# COGNITIVE NEUROSCIENCE OF AGING

## Linking Cognitive and Cerebral Aging

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# 16

# Genetics and the Cognitive Neuroscience of Aging

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Normative aging is associated with decline in different cognitive domains (e.g., Schaie et al., 1998; Rönnlund et al., 2005). Independent of age, there are large inter-individual differences in various cognitive functions, which may increase from early to late adulthood (e.g., de Frias et al., 2007; Tucker-Drob et al., 2014). These individual differences are sometimes paralleled by greater between-person differences in neural processing with advancing age, as revealed by functional imaging techniques (Lindenberger et al., 2013). Conceivably, multiple factors contribute to between-person differences at neural and behavioral levels, including genetic predispositions and lifestyle factors (Nyberg et al., 2012).

In this chapter, we review studies that investigate the effects of candidate genes on behavior, as well as on brain structure and functioning in relatively healthy older adults. The chapter is organized as follows: First, we introduce the resource-modulation notion proffered by Lindenberger and colleagues (2008). This view posits that effects of common genetic variations on brain and behavior may become stronger in old age. Our goal is to give a broad overview of the evidence from behavioral, structural, and functional imaging studies supporting this hypothesis. Next, we briefly introduce the candidate-gene approach and review the extent to which the available data support the resource-modulation hypothesis. We focus on four candidate genes that have attracted considerable attention in cognitive neuroscience of aging: apolipoprotein E gene (*APOE*, rs429358, rs7412), brain-derived neurotrophic factor (*BDNF*, rs6265) Val66Met polymorphism, catechol-O-methyltransferase (*COMT*, rs4680)

Val66Met polymorphism, and the kidney and brain–expressed protein or WW and C2 domain containing 1 (*KIBRA, WWC1*, rs17070145) polymorphism. Of these candidate genes, the number of studies investigating the effects of *APOE* on cognitive and brain integrity is considerably larger compared to the other candidate genes, which is due to the fact that *APOE* e4 is the strongest genetic risk factor for dementia (Ferencz and Gerritsen, 2015). Thus, *APOE* may have also stronger effects on cognition in healthy elderly than the other candidate genes (e.g., Laukka et al., 2013). Given mixed results regarding the replication of effects of candidate genes and the fact that most genes account for only a small fraction of the variance in cognition (Deary et al., 2010), we will delineate potential factors that may limit or enhance the likelihood to observe magnified genetic effects in aging.

## The Resource-Modulation Hypothesis: Aging-Related Magnification of Genetic Effects

The resource-modulation hypothesis assumes that losses in neurochemical (e.g., Bäckman et al., 2006) and anatomical (e.g., Raz et al., 2005) brain resources in normal aging modulate the effects of common genetic variations on cognitive functioning (see Figure 16.1). Whereas genetic effects in younger adults may be small or

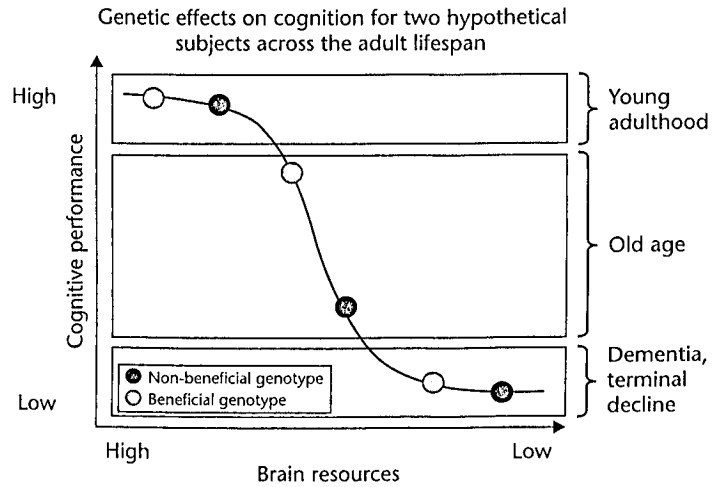


Figure 16.1 The resource-modulation hypothesis assumes that the function relating brain resources to cognition is nonlinear and predicts magnified genetic effects on cognitive performance in old age. In healthy aging, associated with decline in anatomical and chemical brain resources, constant amounts of genetic variation translate into increasingly larger 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 Papenberg, Lindenberger, & Bäckman (2015) with permission from Elsevier.

not detectable, these effects become stronger as people age. The idea is based on the assumption that the function relating brain resources to cognition is nonlinear, so that genetic differences exert increasingly larger effects on cognition as resources recede from high to medium levels. Put differently, older adults may benefit more from beneficial genetic predispositions relative to younger adults and be able to maintain higher brain and cognitive functioning, as a consequence of their more beneficial genetic make-up (Nyberg et al., 2012). Indeed, evidence from heritability studies suggests that acceleration of cognitive decline in old age is strongly associated with genetic factors (e.g., Finkel et al., 2005; Deary et al., 2006; Tucker-Drob et al., 2014). For instance, Tucker-Drob and colleagues (2014) found that one third of individual differences in global cognition changes in late adulthood are attributable to genetic influences. The model depicted in Figure 16.1 also predicts that genetic effects are expected to diminish once individuals have reached very low resource levels, as in terminal decline or dementia. In line with this, heritability for cognition seems to decrease once individuals reach dementia, suggesting that genes account less for individual differences in Alzheimer's disease (AD) patients. More specifically, heritability estimates for different forms of memory are smaller in samples of individuals with AD and their unaffected family members than for unaffected family members alone (Wilson et al., 2011).

