Neuropsychol Rev (2015) 25:47–62
DOI 10.1007/s11065-015-9279-8

REVIEW

Genetics and Functional Imaging: Effects of *APOE*, *BDNF*, *COMT*, and *KIBRA* in Aging

Goran Papenberg · Alireza Salami · Jonas Persson · Ulman Lindenberger · Lars Bäckman

Received: 17 September 2014 / Accepted: 20 January 2015 / Published online: 10 February 2015

Abstract Increasing evidence from cross-sectional and longitudinal molecular-genetic studies suggests that effects of common genetic variations on cognitive functioning increase with aging. We review the influence of candidate genes on brain functioning in old age, focusing on four genetic variations that have been extensively investigated: *APOE*, *BDNF*, *COMT*, and *KIBRA*. Similar to the behavioral evidence, there are reports from age-comparative studies documenting stronger genetic effects on measures of brain functioning in older adults compared to younger adults. This pattern suggests disproportionate impairments of neural processing among older individuals carrying disadvantageous genotypes. We discuss various factors, including gene-gene interactions, study population characteristics, lifestyle factors, and diseases, that need to be considered in future studies and may help understand inconsistent findings in the extant literature.

Keywords Aging · Functional brain imaging · Cognition · Genetics · *APOE* · *BDNF* · *COMT* · *KIBRA*

G. Papenberg (✉) · A. Salami · J. Persson · L. Bäckman
Aging Research Center, Karolinska Institutet and Stockholm University, Gävlegatan 16, 113 30 Stockholm, Sweden
e-mail: goran.papenberg@ki.se

G. Papenberg · U. Lindenberger
Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany

A. Salami
Integrative Medical Biology (Physiology) and Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden

U. Lindenberger
Max Planck University College London Centre of Computational Psychiatry and Ageing Research, London, UK

Introduction

Cognitive decline is commonly observed during the normal aging process (e.g., de Frias et al. 2007; Rönnlund et al. 2005; Schaie et al. 1998). Regardless of age, there are large differences among individuals in various cognitive functions, which may increase from early to late adulthood (de Frias et al. 2007; Lindenberger and Ghisletta 2009). Functional imaging techniques reveal that alongside these individual differences in cognitive functioning, there are also large individual differences in neural processing as people get older (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). The current review focuses on functional imaging and genetics in aging, and thus primarily targets studies that investigate effects of candidate genes on brain functioning in relatively healthy older adults using functional magnetic resonance imaging (fMRI).

The purpose of the review is to give a broad overview of the increasing evidence from behavioral and functional imaging studies that support the resource-modulation hypothesis. We first introduce this hypotheses initially proffered by Lindenberger et al. (2008), which posits that effects of common genetic variations on brain and behavior may become stronger in older age. In the following sections, we will briefly introduce the candidate-gene approach and review effects of select candidate genes on brain and behavior in old age, and establish the extent to which the available data support the resource-modulation hypothesis.

We focus on four candidate that have attracted considerable attention in the cognitive neuroscience of aging literature in the past decade: 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. The narrow perspective of the review stems from the fact that functional imaging studies investigating the effects of other genetic variations relevant for cognitive aging (e.g., IL-1beta, MTHFR, IL-6, TOMM-40) are largely missing. Common genetic variations may influence brain functioning through effects on brain structure. Therefore, we briefly highlight evidence documenting age-magnified effects of candidate genes on brain structure.

Finally, given mixed results regarding the replication of effects of candidate genes and the fact that most genes account for less than 1 % of the variance in cognition (Deary et al. 2010), we will highlight 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 by Lindenberger and colleagues assumes that losses in neurochemical (Bäckman et al. 2006, 2010) and anatomical (Raz et al. 2005, 2008) brain resources in aging modulate the effects of common genetic variations on cognitive functioning (see Fig. 1): Whereas genetic effects in younger adults may be small or undetectable, 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. In other words, 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 found that one third of individual differences in global cognition changes in late adulthood are attributable to genetic influences. The model depicted in Fig. 1 also predicts that genetic effects will diminish once individuals reach very low resource levels, as in terminal decline or dementia. In line with this notion, one study showed that genetic contributions to different aspect of memory are lower for individuals with Alzheimer's disease (AD) and unaffected family members than for unaffected family members alone (Wilson et al. 2011).

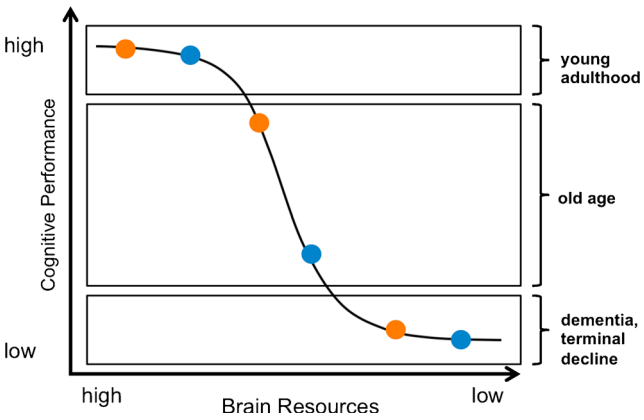

Fig. 1 The resource modulation hypothesis predicts magnified genetic effects on cognitive performance in old age. With healthy aging associated with decline in chemical and structural brain resources, constant amounts of genetic variation translate into increasingly larger performance differences. With resources further depleted, genetic effects are expected to diminish. The *colored circles* represent two individuals with different genetic predispositions as they move from early adulthood through old age to dementia and terminal decline. Adapted from Lindenberger et al. (2008)

Given that brain functioning is an intermediate phenotype for behavior (Harris and Deary 2011), it has been argued that neural indicators are more sensitive to genetic effects than behavioral measures (e.g., Rasch et al. 2010). Unfortunately, the interpretation of fMRI signals is not straightforward, as a higher blood-oxygen-level-dependent (BOLD) signal can actually indicate better or worse neural functioning without the existence of behavioral differences. On the one hand, higher brain activation may reflect less efficient neural processing in order to achieve the same behavioral outcomes, which is typically observed during less demanding cognitive tasks (e.g., Papassotiropoulos et al. 2006; Sambataro et al. 2010). However, the inefficiency argument may not apply in certain circumstances, such as performance differences between allelic groupings in more demanding offline tasks that are more suitable to reveal genetic differences (e.g., Muse et al. 2014). For example, Muse and colleagues documented higher hippocampal activation during a recognition memory task, but better immediate and delayed recall performance outside the scanner for a particular genotype. In these cases, evidence of genetic effects with fMRI 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 that may 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 indicate 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 exhibited more

pronounced decline in their clinical and neurological status, although there were no significant differences in baseline memory performance between individuals with more or less 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. In light of ambiguous findings, it is essential to consider information about the molecular mechanisms of candidate genes for the interpretation of findings from fMRI studies.

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 (Green et al. 2008; 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 sections, we will review associations between four extensively investigated candidate genes and neural functioning in adulthood and aging.

APOE Polymorphism

Apolipoprotein E (APOE) is a low-density lipoprotein that is involved in many steps of lipid homeostasis and injury repair in the brain (e.g., Liu et al. 2013; Mahley et al. 2009). Furthermore, APOE affects immune responses, inflammation, oxidative stress, as well as smooth muscle proliferation and migration (Getz and Reardon 2009). There are three alleles of *APOE*, as defined by the two single-nucleotide polymorphisms (SNPs), rs429358 and rs7412: ε2, ε3, and ε4, of which the ε3 and ε2 alleles are the most and least common, respectively.

The ε4 allele is the strongest genetic risk factor for AD, such that the presence of one or two ε4 alleles is associated with higher risk of developing AD in a dose-dependent manner (Blacker et al. 1997; Farrer et al. 1997; Okuizumi et al. 1995). The ε4 allele is also related to increased risk for mild cognitive impairment (MCI; Boyle et al. 2010) and accelerated cognitive decline during normal aging (Bretsky et al. 2003; Dik et al. 2000; Smith 2002). In line with earlier meta-analytic findings (Small et al. 2004), a recent meta-analysis showed that the ε4 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 ε4 in persons older than 50 years than in those below 50 years (Liu et al. 2010). Similarly, in older adults aged 79 years, the ε4 allele was associated with more rapid decline in verbal memory and abstract reasoning across 8 years (Schiepers et al. 2012). Importantly, one study showed that the relationship of *APOE* to episodic memory and global cognition was attenuated, after exclusion of future dementia cases (Laukka et al. 2013). This suggests that dementia-related processes may contribute to the link between *APOE* and cognition in old age. Indeed, the *APOE* ε4 allele has been associated with conversion to dementia in individuals with MCI (for review, see Modrego 2006). However, *APOE* does not always predict progression from the preclinical stage to AD (Bäckman et al. 2003; Bunce et al. 2004) and does not modulate rate of cognitive decline once individuals have been diagnoses with AD (e.g., Corder et al. 1995; Growdon et al. 1996), in line with the lower end of the function illustrating the resource-modulation hypothesis (see Fig. 1).

Although behavioral data suggest that negative effects of the ε4 allele may increase with age, there is a lack of corresponding longitudinal data and available cross-sectional findings are inconsistent or do not report age-comparative data. Here, we focus on fMRI studies in cognitively normal young, middle-aged, and older adults that investigate neural correlates of episodic memory, the cognitive domain most severely affected by AD. Given that this research has involved different birth cohorts, we review the relevant studies separately beginning with the youngest age groups.

