with healthy controls: in patients with major depressive disorder [76] and panic disorder [75], white-matter integrity was lower for Val homozygotes than for Met carriers, whereas no *COMT* effects were observed for healthy controls. Thus, different study population characteristics may affect whether or not a genetic effect is observed.

Gene–environment interactions

Detrimental effects of disadvantageous genotypes can be counteracted through an advantageous lifestyle. For instance, physical activity has been shown to attenuate negative effects of different genes on both episodic memory [77] and working memory [78]. Similarly, higher levels of education and lifetime intellectual enrichment counteracted the effects of *APOE* e4 on dementia occurrence [79] and cognitive decline [80]. Furthermore, higher blood pressure and increased cardiovascular risk have been shown to interact with risk alleles of *APOE* [81,82], *BDNF* [83], and *KIBRA* [84] in affecting cognition negatively. A healthier diet has also been reported to enhance the protective effects linked to carrying *APOE* e2 or e3 alleles with regard to cognitive performance [85]. Imaging studies investigating interactive effects between genes and environmental factors in older age are scarce. However, one study reported that older *APOE* e4 carriers who are more physically active had higher activity in different task-related brain regions during an episodic memory task than non-carriers or those with lower physical activity levels. In line with this pattern, structural imaging data demonstrate that increased physical activity is protective against the detrimental effects of *APOE* e4 on hippocampal volume across 18 months [86]. Another study showed that higher midlife cognitive activity attenuated amyloid accumulation in e4 carriers compared with non-carriers [87].

Epigenetics

By addressing epigenetic mechanisms [88], research may contribute to our understanding of how environmental and

lifestyle factors affect gene expression, and this may influence whether or not age magnification of genetic effects is observed. Interestingly, twin studies show that monozygotic twins become more discordant in aging with respect to their DNA methylation profiles, suggesting that different lifestyles may regulate gene expression across the lifespan [89]. Note, however, that gene–environment interactions might occur without any epigenetic modification. Moreover, individual differences in epigenetic mechanisms may also be inherited [90]. Therefore, it is vital to show longitudinally that lifestyle changes or interventions directly affect expression of a particular gene through epigenetic mechanisms, and consequently brain and cognition. Given that experimental control of lifestyle factors and their effects on epigenetic mechanisms is extremely difficult to achieve in humans, most findings on epigenetic mechanisms are based on animal data [88,91].

Gene–environment correlations

Gene–environment correlations indicate that a particular genotype is more frequently associated with a particular environment. For instance, individuals with more advantageous genetic predispositions may actively seek a more stimulating environment. Environmental exposure may, in turn, enhance expression of a particular gene via epigenetic mechanisms, thereby increasing inter-individual differences [92]. Such gene–environment interactions may partly account for the increased heritability of cognitive measures in old age, as supported by simulation work [93] and a meta-analysis of correlational ratios in twin studies [6]. Although genetically identical twins may choose similar environments resulting in relatively stable monozygotic (MZ) correlations, dizygotic (DZ) twins may become more different over time owing to different genetically driven environmental choices, leading to a lower correlation between dizygotic twins. Thus, over time, the correlation ratios (MZ/DZ) may increase, suggesting increased heritability in late adulthood, although environmental factors contribute to the enhanced association.

Concluding remarks

Increasing evidence suggests that effects of common genetic variations on brain and behavior become stronger in late life, supporting the resource-modulation hypothesis.

Box 1. Outstanding questions

- Do genetic effects diminish once individuals approach cognitive decline and death? This particular prediction of the resource-modulation hypothesis has not been extensively tested.
- Given that genes may affect both brain structure and function, multimodal imaging studies are necessary to understand the temporal dynamics of genetic effects on brain functioning. Does a particular gene affect brain structure and function independently, or are the functional effects mediated through effects on brain structure?
- Given that genetic variations may differ across generations, longitudinal studies are necessary to replicate the patterns of age magnification observed in cross-sectional studies.
- Is there a direct relationship between mean changes in brain resources and heritability estimates of cognition? Do lower brain resources *per se* lead to increased genetic effects in old age, or are these mediated through lifestyle and epigenetic factors?

Similar patterns have been reported in other populations characterized by reduced brain resources, by contrasting samples with different diseases to healthy controls. So far, the bulk of relevant studies are cross-sectional. Longitudinal behavioral, structural, and functional imaging studies will be necessary to confirm the patterns reported in the cross-sectional data (Box 1). Furthermore, some of the inconsistent patterns reported in candidate gene studies likely stem from gene–gene interactions, and from environmental and lifestyle factors resulting in epigenetic differences. Behavioral and multimodal brain imaging research across long follow-up intervals that target the operation of these factors during the transition from early to late adulthood constitutes a key avenue for future research.

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