As with cognition, there is considerable heritability for brain structure and function (Toga and Thompson, 2005). Furthermore, given that brain integrity is an intermediate phenotype for behavior (Harris and Deary, 2011), it has been argued that neural indicators may be more sensitive to genetic effects than behavioral measures (e.g., Rasch et al., 2010). Older age is associated with reduced grey-matter volumes (e.g., Raz et al., 2005) and lower white-matter integrity (for a review, see Madden et al., 2012), as indicated by different measures of diffusion tensor imaging (DTI). For instance, higher fractional anisotropy (FA) and lower mean diffusivity (MD) reflect more preserved white-matter integrity. Unfortunately, the interpretation of functional magnetic resonance imaging (fMRI) signals is not straightforward, as higher blood-oxygen-level-dependent (BOLD) signal has been suggested to reflect better as well as worse neural functioning in the absence of behavioral differences. On the one hand, higher brain activation may reflect less efficient neural processing to achieve the same behavioral outcomes, a result typically observed during less demanding cognitive tasks (e.g., Papassotiropoulos et al., 2006). That said, the inefficiency argument may not always hold, in light of additional information, such as performance differences between allelic groupings in more demanding offline tasks that may be more suitable to disclose genetic differences (e.g., Muse et al., 2014). For example, Muse and colleagues documented higher hippocampal activation during a recognition memory task and better immediate and delayed recall performance outside the scanner for carriers of the advantageous *KIBRA* T-allele. In these cases, genetic effects at the brain level may simply reflect that neural measures are more sensitive to genetic effects than behavioral measures. Indeed, it has been shown that genetic differences in brain activation remained the same both in the presence of performance differences and in performance-matched groups (Kauppi et al., 2011).

Furthermore, increased activation in additional brain regions are commonly observed in older adults, a phenomenon suggested to reflect decreased selectivity or

dedifferentiation of neural processing, but also compensation for deficits elsewhere in the brain or selection of alternative processing strategies (Grady, 2012; Lindenberger et al., 2013). Finally, greater brain activation may also reflect pathological aging, which may in some cases overshadow genetic effects. In line with this, longitudinal imaging studies have found that older adults with increased and more diffuse brain activation patterns declined more in their clinical and neurological status, although these individuals did not differ in baseline memory performance from those with more distinct activation patterns (Bookheimer et al., 2000; O'Brien et al., 2010). Taken together, higher brain activations may be interpreted to reflect better as well as worse neural processing depending on task demands, behavioral outcomes, and sample characteristics.

## Candidate Gene Approach

In the past decade, there has been an increasing interest in investigating the impact of genetic predispositions on behavioral phenotypes in cognitive neuroscience (Rasch et al., 2010), often with a focus on candidate genes. The general assumption is that individual differences in genetic predispositions result in differences in protein expression in the brain, affecting neural processing and consequently behavior.

Candidate genes are typically selected based on knowledge from previous studies, linking specific genes to a specific protein and the protein's involvement in brain and cognitive functions. In the following, we will focus on four extensively investigated candidate genes and review their associations with behavioral outcomes, brain structure and function in adulthood and aging.

## *APOE* Polymorphism

Apolipoprotein E (*APOE*) is a low-density lipoprotein that modulates cholesterol transport (Mahley et al., 2009) and is implicated in several key mechanisms in the central nervous system, such as neuronal development, brain plasticity, and neural repair (Bu, 2009). There are three isoforms of *APOE*, as defined by the two polymorphisms, rs429358 and rs7412: the e2, e3, and e4, of which e3 and e2 are the most and least common, respectively. The e4 allele is the strongest genetic risk factor for Alzheimer´s disease (AD), such that the presence of one or two ε4 alleles is associated with higher risk of developing AD in a dose-dependent manner (e.g., Okuizumi et al., 1995; Farrer et al., 1997). The e4 allele is also related to increased risk for mild cognitive impairment (MCI; Boyle et al., 2010) and accelerated cognitive decline during normal aging (Smith, 2002; Bretsky et al., 2003). In line with earlier meta-analytic findings (Small et al., 2004), a recent meta-analysis showed that the e4 allele is associated with lower performance on measures of episodic memory, executive functioning, general cognitive ability, and perceptual speed (Wisdom et al., 2011). In addition, genetic effects were more pronounced in older than younger individuals with respect to episodic memory and global cognitive ability. In line with this pattern, longitudinal studies have documented interactions between age and *APOE* on the memory

and learning subdomains of the Adult Verbal Learning Test, with stronger negative effects of e4 in persons older than 50 years than in those below 50 years (Liu et al., 2010; Figure 16.2A). Similarly, in older adults aged 79 years, the e4 allele was associated with more rapid decline in verbal memory and abstract reasoning across 8 years (Schiepers et al., 2012). However, one study showed that the relationship of *APOE* to episodic memory and global cognition was attenuated, after exclusion of future