In young adults, one study reported better episodic memory performance in ε4 carriers compared with non-carriers in a face-profession task, accompanied by a decreased BOLD response in ε4 carriers for a widespread network encompassing the medial temporal lobe (MTL), the temporal cortex, and fronto-parietal regions (Mondadori et al. 2007). Thus, this study suggests better memory and neural efficiency in young ε4 carriers. However, a recent meta-analysis did not find any support for these patterns (Ihle et al. 2012). Also, two other fMRI studies reported increased BOLD responses in the MTL in ε4 carriers relative to non-carriers during scene and visual object encoding tasks, in the absence of performance differences (Dennis et al. 2010; Filippini et al. 2009). The authors speculated that increased MTL activation in ε4 carriers might reflect functional weakness or a hyperactive process that is non-adaptive. Overall, allelic differences in BOLD response in such an early stage of adulthood suggest that the ε4 allele modulates brain function decades before clinical and neurophysiological manifestation of AD.

Five studies included subjects with an average age between 50 and 60 years. One study demonstrated equivalent episodic 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* ε4 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), a network known to be severely affected in MCI and AD. Examining face-name and line-drawing encoding, two other studies reported decreased BOLD activity in left MTL, a critical node of the DMN, in ε4 carriers relative to non-carriers (Fleisher et al. 2009a; Trivedi et al. 2006). Using an identical task, Fleisher and colleagues also reported no BOLD differences between ε4 carriers and non-carriers during encoding (Fleisher et al. 2009b). Instead, encoding-associated deactivations were greater in magnitude among non-ε4 carriers in medial and right lateral parietal cortex. Similar to the findings from Xu et al. (2009), these studies documented functional alterations of DMN areas in ε4 carriers compared to non-carriers. These areas are highly interconnected and belong to critical nodes of the DMN, involved in episodic memory (for review, see Buckner et al. 2008; Ward et al. 2014). Finally, one study with a large number of participants (n=132) reported no BOLD differences between ε4 carriers and non-carriers during encoding of line drawings (Johnson et al. 2006). However, considering first-degree family history of dementia, results indicated that ε4 carriers with and without family history exhibited the least and the greatest signal change in MTL, respectively. Thus, family history may modulate the effect of *APOE* in middle-aged adults, suggesting that other genetic factors and possibly non-genetic risk associated with AD may exacerbate the negative effects of *APOE* ε4 on functional brain measures (e.g., Donix et al. 2012).

Five fMRI studies targeting *APOE* included subjects with a mean age between 60 and 70 years. Two studies reported equivalent task performance between genotypes, accompanied by increased BOLD activation in left MTL and in parietal and prefrontal regions for ε4 carriers during encoding and recall of auditorily presented word pairs and for encoding of visual word pairs (Bookheimer et al. 2000; Fleisher et al. 2005). Using longitudinal assessment over 2 years, Bookheimer and colleagues further showed that the degree of baseline brain activation was linked to the degree of memory decline. The authors suggested a compensatory mechanism such that subjects at genetic risk for AD (i.e., ε4 carriers) had to invest greater cognitive effort to achieve the same performance level as subjects who are not at 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 loss of hippocampal activation over 2 years during a face-name associative memory task. Indeed, employing incidental word encoding and an associative memory task, two other studies demonstrated decreased activity in right MTL for ε4 carriers relative to non-carriers despite similar performance levels (Kauppi et al. 2014; Lind et al. 2006). Lower brain activations in MTL were interpreted as an early sign of hippocampal pathology for individuals at risk for AD.

One study included participants aged 54–73 years and also found less activation in the hippocampus proper for cognitively normal *APOE* ε4 carriers than non-carriers during encoding of a perspective-dependent spatial learning task (Adamson et al. 2011). However, in another study with a large number of participants (n=185), Bassett et al. (2006) failed to find BOLD differences between ε4 carriers and non-carriers during a paired-associate memory task.

Finally, three studies on this topic included participants with an average age between 70 and 80 years. One study found that posteromedial and ventral anterior cingulate cortices, both key regions of the DMN, as well as right middle and inferior prefrontal regions demonstrated reduced task-induced deactivation (during episodic encoding) for ε4 carriers relative to non-carriers (Pihlajamaki et al. 2010). Interestingly, reduced posteromedial deactivation was associated with worse delayed recall. The authors suggested that altered activation of the DMN might be an early indicator of emerging AD. In another study, Han and colleagues found that ε4 carriers displayed greater activation than non-carriers in right MTL, right temporal cortex, right fronto-parietal regions, right occipital cortex and cerebellum for previously encoded word pairs relative to fixation (Han et al. 2007). Elevated BOLD responses for ε4 carriers occurred in the absence of behavioral differences, suggesting a potential compensatory mechanism for ε4 carriers. Similarly, Bondi et al. 2005 showed equivalent memory accuracy accompanied by greater BOLD signal in non-demented older ε4 carriers compared to their ε3 counterparts during learning of new pictures (Bondi et al. 2005). Regions with elevated activations for ε4 carriers included right MTL, bilateral temporal cortex, left fronto-parietal cortex, and left cerebellum. Consistent with a compensatory account, the authors suggested that older adults at genetic risk for AD require additional cognitive effort to achieve normal episodic memory performance.

So far, only two studies investigated the effect of *APOE* genotype on brain function across the adult lifespan. Using a memory encoding task in younger and older individuals, Filippini and colleagues (2011) showed a significant interaction between age and ε4 status in MTL, frontal pole, subcortical nuclei, middle temporal gyrus, and cerebellum, such that aging was associated with decreased activity among ε4 carriers and increased activity in non-carriers, despite preserved

grey matter volume. They also reported generally reduced cerebral blood flow for older ε4 carriers relative to non-carriers, which could partly account for decreased activity in individuals at genetic risk for AD. Data from a life-span study (n=133) suggest an opposite pattern for hippocampal activations in older adults (Nichols et al. 2012). These investigators found decreased hippocampal activity during encoding and retrieval of neutral images with increasing age. In addition, these decreases were stronger for ε2 and ε3 than for ε4 carriers. Given that fMRI task performance was unrelated to age and genotype, the increased BOLD activity for older ε4 carriers may suggest compensatory mechanisms. These two studies provide evidence in line with the resource-modulation hypothesis, although they document opposing effects on neural functioning in older age. With respect to imaging markers of brain structure, interactive effects between age and *APOE* on white-matter microstructure have not been reported (e.g., Heise et al. 2012; Nyberg and Salami 2014; Westlye et al. 2012). In contrast, longitudinal studies have shown more hippocampal atrophy for ε4 homozygotes (e.g., Crivello et al. 2010) and heterozygotes (Cohen et al. 2001; for a thorough review see topic on genetics and brain morphology of the special issue) that may to some extent account for the effects of *APOE* on functional brain activations in some studies.

Taken together, *APOE* status appears to be associated with functional alterations in regions related to AD before behavioral differences can be detected. Overall, however, the findings are inconsistent in terms of location and direction of the effect associated with *APOE* ε4. Most regions that exhibited such alterations map onto the DMN (Raichle et al. 2001), a network involved in episodic memory functioning (Vincent et al. 2006), but which is typically suppressed during performance of most other cognitively demanding tasks (Buckner et al. 2008). Alterations in DMN activation in older individuals at genetic risk for AD may reflect changes in proteolytic processes in the brain, such as amyloid deposition (Buckner et al. 2005). Elevated BOLD activations in ε4 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 activations in ε4 carriers, assumed to reflect pathological disruption (Kauppi et al. 2014; Lind et al. 2006; Pihlajamaki et al. 2010; Xu et al. 2009). Given the strong association of *APOE* ε4 with AD, older ε4 carriers may be subject to positive selection processes in some studies contributing to the inconsistent findings across fMRI studies. To some extent, differences in task difficulty may also account for inconsistent findings. It is generally assumed that older adults at higher risk for cognitive decline may show higher brain activations at lower cognitive loads than individuals at lower risk, with increasing load, however, the pattern may be exactly reversed (Grady 2012). Further, as noted above, longitudinal imaging evidence suggests decreases in hippocampal activations for individuals with higher cognitive declines, despite over-recruitment at baseline (O'Brien et al. 2010). Thus, possibly higher task-related brain activations in ε4 carriers may reflect initial compensatory attempts, which with advancing age and further age-related declines in brain resources may become less efficient, resulting in lower brain activations.

