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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 subprocesses 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.

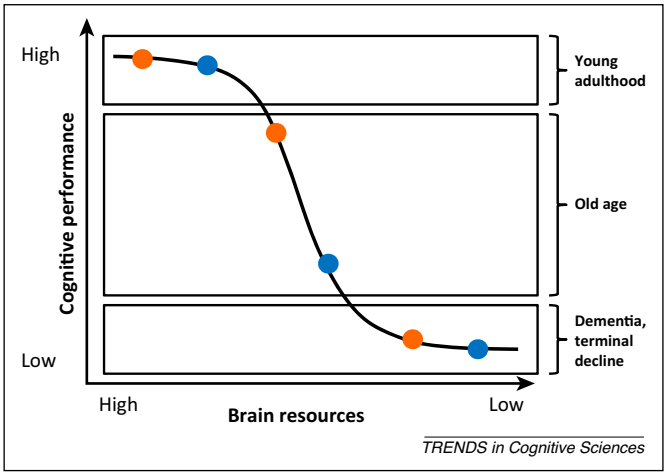

Figure 1. The resource-modulation hypothesis assumes that the function relating brain resources to cognition is non-linear and predicts magnified genetic effects on cognitive performance in old age. In healthy aging, associated with decline in anatomical and chemical brain resources, constant amounts 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

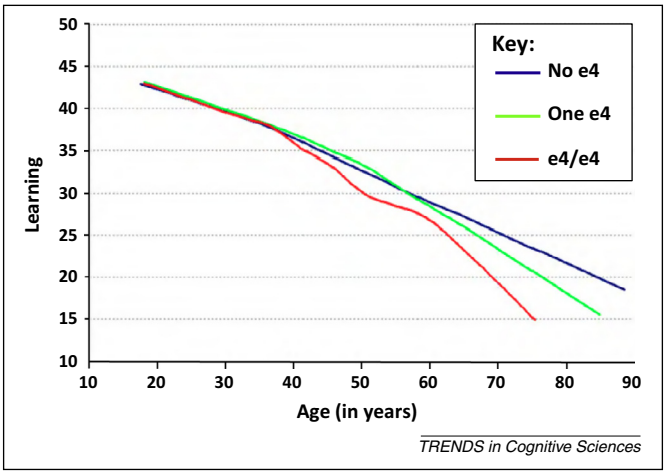

Figure 2. Effects of the apolipoprotein E (*APOE*) polymorphism on learning, with increased negative dose–response effects of the e4 allele across adult age. Learning reflects the number of correctly recalled words in the Rey Auditory Verbal Learning Test. Adapted from [22] with permission from Elsevier.