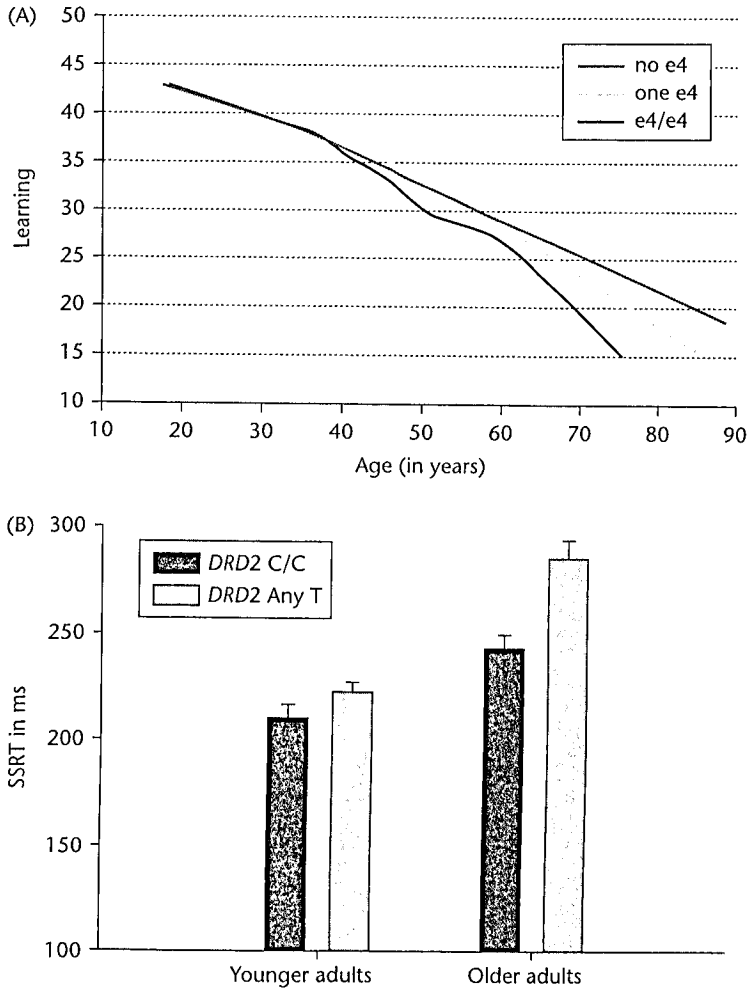


Figure 16.2 (A) Effects of *APOE* on learning, with increased negative dose-response effects of the e4 allele across adult age. Learning reflects number of correctly recalled words in the Rey Auditory Verbal Learning Test. Adapted from Liu et al. 2010. (B) Age-magnification of DRD2 effects on inhibitory control (in ms) measured by the stop-signal reaction time task (SSRT), with older any T carriers (fewer dopamine D2 receptors) showing disproportionate slowing. Reprinted from Papenberg et al. (2015) with permission from Elsevier.

dementia cases (Laukka et al., 2013). This suggests that dementia-related processes may contribute to the link between *APOE* and cognition in old age.

Functional imaging data on *APOE* are less consistent than the available behavioral data. Here we focus on fMRI studies in persons from middle age through old age that investigate neural correlates of episodic memory, the cognitive domain most severely affected by AD. Several fMRI studies have documented that elderly e4 carriers have increased brain activation relative to non-carriers during different episodic memory tasks, with no performance differences between genotypes (e.g., Bookheimer et al., 2000; Bondi et al., 2005; Fleisher et al., 2005; Han et al., 2007). For example, increased BOLD activation have been documented in left MTL, as well as in parietal and prefrontal regions for e4 carriers during episodic encoding and recall (Bookheimer et al., 2000; Fleisher et al., 2005). Using longitudinal assessment over two years, Bookheimer and colleagues further showed that the degree of baseline brain activation was linked to the degree of memory decline. The authors suggest a compensatory mechanism such that individuals at genetic risk for AD (i.e., e4 carriers) have to invest greater cognitive effort to achieve the same performance level as persons with lower genetic risk. However, efficiency of the elevated BOLD response may decline over time as reported in a longitudinal imaging study in individuals with prodromal AD (O'Brien et al., 2010). More specifically, individuals with more rapid cognitive decline were characterized by the highest hippocampal activation at baseline and the greatest reduction of hippocampal activation over two years during an associative memory task.

On the other hand, there is a bulk of evidence documenting decreased brain activation for older e4 carriers during memory tasks (e.g., Lind et al., 2006; Fleisher et al., 2009b; Xu et al., 2009; Kauppi et al., 2014). Employing incidental word encoding and an associative memory task, two studies reported decreased activity in right MTL for e4 carriers relative to non-carriers despite similar performance levels (Kauppi et al., 2014; Lind et al., 2006). Lower MTL activity was interpreted as an early sign of hippocampal pathology for individuals at risk for AD. Another study demonstrated equivalent face recognition performance accompanied by decreased BOLD activity in left posterior cingulate cortex (PCC) and precuneus in the high-risk group (i.e., first-degree family history of dementia and presence of the *APOE* e4 allele) compared to the low-risk group (Xu et al., 2009). The authors speculated that decreased BOLD activity in those regions might disrupt the functional architecture of the default mode network (DMN), which is severely affected in MCI and AD. Related to this argument, genetic differences have been observed with respect to decreased deactivation of the DMN (e.g., Fleisher et al., 2009a; Pihlajamaki et al., 2010). Using an identical memory task, Fleisher and colleagues also reported no BOLD differences between e4 carriers and non-carriers during encoding (Fleisher et al., 2009a). Instead, encoding-associated deactivation was greater in magnitude among non-e4 carriers in medial and right lateral parietal cortex. This finding is consistent with results from Xu and colleagues (2009), demonstrating functional alterations in critical nodes of the DMN for e4 carriers compared to non-carriers.

However, studies with larger numbers of participants ($n > 100$) failed to find BOLD differences between e4 carriers and non-carriers during memory tasks (Bassett et al., 2006; Johnson et al., 2006). Considering first-degree family history of dementia, Johnson and colleagues showed that e4 carriers with and without family history

exhibited the least and the greatest signal change in MTL, respectively. This suggests that other genetic factors and possibly non-genetic risk factors associated with AD may exacerbate the negative effects of *APOE* e4 on functional brain measures (e.g., Donix et al., 2012).