BDNF Polymorphism

The brain-derived neurotrophic factor (BDNF) promotes activity-dependent synaptic plasticity and is critical for learning and memory (Binder and Scharfman 2004; Lu 2003). BNDF belongs to the neurotrophin family of growth factors and is required for the survival, differentiation, and maintenance of a variety of central nervous system neurons. It is expressed in the whole brain, in particular the hippocampus. In animal studies, BDNF has been associated with hippocampal-dependent learning and memory (for a review, see Tyler et al. 2002). BDNF is a critical factor for the formation of long-term potentiation (LTP) associated with memory. Indeed, knockout- mouse experiments demonstrate that adult mice lacking BDNF exhibit hippocampal-dependent learning deficits (Monteggia et al. 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 the *BDNF* polymorphism in old age for episodic memory (Li et al. 2010), with older Val homozygotes performing better on backward serial recall. Also in line with the resource modulation hypothesis, longitudinal data demonstrate exacerbated decline in perceptual speed across 13 years among *BDNF* Met carriers (Ghisletta et al. 2014), 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; Hariri et al. 2003; for meta-analysis, see Kambeitz et al. 2012) and during performance of a virtual navigation task (Banner et al. 2011). However, note that others have failed to find effects of *BDNF* on hippocampal activations during encoding and retrieval of episodic information in young and middle-aged adults (Dodds et al. 2013). Whereas Hariri et al. (2003) found

BDNF-related differences in episodic memory performance 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 life-span 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 (Fig. 2). 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 measures of brain functioning 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 other 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 (Sanchez et al. 2011) and white-matter microstructure (Kennedy et al. 2009). Specifically, Met carriers had lower hippocampal volumes than Val homozygotes after age 65, whereas no such differences were apparent before 65 years (Sanchez et al. 2011). 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), as measured with diffusion tensor imaging, were 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).

Taken together, increasing 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 (Matsumoto et al. 2003; Tunbridge et al. 2006, 2007). 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.

A number of studies with young adults have demonstrated a *COMT* Met advantage in executive functions and memory performance compared to Val homozygotes (for review, see

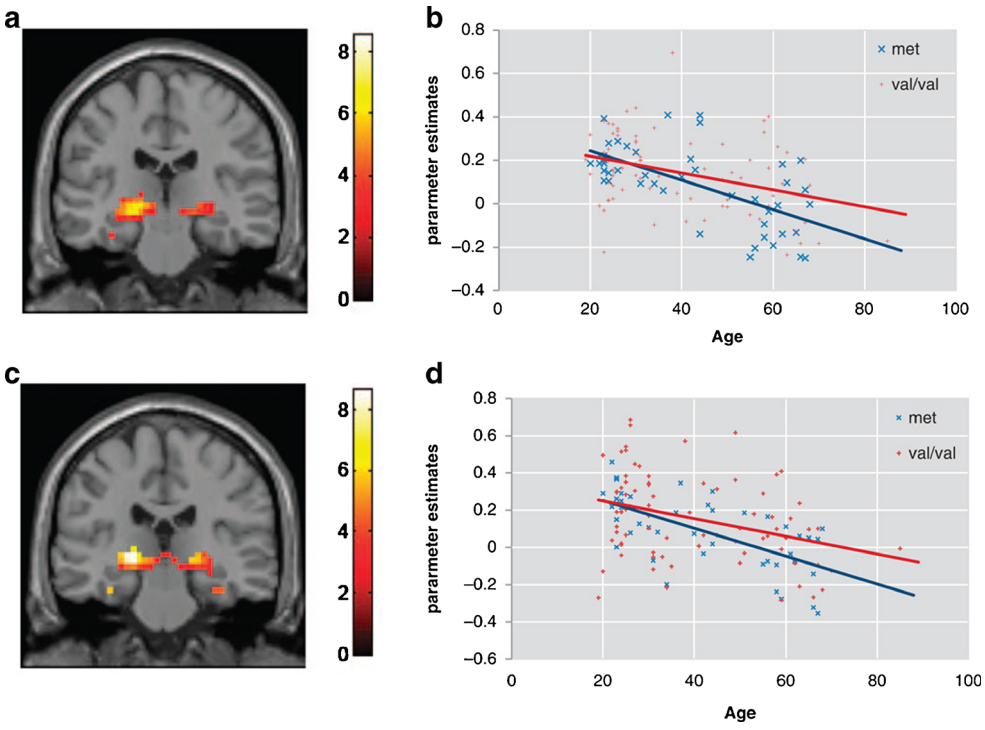

Fig. 2 Effect of *BDNF* polymorphism on age-related decline in hippocampal activation during a simple declarative memory task. Met-allele carriers (n=45) show a steeper negative correlation between age and hippocampal activity during encoding (b) and retrieval (d) phases of the task relative to Val/Val individuals (n=80). Scatterplots show relationship between parameter estimates of the BOLD (blood–oxygen-level dependent) response (measured in arbitrary units) in the left-hippocampus during encoding (b) and retrieval phase (d) and age (in years) for each *BDNF* genotype group. Adapted from Sambataro et al. (2010)

Witte and Flöel 2012). 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 (Blanchard et al. 2011; Bolton et al. 2010; 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, 2008).

Although the effect of the *COMT* Val158Met polymorphism 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. 2013). 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). Furthermore, the *COMT* polymorphism affected the link between episodic and working memory in older, but not in younger, persons (Papenberg et al. 2013), with Val homozygotes having lower performance outcomes. Most importantly, longitudinal data reveal less decline of executive function over a 5-year interval (de Frias et al. 2005) and less episodic-memory decline across 15 years (Josefsson et al. 2012) for *COMT* Met carriers than for Val homozygotes.

Both older age and *COMT* Val status have been associated with altered fronto-striatal dopamine functioning (Klostermann et al. 2012; Slifstein et al. 2008; Volkow 2000) 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 et al. (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., Cappell et al. 2006; 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 et al. (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. 2014b). 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 interacts with proteins involved in 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 et al. (2008) showed that 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

Fig. 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. Papassotiropoulos et al. (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 suggested an advantageous effect of the T-allele on immediate free recall, which increased 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 relatively younger elderly persons (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 may have increased hippocampal activation associated with pathological aging that overshadow the genetic effects. Another lifespan study reported (n=232) 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 min) free recall. In contrast, there were no behavioral differences between genotypes or interactions between age and genotype for the recognition memory task during scanning. However,

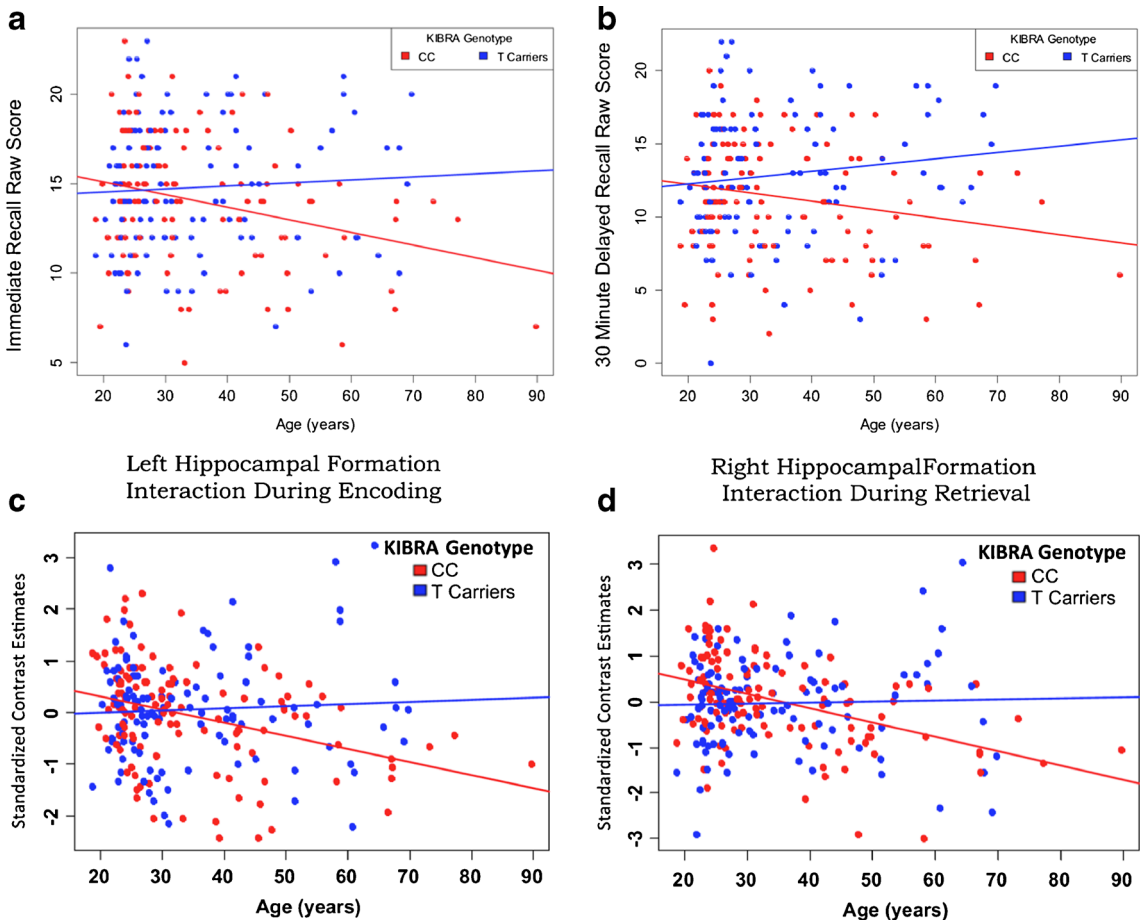

Fig. 3 *KIBRA* genotype groups have significantly different correlations between increasing age and performance on immediate (**a**) and delayed recall (**b**). Raw scores were computed by summing the number of correct responses for each individual. **c**, **d** *KIBRA* genotype group differences in 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 left hippocampal formation neuronal activity during the encoding session, which is not observed for the T allele carrier group (*blue*). The *KIBRA* CC group exhibits a negative correlation between age and right hippocampal formation neuronal activity during the retrieval session, which is not observed for the T allele carrier group. Similar differences between *KIBRA* groups in the relationship between increasing age and episodic memory related activity during retrieval session were also observed in the left hippocampal formation (data not shown). Adapted from Muse et al. (2014)

older, but not younger, C homozygotes had lower hippocampal activation during encoding and retrieval, suggesting stronger genetic effects in advanced age (see Fig. 3c and 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 (see Fig. 3a and b), performed outside the scanner.

Miscellaneous Genes

In this review, we focused on a few of the most extensively investigated polymorphisms, which is due to the fact that functional imaging studies involving other age-relevant polymorphisms are still missing. However, it should be noted that several fMRI studies targeting other polymorphisms have shown similar patterns, documenting magnification of genetic effects on functional brain activity in aging. For instance, 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 et al. (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 et al. (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* ε4 allele (Ponomareva et al. 2013). The *CLU* CC risk variant was associated with an increase of alpha activity only in older adults (50–80 years), whereas there were no genetic effects in younger adults (20–50 years). Interestingly, MCI patients with hippocampal atrophy have also been characterized by an increased upper alpha power (Moretti et al. 2012).

Factors Affecting Age Magnification of Genetic Effects

Taken together, the data reviewed above suggest that effects of common genetic variations on brain functioning may become stronger with increasing adult age, extending the support of the resource-modulation hypothesis to the neural level. Despite increasing evidence of the magnification of genetic effects in aging, the available evidence is not unequivocal. There are several reasons for this fact. First, the reviewed studies have all focused on SNPs. Previous behavioral and imaging studies have reported both gene-gene interactions (e.g., Das et al. 2014; Greenwood et al. 2014; Li et al. 2012; Papenberg et al. 2014a) and additive effects of different polymorphisms (e.g., Kauppi et al. 2014; Sapkota et al. 2014) on brain and behavior in older adults. For instance, Kauppi and colleagues demonstrated that MTL activity during episodic encoding decreased as a function of number of *APOE* ε4 and *BDNF* Met alleles (none, one, or both), yielding stronger effects than those of the individual genes (see Fig. 4).

Second, most genetic fMRI studies may have rather selected older samples. 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 et al. (2013) reported relationships of *APOE* to episodic memory, perceptual speed, and global cognition, with *APOE* ε4 carriers performing worse. 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. Thus, including preclinical dementia cases may make it difficult to observe already small effects of various genetic polymorphisms (see Fig. 1). However, this particular prediction of the resource modulation-hypothesis has still not been directly 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 reduction of amyloid plaques and vascular burden associated with the *APOE* ε4 genotype, relaxing genetic constraints on aging (Raichlen and Alexander 2014). Indeed, physical exercise affects levels of DNA methylation and gene expression in human adipose tissue, supporting metabolic changes through epigenetic

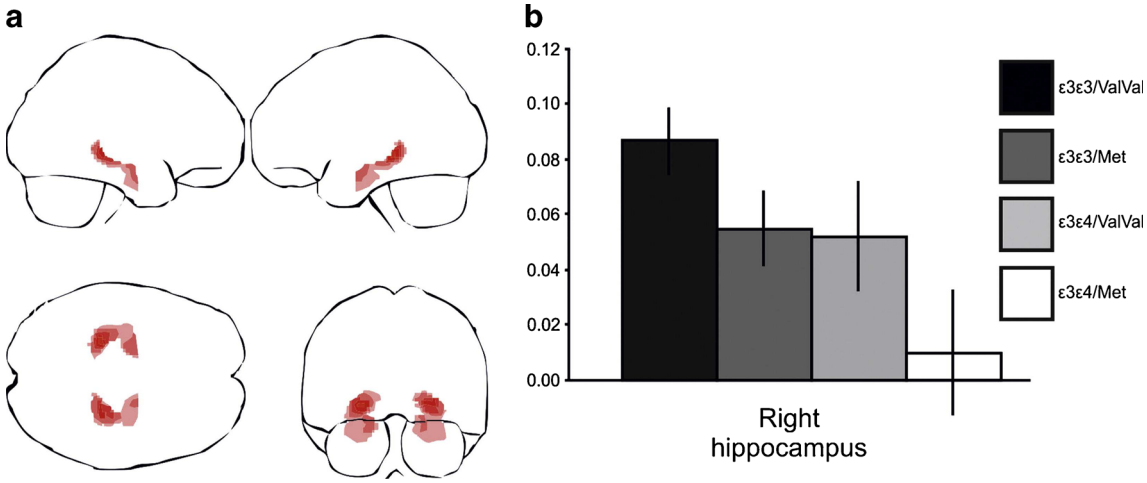

Fig. 4 **a** Main effect of Encoding > Baseline within the hippocampus mask across all participants. **b** Percent BOLD signal change from encoding to baseline across the right hippocampus cluster from (**a**). A significant negative relation between number of *APOE* ε4 and *BDNF* Met alleles (0,1, or 2) and the average BOLD signal change from encoding to baseline were seen across the right hippocampus cluster, and a similar trend was seen in the left hippocampus (data not shown). Adapted from Kauppi et al. (2014)

modifications (Ronn 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* ε4 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 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 functioning. Similarly, it has been reported that *COMT* Val carriers treated with chemotherapy performed worse on tests of attention than healthy controls with 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, the authors found that 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, reflecting inefficient processing.

Another source of variation that may contribute to inconsistent fMRI findings are differences in study designs. For instance, the majority of previous studies comparing BOLD activity during episodic memory tasks for ε4 carriers and non-carriers used a block design. However, the block design precludes a trial-by-trial comparison of the successfully encoded/remembered items. A previous study confirmed that BOLD differences between ε4 carrier and non-carriers during an episodic memory task differed depending on whether stimuli have been subsequently remembered or forgotten (Dennis et al. 2010). Dennis and colleagues showed that relative to non-carriers, ε4 carriers had elevated MTL activation during encoding of the subsequently remembered objects. In contrast, no BOLD difference in MTL was observed between the two genotypes for subsequently forgotten items.

Thus, taking into account different lifestyle factors and individual differences (e.g., diseases) may elucidate the heterogeneity in cognitive and brain aging. This calls for large-scale longitudinal studies in different cohorts 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 behavioral genetic data and the small amounts of variance predicted by common genetic variations related to individual SNPs (Turkheimer 2011). However, it is noteworthy that the small effects of common genetic polymorphisms still explain a large amount of phenotypic variance. A recent study has shown that SNP-based heritability estimates for working memory performance measures range between 31 and 41 %, indicating a substantial SNP-based heritability for this particular trait (Vogler et al. 2014). With respect to measures of fMRI, the SNP-based heritability for the response of facial expressions in adolescents has been estimated to be between 40 and 50 % (Dickie et al. 2014).

Common genetic variations may directly affect both brain structure and function. Alternatively, genetic variations may influence brain functioning through effects on brain structure. Therefore, multi-modal 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 suggest that effects of common genetic variations become stronger in late life, accounting for more between-person variance in older relative to younger adults. The available data extend the support for the resource-modulation hypothesis to the neural level, suggesting that genetic influences may be stronger when brain resources decrease with aging. Similar patterns have been reported in other populations characterized by reduced brain resources, when investigators compare samples with different diseases and healthy controls. So far, the bulk of genetic functional brain-imaging studies are cross-sectional and only a few studies have collected data covering the adult lifespan. Longitudinal functional imaging studies are needed to confirm the patterns reported in the cross-sectional imaging data. Furthermore, some of the inconsistent patterns in the genetic imaging literature likely stem from gene-gene interactions, and from environmental and lifestyle factors that result in epigenetic differences. Structural and functional imaging studies that consider the operation of these factors during the transition from early to late adulthood are scarce at best.

Acknowledgments Preparation of this review was supported by grants from the Swedish Research Council, the Swedish Research Council for Health, Working Life, and Welfare, Swedish Brain Power, an Alexander von Humboldt Research Award, and a donation from the af Jochnick Foundation to Lars Bäckman.

References

Adamson, M. M., Benjamin Hutchinson, J., Shelton, A., Wagner, A. D., & Taylor, J. L. (2011). Reduced hippocampal activity during encoding in cognitively normal adults carrying the APOE ε4 allele. *Neuropsychologia, 49*(9), 2448–2455. doi:10.1016/j.neuropsychologia.2011.04.022.

Almeida, O. P., Schwab, S. G., Lautenschlager, N. T., Morar, B., Greenop, K. R., Flicker, L., & Wildenauer, D. (2008). KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. *Journal of Cellular and Molecular Medicine, 12*(5A), 1672–1676. doi:10.1111/j.1582-4934.2008.00229.x.

Bäckman, L., Jones, S., Small, B. J., Agüero-Torres, H., & Fratiglioni, L. (2003). Rate of cognitive decline in preclinical Alzheimer's disease: the role of comorbidity. *Journals of Gerontology. Series B, Psychological, 58*, 228–236. doi:10.1093/geronb/58.4.P228.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neuroscience and Biobehavioral Reviews, 30*(6), 791–807. doi:10.1016/j.neubiorev.2006.06.005.

Bäckman, L., Lindenberger, U., Li, S.-C., & Nyberg, L. (2010). Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. *Neuroscience & Biobehavioral Reviews, 34*(5), 670–677. doi:10.1016/j.neubiorev.2006.06.005.