So far, only two studies investigated the effect of the *APOE* genotype on brain function across the adult lifespan. Using a memory encoding task in younger (aged 20 to 35) and older individuals (aged 50 to 78), Filippini and colleagues (2011) showed a significant interaction between age and e4 status in MTL, frontal pole, subcortical nuclei, middle temporal gyrus, and cerebellum, such that aging was associated with decreased activity in e4 carriers and increased activity in non-carriers. Further, cerebral blood flow was reduced for older e4 carriers relative to non-carriers, which could partly account for decreased activity in individuals at genetic risk for AD. However, data from another lifespan sample (aged 19–77 years) suggested an opposite pattern for hippocampal activation in older adults (Nichols et al., 2012). 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. During more difficult tasks, the pattern may be reversed (Grady, 2012). In line with this notion, participants were instructed to remember images in the study where older e4 carriers had lower brain activity at encoding (Filippini et al., 2011). 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 (Nichols et al., 2012). With respect to markers of brain structure, interactive effects between age and *APOE* on white matter microstructure have not been reported (e.g., Heise et al., 2011; Westlye et al., 2012; Nyberg and Salami, 2014). However, longitudinal studies have documented more hippocampal atrophy for e4 carriers than for non-carriers (Cohen et al., 2001; Crivello et al., 2010) among healthy elderly persons.

Taken together, elevated BOLD activation in e4 carriers relative to non-carriers were interpreted as a compensatory mechanism to circumvent initial AD-related damage using more cognitive effort (Bookheimer et al., 2000; Han et al., 2007). Some studies, however, have reported decreased BOLD activation in e4 carriers, assumed to reflect pathological disruption (Kauppi et al., 2014; Lind et al., 2006; Pihlajamaki et al., 2010; Xu et al., 2009). To some extent, differences in task difficulty may account for inconsistent findings across studies. Older adults at higher risk for cognitive decline may show higher brain activation at lower cognitive loads than individuals at less risk (Grady, 2012). With increasing load, however, the pattern may be reversed. Further, as noted above, longitudinal imaging evidence suggests decreases in hippocampal activation for individuals with greater cognitive decline, despite over-recruitment at baseline (O'Brien et al., 2010). Thus, higher task-related brain activation for e4 carriers may reflect initial compensatory attempts, which with advancing age and further age-related decline in

brain resources become less efficient, resulting in lower brain activation. Although behavioral and structural imaging data suggest that negative effects of the e4 allele may increase with age, corresponding longitudinal fMRI data are lacking and age-comparative cross-sectional research is scarce.

## *BDNF* Polymorphism

The brain-derived neurotrophic factor (BDNF) promotes activity-dependent synaptic plasticity and is critical for learning and memory (e.g., Binder and Scharfman, 2004). The Val66Met polymorphism (rs6265) of the *BDNF* gene is associated with individual differences in secretion of BDNF, which is higher in Val homozygotes than in Met carriers (Egan et al., 2003). At the behavioral level, older Val homozygotes have exhibited superior episodic memory, but also processing speed and general intelligence compared to any Met carriers (Miyajima et al., 2008). Indeed, meta-analytic evidence confirms adverse effects of the *BDNF* Met allele on human episodic memory (Kambeitz et al., 2012). Adult age-comparative studies have reported magnified effects of *BDNF* in old age for episodic memory (Li et al., 2010), with older Val homozygotes performing better on backward serial recall. In line with the resource-modulation hypothesis, longitudinal data demonstrate exacerbated decline in perceptual speed across 13 years among older *BDNF* Met carriers (Ghisletta et al., 2014; Figure 16.3A), an effect that remained after excluding prodromal dementia cases. Similarly, Sanchez et al. (2011) reported that pilots carrying the Met allele (aged 40–69 years) declined disproportionately in flight-simulator performance, presumably reflecting executive functioning.

In young adults, *BDNF* Met carriers have shown lower activity in hippocampus during encoding and retrieval of episodic memories (e.g., Egan et al., 2003; for meta-analysis, see Kambeitz et al., 2012; Hariri et al., 2003) and during performance of a virtual navigation task (Banner et al., 2011). Whereas Hariri and colleagues (2003) found *BDNF*-related differences in episodic memory, accompanied by differences in hippocampal activation during encoding and retrieval, other studies have failed to find behavioral genotype differences, although Met carriers had lower hippocampal activity during encoding of episodic memories (Hashimoto et al., 2008). Of particular interest, one lifespan study ($n$ = 125; aged 19–85 years) showed more pronounced decrease in hippocampal activity with advancing age for Met carriers than for Val homozygotes (Sambataro et al., 2010). This pattern was evident during both episodic encoding and retrieval (Figure 16.3B). Importantly, after adjusting for inter-individual differences in hippocampal volume, the differential activation pattern remained. Again, however, this study did not find any behavioral genotype differences, supporting the notion that neural measures may be more sensitive to genetic differences than behavioral measures (e.g., Rasch et al., 2010).