Banner, H., Bhat, V., Etchamendy, N., Joober, R., & Bohbot, V. D. (2011). The brain-derived neurotrophic factor Val66Met polymorphism is associated with reduced functional magnetic resonance imaging activity in the hippocampus and increased use of caudate nucleus-dependent strategies in a human virtual navigation task. *European Journal of Neuroscience, 33*(5), 968–977. doi:10.1111/j.1460-9568.2010.07550.x.

Barnett, J. H., Jones, P. B., Robbins, T. W., & Müller, U. (2007). Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. *Molecular Psychiatry, 12*(5), 502–509.

Barnett, J. H., Scoriels, L., & Munafò, M. R. (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biological Psychiatry, 64*(2), 137–144. doi:10.1016/j.biopsych.2008.01.005.

Bassett, S. S., Yousem, D. M., Cristinzio, C., Kusevic, I., Yassa, M. A., Caffo, B. S., & Zeger, S. L. (2006). Familial risk for Alzheimer's disease alters fMRI activation patterns. *Brain: A Journal of Neurology, 129*(Pt 5), 1229–1239. doi:10.1093/brain/awl089.

Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth Factors, 22*(3), 123–131. doi:10.1080/08977190410001723308.

Blacker, D., Haines, J. L., Rodes, L., Terwedow, H., Go, R., Harrell, L. E., & Tanzi, R. E. (1997). ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. *Neurology, 48*, 139–147. doi:10.1212/WNL.48.1.139.

Blanchard, M. M., Chamberlain, S. R., Roiser, J., Robbins, T. W., & Müller, U. (2011). Effects of two dopamine-modulating genes (DAT1 9/10 and COMT Val/Met) on n-back working memory performance in healthy volunteers. *Psychological Medicine, 41*(3), 611–618. doi:10.1017/S003329171000098X.

Bolton, J. L., Marioni, R. E., Deary, I. J., Harris, S. E., Stewart, M. C., Murray, G. D., & Price, J. F. (2010). Association between polymorphisms of the dopamine receptor D2 and catechol-o-methyl transferase genes and cognitive function. *Behavioral Genetics, 40*(5), 630–638. doi:10.1007/s10519-010-9372-y.

Bondi, M. W., Houston, W. S., Eyler, L. T., & Brown, G. G. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology, 64*(3), 501–508. doi:10.1212/01.WNL.0000150885.00929.7E.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine, 343*(7), 450–456. doi:10.1056/NEJM200008173430701.

Boyle, P. A., Buchman, A. S., Wilson, R. S., Kelly, J. F., & Bennett, D. A. (2010). The APOE ε4 allele is associated with incident mild cognitive impairment among community-dwelling older persons. *Neuroepidemiology, 34*(1), 43–49. doi:10.1159/000256662.

Bretsky, P., Guralnik, J. M., Launer, L., Albert, M., & Seeman, T. E. (2003). The role of APOE- 4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Neurology, 60*(7), 1077–1081. doi:10.1212/01.wnl.0000055875.26908.24.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., & Mintun, M. A. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal*

of Neuroscience, 25(34), 7709–7717. doi:10.1523/JNEUROSCI.2177-05.2005.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1–38. doi:10.1196/annals.1440.011.

Bunce, D., Fratiglioni, L., Small, B. J., Winblad, B., & Bäckman, L. (2004). APOE and cognitive decline in preclinical Alzheimer's disease and non-demented aging. *Neurology, 63*, 816–821. doi:10.1212/01.WNL.0000137041.86153.42.

Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Li, S. C., Lindenberger, U., Backman, L., & Heekeren, H. R. (2011). Microstructure of frontoparietal connections predicts cortical responsivity and working memory performance. *Cerebral Cortex, 21*(10), 2261–2271. doi:10.1093/cercor/bhq293.

Cappell, K. A., Gmeindl, L., & Reuter-Lorenz, P. A. (2006). *Age differences in DLPFC recruitment during verbal working memory maintenance depend on memory load.* Paper presented at the Society for Neuroscience, Atlanta, GA.

Ceaser, A., Csernansky, J. G., & Barch, D. M. (2013). COMT influences on prefrontal and striatal blood oxygenation level-dependent responses during working memory among individuals with schizophrenia, their siblings, and healthy controls. *Cognitive Neuropsychiatry, 18*(4), 257–283. doi:10.1080/13546805.2012.698100.

Cohen, R. M., Small, C., Lalonde, F., Friz, J., & Sunderland, T. (2001). Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. *Neurology, 57*, 2223–e2228. doi:10.1212/WNL.57.12.2223.

Corder E. H., Saunders A. M., Strittmatter W. J., Schmechel D. E., Gaskell P. C., Rimmler J. B., … Haines J. L. (1995). Apolipoprotein E, survival in Alzheimer's disease patients, and the competing risks of death and Alzheimer's disease. *Neurology*, 45, 1323–1328. doi:10.1212/WNL.45.7.1323.

Crivello, F., Lemaitre, H., Dufouil, C., Grassiot, B., Delcroix, N., Tzourio-Mazoyer, N., Tzourio, C., & Mazoyer, B. (2010). Effects of ApoE-epsilon4 allele load and age on the rates of grey matter and hippocampal volumes loss in a longitudinal cohort of 1186 healthy elderly persons. *NeuroImage, 53*, 1064–e1069. doi:10.1016/j.neuroimage.2009.

Das, D., Tan, X., Bielak, A. A., Cherbuin, N., Easteal, S., & Anstey, K. J. (2014). Cognitive ability, intraindividual variability, and common genetic variants of catechol-O-methyltransferase and brain-derived neurotrophic factor: a longitudinal study in a population-based sample of older adults. *Psychology and Aging, 29*(2), 393–403. doi:10.1037/a0035702.

de Frias, C. M., Annerbrink, K., Westberg, L., Eriksson, E., Adolfsson, R., & Nilsson, L. G. (2005). Catechol O-methyltransferase Val158Met polymorphism is associated with cognitive performance in nondemented adults. *Journal of Cognitive Neuroscience, 17*(7), 1018–1025. doi:10.1162/0898929054475136.

de Frias, C. M., Lövdén, M., Lindenberger, U., & Nilsson, L.-G. (2007). Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. *Intelligence, 35*(4), 381–392. doi:10.1016/j.intell.2006.07.011.

Deary, I. J., Spinath, F. M., & Bates, T. C. (2006). Genetics of intelligence. *European Journal of Human Genetics, 14*, 690–700. doi:10.1038/sj.ejhg.5201588.

Deary, I. J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. *Nature Review Neuroscience, 11*(3), 201–211. doi:10.1038/nrn2793.

Dennis, N. A., Browndyke, J. N., Stokes, J., Need, A., Burke, J. R., Welsh-Bohmer, K. A., & Cabeza, R. (2010). Temporal lobe functional activity and connectivity in young adult APOE varepsilon4 carriers. *Alzheimers Dement, 6*, 303–311. doi:10.1016/j.jalz.2009.07.003.

Dickie, E. W., Tahmasebi, A., French, L., Kovacevic, N., Banaschewski, T., Barker, G. J., …, & Paus, T. (2014). Global genetic variations predict brain response to faces. *PLoS Genet*, *10*(8), e1004523. doi:10.1371/journal.pgen.1004523.

Dik, M. G., Deeg, D. J. H., Bouter, L. M., Corder, E. H., Kok, A., & Jonker, C. (2000). Stroke and Apolipoprotein E 4 are independent risk factors for cognitive decline: a population-based study. *Stroke, 31*(10), 2431–2436. doi:10.1161/01.str.31.10.2431.

Dodds, C. M., Henson, R. N., Suckling, J., Miskowiak, K. W., Ooi, C. Tait, R., …, Nathan, P. J. (2013). Effects of the BDNF Val66Met polymorphism and met allele load on declarative memory related neural networks. *PLoS One*, *8(11)*, e74133. doi:10.1371/journal.pone.0074133.eCollection2013.

Donix, M., Small, G. W., & Bookheimer, S. Y. (2012). Family history and APOE-4 genetic risk in Alzheimer's Disease. *Neuropsychology Review, 60*(1), 298–309. doi:10.1007/s11065-012-9193-2.

Ebner, N. C., Maura, G. M., Macdonald, K., Westberg, L., & Fischer, H. (2013). Oxytocin and socioemotional aging: current knowledge and future trends. *Frontiers in Human Neuroscience, 7*, 487. doi:10.3389/fnhum.2013.00487.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., & Weinberger, D. G. (2001). Effect of COMT $Val^{108/158}$ Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences in the U S A, 98*(12), 6917–6922. doi:10.1073/pnas.111134598.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., . . . Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*(2), 257–269. doi:10.1016/S0092-8674(03)00035-7.

Erickson, K. I., Banducci, S. E., Weinstein, A. M., Macdonald, A. W., Ferrell, R. E., Halder, I., & Manuck, S. B. (2013). The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance. *Psychological Science, 24*, 1770–1779. doi:10.1177/0956797613480367.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., & Van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA, 278*, 1349–1356. doi:10.1001/jama.1997.03550160069041.

Ferencz, B., Laukka, E. J., Welmer, A. K., Kalpouzos, G., Angleman, S., … Bäckman, L. (2014). The benefits of staying active in old age: physical activity counteracts the negative influence of PICALM, BIN1, and CLU risk alleles on episodic memory functioning. *Psychology Aging*, *29*(2), 440–449. doi:10.1037/a0035465.

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., Matthews, P. M., Beckmann, C. F., & Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 7209–7214. doi:10.1016/j.neuroimage.2010.08.009.

Filippini, N., Ebmeier, K. P., MacIntosh, B. J., Trachtenberg, A. J., Frisoni, G. B., Wilcock, G. K., & Mackay, C. E. (2011). Differential effects of the APOE genotype on brain function across the lifespan. *NeuroImage, 54*(1), 602–610. doi:10.1016/j.neuroimage.2010.08.009.

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2005). The longitudinal relationship between processing speed and cognitive ability: genetic and environmental influences. *Behavior Genetics, 35*, 535–549. doi:10.1007/s10519-005-3281-5.

Fleisher, A. S., Houston, W. S., Eyler, L. T., Frye, S., Jenkins, C., Thal, L. J., & Bondi, M. W. (2005). Identification of Alzheimer disease risk by functional magnetic resonance imaging. *Archives of Neurology, 62*, 1881–1888. doi:10.1001/archneur.62.12.1881.

Fleisher, A. S., Podraza, K. M., Bangen, K. J., Taylor, C., Sherzai, A., Sidhar, K., & Buxton, R. B. (2009a). Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. *Neurobiology of Aging, 30*(11), 1737–1748. doi:10.1016/j.neurobiolaging.2008.01.012.

Fleisher, A. S., Sherzai, A., Taylor, C., Langbaum, J. B., Chen, K., & Buxton, R. B. (2009b). Resting-state BOLD networks versus task-associated functional MRI for distinguishing Alzheimer's disease risk groups. *NeuroImage, 47*(4), 1678–1690. doi:10.1016/j.neuroimage.2009.06.021.

Getz, G. S., & Reardon, C. A. (2009). Apoprotein E as a lipid transport and signaling protein in the blood, liver, and artery wall. *Journal of Lipid Research, 50*(Suppl), S156–S161. doi:10.1194/jlr. R800058-JLR200.

Ghisletta, P., Bäckman, L., Bertram, L., Brandmaier, A. M., Gerstorf, D., Liu, T., & Lindenberger, U. (2014). The Val/Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene predicts decline in perceptual speed in older adults. *Psychology and Aging, 29*(2), 384–392. doi:10.1037/a0035201.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Review Neuroscience, 13*(7), 491–505. doi:10.1038/nrn3256.

Green, A. E., Munafo, M. R., DeYoung, C. G., Fossella, J. A., Fan, J., & Gray, J. R. (2008). Using genetic data in cognitive neuroscience: from growing pains to genuine insights. *Nature Review Neuroscience, 9*(9), 710–720. doi:10.1038/nrn2461.

Greenwood, P. M., Lin, M. K., Sundararajan, R., Fryxell, K. J., & Parasuraman, R. (2014). Healthy aging increases the cognitive effects of two genes that influence extracellular dopamine. *Psychology and Aging, 29*(2), 363–373. doi:10.1037/a0036109.

Growdon, J. H., Locascio, J. J., Corlin, S., Gomezsla, T., & Hyman, B. T. (1996). Apolipoprotein E genotype does not influence rates of cognitive decline in Alzheimer's disease. *Neurology, 47*, 444–448. doi:10.1212/WNL.47.2.444.

Han, S. D., Houston, W. S., Jak, A. J., Eyler, L. T., Nagel, B. J., Fleisher, A. S., & Bondi, M. W. (2007). Verbal paired-associate learning by APOE genotype in non-demented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiology of Aging, 28*(2), 238–247. doi:10.1016/j.neurobiolaging.2005.12.013.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *Journal of Neuroscience, 23*(17), 6690–6694. doi:23/17/6690.

Harris, S. E., & Deary, I. J. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Science, 15*(9), 388–394. doi:10.1016/j.tics.2011.07.004.

Hashimoto, R., Moriguchi, Y., Yamashita, F., Mori, T., Nemoto, K., Okada, T., & Ohnishi, T. (2008). Dose-dependent effect of the Val66Met polymorphism of the brain-derived neurotrophic factor gene on memory-related hippocampal activity. *Neuroscience Research, 61*(4), 360–367. doi:10.1016/j.neures.2008.04.003.

Heise, V., Filippini, N., Ebmeier, K. B., & Mackay, C. E. (2012). The APOE ε4 allele modulates brain white matter integrity in healthy adults. *Molecular Psychiatry, 16*, 908–916. doi:10.1038/mp.2010.90.

Ihle, A., Bunce, D., & Kliegel, M. (2012). APOE ε4 and cognitive function in early life: a meta-analysis. *Neuropsychology, 23*(3), 267–277. doi:10.1037/a0026769.

Ikeda, O., Murakami, M., Ino, H., Yamazaki, M., Koda, M., Nakayama, C., & Moriya, H. (2002). Effects of brain-derived neurotrophic factor (BDNF) on compression-induced spinal cord injury: BDNF attenuates down-regulation of superoxide dismutase expression and promotes up-regulation of myelin basic protein expression. *Journal of Neuropathology and Experimental Neurology, 61*(2), 142–153.

Johnson, S. C., Schmitz, T. W., Trivedi, M. A., Ries, M. L., Torgerson, B. M., Carlsson, C. M., & Sager, M. A. (2006). The influence of Alzheimer disease family history and apolipoprotein E epsilon4 on mesial temporal lobe activation. *Journal of Neuroscience, 26*(22), 6069–6076. doi:10.1523/JNEUROSCI.0959-06.2006.

Jonsson, E. G., Nothen, M. M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P., & Sedvall, G. C. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry, 4*(3), 290–296. doi:10.1038/sj.mp.4000532.

Josefsson, M., de Luna, X., Pudas, S., Nilsson, L. G., & Nyberg, L. (2012). Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *Journal of the American Geriatrics Society, 60*(12), 2308–2312. doi:10.1111/jgs.12000.

Kambeitz, J. P., Bhattacharyya, S., Kambeitz-Ilankovic, L. M., Valli, I., Collier, D. A., & McGuire, P. (2012). Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis. *Neuroscience and Biobehavioral Reviews, 36*(9), 2165–2177. doi:10.1016/j.neubiorev.2012.07.002.

Kauppi, K., Nilsson, L. G., Adolfsson, R., Eriksson, E., & Nyberg, L. (2011). KIBRA polymorphism is related to enhanced memory and elevated hippocampal processing. *Journal of Neuroscience, 31*(40), 14218–14222. doi:10.1523/JNEUROSCI.3292-11.2011.

Kauppi, K., Nilsson, L. G., Persson, J., & Nyberg, L. (2014). Additive genetic effect of APOE and BDNF on hippocampus activity. *NeuroImage, 89*, 306–313. doi:10.1016/j.neuroimage.2013.11.049.

Kennedy, K. M., Rodrigue, K. M., Land, S. J., & Raz, N. (2009). BDNF Val66Met polymorphism influences age differences in microstructure of the Corpus Callosum. *Frontiers in Human Neuroscience, 3*, 19. doi:10.3389/neuro.09.019.2009.

Klostermann, E. C., Braskie, M. N., Landau, S. M., O'Neil, J. P., & Jagust, W. J. (2012). Dopamine and frontostriatal networks in cognitive aging. *Neurobiology of Aging, 33*(3), e15–e24. doi:10.1016/j.neurobiolaging.2011.03.002.

Laukka, E. J., Lövdén, M., Herlitz, A., Karlsson, S., Ferencz, B., Pantzar, A., & Bäckman, L. (2013). Genetic effects on old-age cognitive functioning: a population-based study. *Psychology and Aging, 28*(1), 262–274. doi:10.1037/a0030829.

Li, S.-C., Chicherio, C., Nyberg, L., von Oertzen, T., Nagel, I. E., Papenberg, G., & Backman, L. (2010). Ebbinghaus revisited: influences of the BDNF Val66Met polymorphism on backward serial recall are modulated by human aging. *Journal of Cognitive Neuroscience, 22*(10), 2164–2173. doi:10.1162/jocn.2009.21374.

Li, S.-C., Papenberg, G., Nagel, I. E., Preuschhof, C., Schroder, J., Nietfeld, W., . . . Backman, L. (2012). Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory. *Neurobiology Aging*. doi:10.1016/j.neurobiolaging.2012.08.001.

Lim, Y. Y., Villemagne, V. L., Laws, S. M., Ames, D., Pietrzak, R. H., Ellis, K. A., . . . Group, Aibl Research. (2014). Effect of BDNF Val66Met on memory decline and hippocampal atrophy in prodromal Alzheimer's disease: a preliminary study. *PLoS One, 9*(1), e86498. doi:10.1371/journal.pone.0086498.

Lind, J., Persson, J., Ingvar, M., Larsson, A., Cruts, M., Van Broeckhoven, C., . . . Nyberg, L. (2006). Reduced functional brain activity response in cognitively intact apolipoprotein E epsilon4 carriers. *Brain: A Journal Of Neurology, 129*(Pt 5), 1240–1248. doi:10.1093/brain/awl054.

Lindenberger, U., & Ghisletta, P. (2009). Cognitive and sensory declines in old age: gauging the evidence for a common cause. *Psychology and Aging, 24*(1), 1–16. doi:10.1037/a0014986.