Age magnification of the effects of *BDNF* has also been documented for measures of brain integrity, emphasizing the role of BDNF in modulating myelin expression (Ikeda et al., 2002) and survival of neurons in the adult brain (Morse et al., 1993). Cross-sectional imaging studies have shown age magnification of the effects of *BDNF* for grey matter volumes and white matter microstructure. Specifically, Met carriers

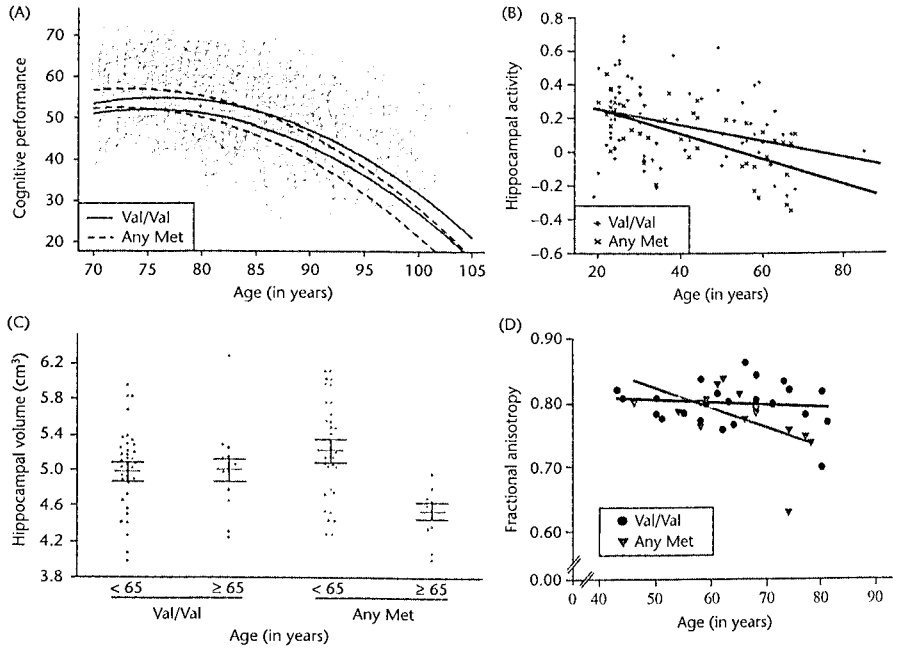


Figure 16.3 Effects of *BDNF* on (A) longitudinal decline in perceptual speed across 13 years, with steeper decline for *BDNF* Met carriers. Perceptual speed is measured using the digit-letter task, which required participants to name letters associated with a digit, according to a template. The y-axis indicates total number of correct responses after 3 min. Adapted from Ghisletta et al. (2014). 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 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. Reprinted from Papenberg et al. (2015) with permission from Elsevier. (See color plate also)

had lower hippocampal volumes after age 65 than Val homozygotes, whereas no such differences were apparent before 65 (Sanchez et al., 2011; Figure 16.3C). Critically, age was uncorrelated with hippocampal volume in Val homozygotes, supporting the idea that brain maintenance in old age may be partly due to genetic factors (Nyberg et al., 2012). Another study in individuals with prodromal AD reported that the Met allele was associated with increased memory decline, paralleled by more hippocampal atrophy, across three years (Lim et al., 2014). Similarly, age-related decline in white matter microstructure (i.e., lower fractional anisotropy) was found for Met carriers in the splenium of the corpus callosum, although no age-related decline was evident for Val homozygotes (Kennedy et al., 2009; Figure 16.3D).

Taken together, behavioral evidence as well as data from functional and structural imaging studies suggest magnified effects of *BDNF* on brain and cognition in aging, with greater decline in functioning for older Met carriers.

## *COMT* Polymorphism

The *COMT* Val158Met polymorphism (rs4680) is the most studied dopamine-related polymorphism. The COMT enzyme is involved in extracellular degradation of synaptically released dopamine in the prefrontal (PFC) cortex (e.g., Matsumoto et al., 2003). Dopamine concentration increases neuronal signal-to-noise ratio in PFC, critical to efficient cognitive processing (Egan et al., 2001). *COMT* Val homozygotes have three to four times higher turnover rates of this enzyme than Met homozygotes (Lotta et al., 1995), resulting in lower prefrontal DA availability and presumably less efficient processing.

Studies with young adults have demonstrated a *COMT* Met advantage in executive functions and memory performance compared to Val homozygotes (for review, see Witte and Flöel, 2011). Such cognitive benefits have been found to correlate with lower brain activation, indicating more efficient information processing (Egan et al., 2001; Sambataro et al., 2009). However, several studies have failed to replicate these findings (Bolton et al., 2010; de Frias et al., 2010; Blanchard et al., 2011; Stuart et al., 2014), and two meta-analyses only documented a *COMT* Met superiority on measures of general cognition, such as IQ (Barnett et al., 2007; Barnett et al., 2008).

Although the effect of *COMT* on cognition in healthy aging has received less attention, there is evidence that *COMT*-related differences become more apparent with increasing adult age (de Frias et al., 2005; Nagel et al., 2008; Papenberg et al., 2013b). For instance, evidence for such age interactions comes from cross-sectional studies demonstrating faster response times for Met homozygotes during spatial working memory in older, but not in younger individuals (Nagel et al., 2008). Most importantly, longitudinal data reveal less decline of executive function over a five-year interval (de Frias et al., 2005) and less episodic memory decline across 15 years (Josefsson et al., 2012) for middle-aged and older *COMT* Met carriers than for Val homozygotes.

Both older age and *COMT* Val status have been associated with altered fronto-striatal dopamine functioning (e.g., Slifstein et al., 2008; Klostermann et al., 2012) that might translate into reduced neural efficiency and lower cognitive performance. Although only a few studies have tested whether aging modulates the link between *COMT* and brain functioning, there is some evidence suggesting the existence of such interactions. In a recent fMRI study, Nyberg and colleagues (2014) investigated the independent effects of aging and *COMT* on working memory performance and patterns of brain activation in a large population-based sample. Given previous observations in older adults (e.g., Nagel et al., 2009), they predicted weaker PFC response during high working-memory load (manipulation), along with increased BOLD response during low working-memory load (maintenance) in older adults and *COMT* Val carriers compared to younger adults and *COMT* Met carriers. In line with the predictions, older individuals had weaker BOLD modulation in PFC during working-memory manipulation. Also, the weakest PFC activation during manipulation was observed in *COMT* Val carriers. Conversely, older adults and Val carriers had elevated BOLD response in PFC during the less cognitively taxing maintenance condition.