Lindenberger, U., Nagel, I. E., Chicherio, C., Li, S. C., Heekeren, H. R., & Bäckman, L. (2008). Age-related decline in brain resources modulates genetic effects on cognitive functioning. *Frontiers in Neuroscience, 2*(2), 234–244. doi:10.3389/neuro.01.039.2008.

Lindenberger, U., Burzynska, A. Z., & Nagel, I. E. (2013). Heterogeneity in frontal lobe aging. In D. T. Stuss & R. T. Knight (Eds.), *Principles*

of frontal lobe functions (Vol. 2nd. ed.). New York: Oxford University Press.

Liu, F., Pardo, L. M., Schuur, M., Sanchez-Juan, P., Isaacs, A., Sleegers, K., & van Duijn, C. M. (2010). The apolipoprotein E gene and its age-specific effects on cognitive function. *Neurobiology of Aging, 31*(10), 1831–1833. doi:10.1016/j.neurobiolaging.2008.09.015.

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology, 9*(2), 106–118. doi:10.1038/nrneurol.2012.263.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., & Taskinen, J. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry, 34*(13), 4202–4210. doi:10.1021/bi00013a008.

Lu, B. (2003). BDNF and activity-dependent synaptic modulation. *Learning and Memory, 10*(2), 86–98. doi:10.1101/lm.54603.

Mahley, R. W., Weisgraber, K. H., & Huang, Y. (2009). Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *Journal of Lipid Research, 50*(Suppl), S183–S188. doi:10.1194/jlr.R800069-JLR200.

Matsumoto, M., Weickert, C. S., Akil, M., Lipska, B. K., Hyde, T. M., Herman, M. M., . . . Weinberger, D. R. (2003). Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. *Neuroscience, 116*(1), 127–137. doi:10.1016/S0306-4522(02)00556-0.

Mier, D., Kirsch, P., & Meyer-Lindenberg, A. (2010). Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Molecular Psychiatry, 15*(9), 918–927. doi:10.1038/mp.2009.36.

Milnik, A., Heck, A., Vogler, C., Heinze, H. J., de Quervain, D. J., & Papassotiropoulos, A. (2012). Association of KIBRA with episodic and working memory: a meta-analysis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 159B*(8), 958–969. doi:10.1002/ajmg.b.32101.

Miyajima, F., Ollier, W., Mayes, A., Jackson, A., Thacker, N., Rabbitt, P., & Payton, A. (2008). Brain-derived neurotrophic factor polymorphism Val66Met influences cognitive abilities in the elderly. *Genes, Brain and Behavior, 7*(4), 411–417. doi:10.1111/j.1601-183X.2007.00363.x.

Modrego, P. J. (2006). Predictors of conversion to dementia of probable Alzheimer type in patients with mild cognitive impairment. *Current Alzheimer Research, 3*(2), 161–170. doi:10.2174/156720506776383103.

Mondadori, C. R., de Quervain, D. J., Buchmann, A., Mustovic, H., Wollmer, M. A., Schmidt, C. F., Boesiger, P., Hock, C., Nitsch, R. M., Papassotiropoulos, A., & Henke, K. (2007). Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. *Cerebral Cortex, 17*, 1934–1947. doi:10.1093/cercor/bhl103.

Monteggia, L. M., Barrot, M., Powell, C., Berton, O., Galanis, V., Nagy, A., …, & Nestler, E. J. (2004) Essential role of BDNF in adult hippocampal function and depression. *Proceedings of the National Academy of Sciences*, *101*(29), 10827–10832. doi:10.1073/pnas.0402141101.

Moretti, D. V., Prestia, A., Fracassi, C., Binetti, G., Zanetti, O., & Frisoni, G. B. (2012). Specific EEG changes associated with atrophy of hippocampus in subjects with mild cognitive impairment and Alzheimer's disease. *International Journal of Alzheimer's Disease, 2012*, 253153. doi:10.1155/2012/253153.

Morse, J. K., Wiegand, S. J., Anderson, K., You, Y., Cai, N., Carnahan, J., . . . et al. (1993). Brain-derived neurotrophic factor (BDNF) prevents the degeneration of medial septal cholinergic neurons following fimbria transection. *Journal of Neuroscience, 13*(10), 4146–4156.

Muse, J., Emery, M., Sambataro, F., Lemaitre, H., Tan, H. Y., Chen, Q., . . . Mattay, V. S. (2014). WWC1 genotype modulates age-related decline in episodic memory function across the adult life span. *Biology Psychiatry, 75*(9), 693–700. doi:10.1016/j.biopsych.2013.09.036.

Nagel, I. E., Chicherio, C., Li, S.-C., von Oertzen, T., Sander, T., Villringer, A., . . . Lindenberger, U. (2008). Human aging magnifies genetic effects on executive functioning and working memory. *Frontiers in Human Neuroscience, 2*, 1. doi:10.3389/neuro.09.001.2008.

Nagel, I. E., Preuschhof, C., Li, S. C., Nyberg, L., Bäckman, L., Lindenberger, U., & Heekeren, H. R. (2009). Performance level modulates adult age differences in brain activation during spatial working memory. *Proceedings of the National Academy of Sciences in the U S A, 106*(52), 22552–22557. doi:10.1073/pnas.0908238106.

Nichols, L. M., Masdeu, J. C., Mattay, V. S., Kohn, P., Emery, M., Sambataro, F., …, Berman, K. F. (2012). Interactive effect of apolipoprotein e genotype and age on hippocampal activation during memory processing in healthy adults. *Archives of General Psychiatry*, 69(8), 804–13. doi:10.1001/archgenpsychiatry.2011.1893.

Nyberg, L., & Salami, A. (2014). The APOE ε4 allele in relation to brain white-matter microstructure in adulthood and aging. *Scandinavian Journal of Psychology, 55*, 263–267. doi:10.1111/sjop.12099.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Science, 16*(5), 292–305. doi:10.1016/j.tics.2012.04.005.

Nyberg, L., Andersson, M., Kauppi, K., Lundquist, A., Persson, J., Pudas, S., & Nilsson, L. G. (2014). Age-related and genetic modulation of frontal cortex efficiency. *Journal of Cognitive Neuroscience, 26*(4), 746–754. doi:10.1162/jocn_a_00521.

O'Brien, J. L., O'Keefe, K. M., LaViolette, P. S., DeLuca, A. N., Blacker, D., Dickerson, B. C., & Sperling, R. A. (2010). Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology, 74*(24), 1969–1976. doi:10.1212/WNL.0b013e3181e3966e.

Okuizumi, K., Onodera, O., Namba, Y., Ikeda, K., Yamamoto, T., Seki, K., . . . Tsuji, S. (1995). Genetic association of the very low density lipoprotein (VLDL) receptor gene with sporadic Alzheimer's disease. *Nature Genetic, 11*, 207–209. doi:10.1038/ng1095-207.

Pantzar, A., Laukka, E. J., Atti, A. R., Papenberg, G., Keller, L., Graff, C., . . . Backman, L. (2014). Interactive effects of KIBRA and CLSTN2 polymorphisms on episodic memory in old-age unipolar depression. *Neuropsychologia*. doi:10.1016/j.neuropsychologia.2014.07.020.

Papassotiropoulos, A., Stephan, D. A., Huentelman, M. J., Hoerndli, F. J., Craig, D. W., Pearson, J. V., . . . de Quervain, D. J. (2006). Common Kibra alleles are associated with human memory performance. *Science, 314*(5798), 475–478. doi:10.1126/science.1129837.

Papenberg, G., Backman, L., Nagel, I. E., Nietfeld, W., Schroder, J., Bertram, L., . . . Li, S. C. (2013). COMT polymorphism and memory dedifferentiation in old age. *Psychology Aging*. doi:10.1037/a0033225.

Papenberg, G., Li, S. C., Nagel, I. E., Nietfeld, W., Schjeide, B. M., Schroder, J., . . . Backman, L. (2014a). Dopamine and glutamate receptor genes interactively influence episodic memory in old age. *Neurobiology Aging, 35*(5), 1213 e1213-1218. doi:10.1016/j.neurobiolaging.2013.11.014.

Papenberg, G., Lövdén, M., Laukka, E. J., Kalpouzos, G., Keller, L., Graff, C., . . . Bäckman, L. (2014b). Magnified effects of the COMT gene on white-matter microstructure in very old age. *Brain Structure & Function*. doi:10.1007/s00429-014-0835-4.

Persson, J., Rieckmann, A., Kalpouzos, G., Fischer, H., & Bäckman, L. (2014). Influences of a DRD2 polymorphism on updating of long-term memory representations and caudate BOLD activity: magnification in aging. *Human Brain Mapping*. doi:10.1002/hbm.22704.

Pihlajamaki, M., K, O' Keefe, Bertram, L., Tanzi, R. E., Dickerson, B. C., Blacker, D., . . . Sperling, R. A. (2010). Evidence of altered posteromedial cortical FMRI activity in subjects at risk for Alzheimer disease. *Alzheimer Disease and Associated Disorders, 24*(1), 28–36. doi:10.1097/WAD.0b013e3181a785c9.

Ponomareva, N., Andreeva, T., Protasova, M., Shagam, L., Malina, D., Goltsov, A., . . . Rogaev, E. (2013). Age-dependent effect of Alzheimer's risk variant of CLU on EEG alpha rhythm in non-demented adults. *Front Aging Neuroscience, 5*, 86. doi:10.3389/fnagi.2013.00086.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, USA, 98*(2), 676–682. doi:10.1073/pnas.98.2.676.

Raichlen, D. A, & Alexander, G. E. (2014). Exercise, APOE genotype, and the evolution of the human lifespan. *Trends in Neurosciences, 37*(5), 247–55. doi:10.1016/j.tins.2014.03.001.

Rasch, B., Papassotiropoulos, A., & de Quervain, D. F. (2010). Imaging genetics of cognitive functions: focus on episodic memory. *NeuroImage, 53*(3), 870–877. doi:10.1016/j.neuroimage.2010.01.001.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., . . . Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex, 15*(11), 1676–1689. doi:10.1093/cercor/bhi044.

Raz, N., Lindenberger, U., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2008). Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cerebral Cortex, 18*(3), 718–726. doi:10.1093/cercor/bhm108.

Ronn, T., Volkov, P., Davegardh, C., Dayeh, T., Hall, E., Olsson, A. H., . . . Ling, C. (2013). A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLoS Genet, 9*(6), e1003572. doi:10.1371/journal.pgen.1003572.

Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L. G. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychology and Aging, 20*(1), 3–18. doi:10.1037/0882-7974.20.1.3.

Sambataro, F., Reed, J. D., Murty, V. P., Das, S., Tan, H. Y., Callicott, J. H., . . . Mattay, V. S. (2009). Catechol-O-methyltransferase valine(158)methionine polymorphism modulates brain networks underlying working memory across adulthood. *Biological Psychiatry, 66*(6), 540–548. doi:10.1016/j.biopsych.2009.04.014.

Sambataro, F., Murty, V. P., Lemaitre, H. S., Reed, J. D., Das, S., Goldberg, T. E., . . . Mattay, V. S. (2010). BDNF modulates normal human hippocampal ageing [corrected]. *Molecular Psychiatry, 15*(2), 116–118. doi:10.1038/mp.2009.64.

Sanchez, M. M., Das, D., Taylor, J. L., Noda, A., Yesavage, J. A., & Salehi, A. (2011). BDNF polymorphism predicts the rate of decline in skilled task performance and hippocampal volume in healthy individuals. *Transl Psychiatry, 1*, e51. doi:10.1038/tp.2011.47.

Sapkota, S., Vergote, D., Westaway, D., Jhamandas, J., & Dixon, R. A. (2014). Synergistic associations of COMT and BDNF with executive function in aging are selective and modified by APOE. *Neurobiology of Aging*. doi:10.1016/j.neurobiolaging.2014.06.020.

Schaie, K. W., Maitland, S. B., Willis, S. L., & Intrieri, R. C. (1998). Longitudinal invariance of adult psychometric ability factor structures across 7 years. *Psychology and Aging, 13*(1), 8–20. doi:10.1037//0882-7974.13.1.8.

Schiepers, O. J., Harris, S. E., Gow, A. J., Pattie, A., Brett, C. E., Starr, J. M., & Deary, I. J. (2012). APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. *Molecular Psychiatry, 17*(3), 315–324. doi:10.1038/mp.2010.137.

Schneider, A., Huentelman, M. J., Kremerskothen, J., Duning, K., Spoelgen, R., & Nikolich, K. (2010). KIBRA: a new gateway to learning and memory? *Frontiers in Aging Neuroscience, 2*, 4. doi:10.3389/neuro.24.004.2010.

Schuck, N. W., Doeller, C. F., Schjeide, B. M., Schroder, J., Frensch, P. A., Bertram, L., & Li, S. C. (2013). Aging and KIBRA/WWC1 genotype affect spatial memory processes in a virtual navigation task. *Hippocampus, 23*(10), 919–930. doi:10.1002/hipo.22148.

Schwab, L. C., Luo, V., Clarke, C. L., & Nathan, P. J. (2014). Effects of the KIBRA single nucleotide polymorphism on synaptic plasticity and memory: a review of the literature. *Current Neuropharmacology, 12*(3), 281–288. doi:10.2174/1570159X11666140104001553.

Slifstein, M., Kolachana, B., Simpson, E. H., Tabares, P., Cheng, B., Duvall, M., & Abi-Dargham, A. (2008). COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. *Molecular Psychiatry, 13*(8), 821–827. doi:10.1038/mp.2008.19.

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein E and cognitive performance: a meta-analysis. *Psychology and Aging, 19*(4), 592–600. doi:10.1037/08827974.19.4.592.supp10.1037/0882-.

Small, B. J., Rawson, K. S., Walsh, E., Jim, H. S. L., Hughes, T. F., Iser, L., … Jacobsen. P. B. (2011). Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer*, *117*, 1369–1376. doi:10.1002/cncr.25685.

Smith, J. D. (2002). Apolipoproteins and aging: emerging mechanisms. *Ageing Research Reviews, 1*, 345–365. doi:10.1016/S1568-1637(02)00005-3.

Stuart, K., Summers, M. J., Valenzuela, M. J., & Vickers, J. C. (2014). BDNF and COMT polymorphisms have a limited association with episodic memory performance or engagement in complex cognitive activity in healthy older adults. *Neurobiology of Aging, 110*, 1–7.

Sweatt, D. J. (2013). The emerging field of neuroepigenetics. *Neuron, 80*(3), 624–632. doi:10.1016/j.neuron.2013.10.023.

Thorvaldsson, V., Macdonald, S. W., Fratiglioni, L., Winblad, B., Kivipelto, M., Laukka, E. J., & Backman, L. (2011). Onset and rate of cognitive change before dementia diagnosis: findings from two Swedish population-based longitudinal studies. *Journal of International Neuropsychological Society, 17*(1), 154–162. doi:10.1017/S1355617710001372.

Trivedi, M. A., Schmitz, T. W., Ries, M. L., Torgerson, B. M., Sager, M. A., Hermann, B. P., & Johnson, S. C. (2006). Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: a cross-sectional study. *BMC Medicine, 4*, 1. doi:10.1186/1741-7015-4-1.

Tucker-Drob, E. M., Reynolds, C. A., Finkel, D., & Pedersen, N. L. (2014). Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. *Developmental Psychology, 50*, 152–166. doi:10.1037/a0032468.

Tunbridge, E. M., Harrison, P. J., & Weinberger, D. R. (2006). Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biological Psychiatry, 60*(2), 141–151. doi:10.1016/j.biopsych.2005.10.024.

Tunbridge, E. M., Weickert, C. S., Kleinman, J. E., Herman, M. M., Chen, J., Kolachana, B. S., . . . Weinberger, D. R. (2007). Catechol-o-methyltransferase enzyme activity and protein expression in human prefrontal cortex across the postnatal lifespan. *Cerebral Cortex, 17*(5), 1206–1212. doi:10.1093/cercor/bhl032.

Turkheimer, E. (2011). Still missing. *Research in Human Development, 8*, 227–241. doi:10.1080/15427609.2011.625321.

Tyler, W. J., Alonso, M., Bramham, C. R., & Pozzo-Miller, L. D. (2002). From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learning and Memory, 9*, 224–237. doi:10.1101/lm.51202.

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., & Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of Neurophysiology, 96*(6), 3517–3531. doi:10.1152/jn.00048.2006.

Vogler, C., Gschwind, L., Coynel, D., Freytag, V., Milnik, A., …, Papassotiropoulos, A. (2014). Substantial SNP-based heritability

estimates for working memory performance. *Translational Psychiatry, 4*, e438. doi:10.1038/tp.2014.81.

Volkow, N. D. (2000). Association between age-related decline in dopamine activity and impairment in frontal and cingulate matabolism. *American Journal of Psychiatry, 157*, 75–80.

Ward, A. M., Schultz, A. P., Huijbers, W., Van Dijk, K. R., Hedden, T., & Sperling, R. A. (2014). The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system. *Human Brain Mapping, 35*(3), 1061–1073. doi:10.1002/hbm.22234.

Westlye, L. T., Reinvang, I., Rootwelt, H., & Espeseth, T. (2012). Effects of APOE on brain white matter microstructure in healthy adults. *Neurology, 79*, 1961–1969. doi:10.1212/WNL.0b013e3182735c9c.

Wilson, R. S., Barral, S., Lee, J. H., Leurgans, S. E., Foroud, T. M., Sweet, R. A., …, Bennett, D. A. (2011). Heritability of different forms of memory in the Late Onset Alzheimer's Disease Family Study. *Journal of Alzheimers Disease*, *23(2)*, 249–255. doi:10.3233/JAD-2010-101515

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiology of Aging, 32*(1), 63–74. doi:10.1016/j.neurobiolaging.2009.02.003.

Witte, A. V., & Flöel, A. (2012). Effects of COMT polymorphisms on brain function and behavior in health and disease. *Brain Research Bulletin, 88*(5), 418–428. doi:10.1016/j.brainresbull.2011.11.012.

Xu, G., McLaren, D. G., Ries, M. L., Fitzgerald, M. E., Bendlin, B. B., Rowley, H. A., & Johnson, S. C. (2009). The influence of parental history of Alzheimer's disease and apolipoprotein E epsilon4 on the BOLD signal during recognition memory. *Brain: A Journal of Neurology, 132*(Pt 2), 383–391. doi:10.1093/brain/awn254.