In another fMRI study, Sambataro and colleagues (2009) took a multivariate approach to investigate the effects of *COMT* on brain-network connectivity using a low-load working memory task. They found that a network including left PFC and

parietal cortex was modulated by *COMT*, with Val homozygotes showing increased connectivity from dorsolateral PFC to other components in this network compared to Met homozygotes. Notably, the largest *COMT*-related difference was seen in older, relative to younger, individuals. This suggests additive effects of age-related dopamine deterioration and *COMT*. The findings from these two studies of increased PFC activation and functional connectivity in older individuals and Val carriers is in agreement with the efficiency hypothesis of *COMT* influences on brain functioning (Mier et al., 2010).

In conclusion, there is preliminary evidence to support the notion that the *COMT* Val158Met polymorphism and age jointly modulate dopamine and PFC efficiency such that older Val carriers display limited PFC upregulation in response to increased task demands. Moreover, initial evidence suggests that there is an interaction between age and *COMT* on measures of PFC functioning. Relatedly, a structural-imaging study in a population-based sample found that *COMT* Val status was associated with reduced white matter integrity, reflected by lower fractional anisotropy and higher mean diffusivity, of several prefrontal white-matter tracts in the oldest age group (81–87 years), although there were no reliable associations between *COMT* and white matter microstructure in two younger age groups (60–66 and 72–78 years; Papenberg et al., 2014a). This finding is particularly relevant, as BOLD responsivity does not predict working-memory performance after controlling for individual differences in white matter integrity (Burzynska et al., 2011). This raises the question of whether the magnified effects of *COMT* on white matter microstructure may be related to those on functional brain activity.

## *KIBRA* Polymorphism

A genetic variation (rs17070145) in the WWC1 gene, which encodes the KIBRA protein, has been associated with episodic memory in humans through genome-wide screening, with T-allele carriers exhibiting better performance (Papassotiropoulos et al., 2006). In the human brain, KIBRA is mainly expressed in hippocampus and has been linked to long-term potentiation and synaptic plasticity (Schneider et al., 2010). A meta-analysis reported a reliable association between rs17070145 and episodic memory as well as working memory, explaining 0.5% and 0.1% of variance, respectively (Milnik et al., 2012; for review, see Schwab et al., 2014). In line with the resource-modulation hypothesis, a recent behavioral study reported that older adults carrying the T-allele showed better spatial learning compared to C homozygotes, whereas no genotype effects were found in younger adults (Schuck et al., 2013). Interestingly, Almeida and colleagues (2008) showed better episodic memory for older *KIBRA* T-carriers, but there was no effect of this polymorphism in a sample of older adults with mild cognitive impairment. This pattern is supportive of the lower end of the distribution portraying the resource-modulation hypothesis (see Figure 16.1), predicting genetic effects to diminish once individuals approach dementia or death.

fMRI studies have documented lower as well as higher brain activation for carriers of the beneficial T-allele. Papassoptiropolous and colleagues (2006) reported lower hippocampal activity during episodic retrieval for young T-allele carriers, in

the absence of behavioral differences in the scanner task. The authors interpreted this pattern in terms of more efficient processing for T-allele carriers. A different pattern was reported by a more recent fMRI study with elderly persons (Kauppi et al., 2011). Specifically, the behavioral data in a sample of 2230 participants (aged 35–85 years) suggested an advantageous effect of the T-allele on immediate free recall, which was magnified with increasing age. Further, in a subsample (n = 83), Kauppi and colleagues demonstrated increased hippocampal activity in T-allele carriers, which was evident when the genotype groups differed in memory performance, but also when the groups were matched for in-scanner task performance. However, *KIBRA* modulated episodic memory and hippocampal activation only in middle-aged adults (aged 55 to 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 with the disadvantageous genotype might have increased hippocampal activation associated with pathological aging that overshadow the genetic effects. Another lifespan study reported further evidence in favor of the resource-modulation hypothesis (Muse et al., 2014). First, increasing age was associated with stronger effects of the disadvantageous C-allele on immediate and delayed (30 minute) free recall (Figure 16.4A, B). In contrast, there were no behavioral differences between genotypes or interactions between age and genotype for the recognition memory task during scanning. However, older, but not younger, C homozygotes had lower hippocampal activation during encoding and retrieval, suggesting stronger genetic effects in advanced age (Figure 16.4C, D). The latter study provides additional support for the resource-modulation hypothesis and the notion that brain measures are more sensitive to genetic effects; genetic effects on behavior became evident only during more demanding episodic-recall tasks, performed outside the scanner.

## Miscellenous Genes and Gene–Gene Interaction

Taken together, the data reviewed above suggest that effects of common genetic variations on behavior, brain structure and functioning may become stronger with increasing adult age, supporting the resource-modulation hypothesis. We focused on a few of the most extensively investigated polymorphisms. However, several other studies investigating relationships of common genetic variations to brain and behavior have also found stronger genetic effects in old age. Notably, studies have also documented gene–gene interactions and additive effects of different polymorphisms on brain and behavior in older adults, emphasizing the importance of investigating effects of multiple genes.

Examining the association between a dopamine D2 receptor (*DRD2*, C957T, rs6277) polymorphism and inhibitory control, Colzato and colleagues (2013) reported that genetic predisposition for higher density of extrastriatal D2 receptors (*DRD2* CC) was associated with better inhibition of unwanted action tendencies (Figure 16.2B), an effect that was most pronounced in older adults. In another study, *DRD2* interacted with the dopamine transporter (*DAT*) gene on backward serial recall (Li et al., 2012): Homozygotes for the *DRD2* C and *DAT* 9-repeat alleles (associated

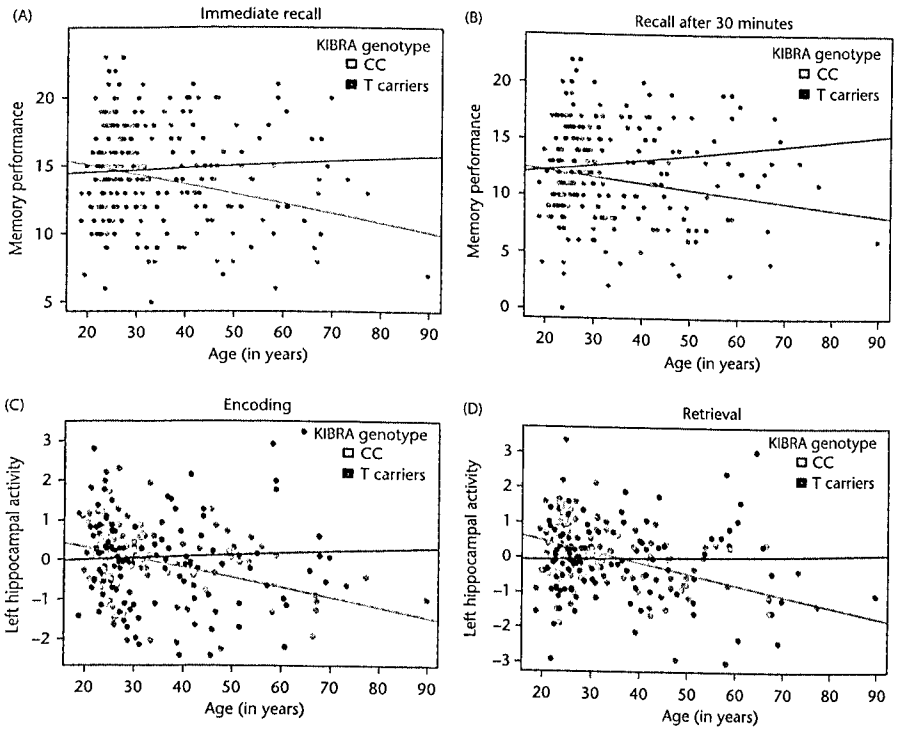


Figure 16.4 *KIBRA* genotype groups show different correlations between increasing age and performance on (A) immediate and (B) 30-minute delayed recall of a story, as measured with the Wechsler Memory Scale. (c, d) *KIBRA* genotype group differences in the correlation between age and brain activation 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. Reprinted from Papenberg et al. (2015) with permission from Elsevier. (See color plate also)

with higher synaptic DA levels) showed overall higher recall accuracy. The genetic main effects and the gene–gene interaction were again larger in older than in younger adults. Similarly, age magnification of the effects of two other dopamine-related polymorphisms, namely *COMT* and the dopamine betahydroxylase (*DBH*; C-1021T; rs1611115), were observed on working memory (Greenwood et al., 2014), with older adults with lowest synaptic dopamine performing worst. As both the dopaminergic and glutamatergic systems modulate episodic memory consolidation, one study investigated whether *DRD2* and a variation of the N-methyl-D-aspartate 3A (*NR3A*; rs10989591) gene, coding for the NR3A subunit of the glutamate N-methyl-D-aspartate (NMDA) receptor, interactively modulate episodic memory (Papenberg et al., 2014b). The gene–gene interaction was observed in older adults only, with individuals

carrying genotypes associated with greater D2 and NMDA receptor efficacy showing the highest episodic memory performance. In another study, genetic predispositions for DA-relevant genes affecting DAT expression and D2-like receptors (i.e., D2 and D3) were aggregated into a composite gene score (Papenberg et al., 2013a). Older adults carrying more beneficial alleles showed an episodic memory advantage, this time in terms of less forgetting after 1 week. No genetic effects were observed in younger adults. Recently, additive adverse effects of *COMT* Val/Val, *BDNF* Any Met, and age have been reported on executive functioning in middle-aged and older adults (53–95 years), indicating that older adults with a high-risk combination performed worse. The effects were further intensified by the presence of the *APOE* e4 allele (Sapkota et al., 2014). In addition, a genome-wide association study demonstrated effects of *APOE* (rs769449) on rate of cognitive decline (Zhang and Pierce, 2014), thereby supporting the magnification notion.

With respect to fMRI studies, the TaqIA polymorphism of the dopamine D2 receptor (*DRD2*)/ANKK1 gene (rs1800497) has been related to striatal dopamine receptors, with A1 allele carriers having reduced density of D2 receptors (Jonsson et al., 1999). Persson and colleagues (2014) showed lower performance in long-term memory updating among older A1 carriers compared to non-carriers. In addition, older A1-carriers had less BOLD activation in left caudate nucleus, a region critical to updating. None of these effects were present in younger adults. Ebner and colleagues (2013) investigated the association of the oxytocin receptor (*OXTR*, rs237887) polymorphism, previously associated with susceptibility to prosocial behavior, to face recognition and BOLD activity in younger and older adults. Results showed that *OXTR* modulated activity in anterior cingulate cortex of older adults only. Specifically, higher brain activity, indicating more affective processing of happy compared to angry faces, were observed for older A homozygotes compared to Any G carriers. Behaviorally, this was reflected in faster response times in identifying happy faces for older A homozygotes. Further, an electroencephalography study examined the association between the AD-related clusterin (*CLU*; rs11136000) polymorphism and resting-state alpha-rhythm activity in healthy non-carriers of the *APOE* e4 allele (Ponomareva et al., 2013). *CLU* modulated alpha activity only in older adults (50–80 years), with no genetic effects in younger adults (20–50 years). Imaging studies investigating additive or interactive genetic effects in old age are rare. However, data suggest that considering more than one polymorphism may help explain more variance in brain activity. For instance, Kauppi and colleagues (2014) demonstrated that MTL activity during episodic encoding decreased as a function of number of *APOE* e4 and *BDNF* Met alleles (none, one, or both), yielding stronger effects than those of the individual genes.

## Factors Affecting Age Magnification of Genetic Effects

Despite increasing evidence in favor of the resource-magnification model, the available evidence is not unequivocal. Other than the gene–gene interactions reported above, there are several reasons for this fact. Whereas most age-comparative studies include carefully selected convenience samples, use of population-based samples likely introduces many lifestyle and individual-difference factors that may wash

out genetic effects. For example, in a large-scale population-based study, Laukka and colleagues (2013) reported relationships of *APOE* to episodic memory, perceptual speed, and global cognition. However, no associations were found for *COMT, BDNF*, or *KIBRA*. Similarly, some authors have argued that higher BOLD activity may reflect pathological processes associated with a disadvantageous genotype, which may overshadow genetic effects in older age (e.g., Kauppi et al., 2011), or lead to inconsistent results across studies. Indeed, most available 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 more than 10 years before clinical diagnosis (Thorvaldsson et al., 2011). The resource-modulation hypothesis holds that genetic effects become weaker when individuals approach dementia or terminal decline. For instance, *APOE* genotype does not modify rate of decline in AD after the clinical diagnosis has been made (e.g., Corder et al., 1995), and even progression from the preclinical stage to clinically verified AD is indistinguishable for carriers and non-carriers of the e4 allele (e.g., Bunce et al., 2004). Thus, including preclinical dementia cases may make it difficult to observe already small effects of various genetic polymorphisms (Figure 16.1). However, the prediction of the resource-modulation hypothesis that genetic effects become weaker once individuals approach the preclinical stage of dementia and eventually dementia diagnosis has still not been extensively tested.

Research further suggests that once additional factors are taken into account, it may be easier to disclose genetic effects in old age. Lifestyle factors, such as physical activity, may modulate genetic effects on brain and cognition. It has been suggested that the evolution of physical activity approximately 2 million years ago resulted in the reduction of amyloid plaques and vascular burden associated with the *APOE* e4 genotype, relaxing genetic constraints on aging (Raichlen and Alexander, 2014). Indeed, increased physical exercise changes levels of DNA methylation and gene expression in human adipose tissue, supporting metabolic changes through epigenetic modifications (Rönn et al., 2013). So far, 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 posterior temporal and parietal regions during an episodic memory task than non-carriers or those with lower physical activity levels. These data suggest that physical activity may circumvent the negative effects of carrying a disadvantageous genotype on brain functioning (see also Erickson et al., 2013; Ferencz et al., 2014). Similar to lifestyle factors, behavior-genetic studies indicate that different diseases may lower resources and make it easier to disclose genetic effects. For instance, interactive effects of *KIBRA* and the calsyntenin 2 (*CLSTN2;* rs6439886) polymorphism have been observed for episodic memory in older adults with depression, with individuals carrying both risk alleles (*KIBRA* CC and *CLSTN2* TT) performing the worst (Pantzar et al., 2014). However, no genetic effects were observed in non-depressed individuals, suggesting that genetic effects are most easily detected at suboptimal levels of brain integrity. Similarly, *COMT* Any Val carriers treated with chemotherapy performed worse on tests of attention than healthy controls with the same genotype, but no history of breast cancer (Small et al., 2011). Relatedly, an imaging study reported stronger effects of *COMT* in populations with reduced brain

resources (Ceaser et al., 2013) compared to healthy controls. Specifically, patients with schizophrenia and their siblings, but not healthy controls, who were Val homozygotes displayed greater activity in frontal regions, striatum, and cerebellum during a working memory task, presumably reflecting inefficient processing.

Thus, taking into account different lifestyle and disease-related factors may further elucidate the heterogeneity in brain and cognitive aging. Importantly, most studies reviewed in this chapter do not report data from middle-aged adults. This calls for large-scale longitudinal studies covering the whole lifespan to better understand the temporal dynamics of genetic influences on brain functioning and behavior, including their interactions with lifestyle factors and different diseases. Longitudinal studies that seek to address epigenetic mechanisms (e.g., Sweatt, 2013) may help to close the gap between heritability estimates derived from behavior-genetic data and the small amounts of variance predicted by common genetic variation related to individual polymorphisms (Turkheimer, 2011). Given that common genetic variations may affect both brain structure and function, multimodal imaging studies are imperative to uncover genetic and epigenetic effects on individual differences in the aging of brain and behavior.

## Conclusion

Increasing evidence at behavioral and neural levels of analysis suggests that effects of common genetic variations on behavior and brain become stronger in late life, supporting the resource-modulation hypothesis. Similar patterns have been reported in other populations characterized by reduced brain resources, by contrasting samples with different diseases and healthy controls. So far, the bulk of studies are cross-sectional. In particular, longitudinal structural and functional imaging studies are needed to confirm the patterns reported in the cross-sectional imaging data. Furthermore, some of the inconsistent patterns likely stem from gene–gene interactions, and from environmental and lifestyle factors that result in epigenetic differences. Behavioral, structural, and functional imaging studies are needed that consider the operation of these factors during the transition from early to late adulthood.

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