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Article *in* Psychology and Aging · June 2014

DOI: 10.1037/a0036893 · Source: PubMed

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Psychology and Aging
2014, Vol. 29, No. 2, 359–362

0882-7974/14/$12.00 http://dx.doi.org/10.1037/a0036893

Genetic Variants and Cognitive Aging: Destiny or a Nudge?

Naftali Raz
Wayne State University

Cindy Lustig
University of Michigan

One would be hard-pressed to find a human trait that is not heritable at least to some extent, and genetics have played an important role in behavioral science for more than half a century. With the advent of high-throughput molecular methods and the increasing availability of genomic analyses, genetics have acquired a firm foothold in public discourse. However, although the proliferation of genetic association studies and ever-expanding library of single-nucleotide polymorphisms have generated some fascinating results, they have thus far fallen short of delivering the anticipated dramatic breakthroughs. In this collection of eight articles, we present a spectrum of efforts aimed at finding more nuanced and meaningful ways of integrating genomic findings into the study of cognitive aging. The articles present examples of Mendelian randomization in the service of investigating difficult-to-manipulate biochemical properties of human participants. Furthermore, in an important step forward, they acknowledge the interactive effects of genes and physiological risk factors on age-related difference and change in cognitive performance, as well as the possibility of modifying the negative effect of genetic variants by lifestyle changes.

Keywords: single-nucleotide polymorphisms, aging, cognition, genetics, vascular risk factors

"Genetics began by being ignored. Now it has the opposite problem."
—S. Jones & B. Van Loon[1]

In the past few decades, genetics has emerged from the realm of wrinkled peas and swarming fruit flies into the living rooms and everyday discourse of average citizens to the extent that some argue it significantly affects ordinary people's social attributions and judgments (Dar-Nimrod & Heine, 2011). Today, hospitals and headlines tout genetically tailored personalized medicine and one can send a saliva sample to a commercial lab, log into a Web site, and examine a slice of one's genetic individuality, all for a price of used car. Thus, the notion of ignoring genetics seems as preposterous as the idea of dinosaurs taking passage on Noah's ark. Genetics is one of the National Institute of Health's (NIH) largest funding categories, second only to clinical research (http://report.nih.gov/categorical_spending.aspx). The U.S. Food and Drug Administration (2013) found the notion of personalized medicine sufficiently important to issue a detailed position article on the topic (http://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf), and it is generally accepted that genes make significant contributions to almost every physiological or behavioral characteristic. Indeed, as Eric Turkheimer postulated in his first law of behavioral genetics: "All human behavioral traits are heritable" (Turkheimer, 2000).

Naftali Raz, Department of Psychology and Institute of Gerontology, Wayne State University; Cindy Lustig, Department of Psychology, University of Michigan.

Naftali Raz is partially supported by an NIH grant R37 AG011230, and Cindy Lustig by an NIH grant R01 MH086530.

Correspondence concerning this article should be addressed to Naftali Raz, Institute of Gerontology, 87 East Ferry Street, Detroit, MI 48202. E-mail: nraz@wayne.edu

However, anyone hoping that genetics would deliver a simple explanation for variability in human cognition and behavior is by this time sorely disappointed. Instead, the extant genetic association literature is plagued by small effect sizes and difficulties in replication. These studies failed to unveil the "end of history" by ushering in the reign of genetics. Plomin and Daniels (1987) introduced the "gloomy prospect" that unshared environmental influences on behavior might be difficult to understand if such influences were unsystematic, but Turkheimer (2000) warned that a search for simple relations between individual genes and complex behaviors would face an equally gloomy future.

Nearly 15 years later, many aspects of this dire prediction seem to have materialized. The very notion of "personalized medicine" has been called into question (Smith, 2011), and as summarized by Slagboom (in Barzilai et al., 2012),

> ". . . for all complex phenotypes, the small, joint influence of common variants can only be considered to be robust if it is observed in large sample sizes, with the same allele having the same direction of effect and sufficient replication of positive results in independent studies. Most studies into candidate genes, with the candidates originating from animal studies, do not fulfil these criteria." (p. 593)

Indeed, one is hard pressed to come up with an example of a replicable association between a genetic variant and a cognitive ability that reflects more than a small share of the variance in cognitive performance. Even the most robustly replicated genetic association, between APOEε4 allele and risk for Alzheimer's disease (Roses, 1996) pertains only to a very broadly defined syndrome of mental decline, not to its particular cognitive components affected by normal aging (Reinvang et al., 2013). Moreover, even if a robust association between a gene and a cognitive

[1] "Introducing Genetics" p. 173.

trait is established, it existence does not necessarily inform about the causal links between the former and the latter.

Does it mean that we should stop trying? The articles collected in this Special Section suggest that instead of cursing the darkness, we can light a candle by acknowledging the complexity of genetic effects and interactions of genes with each other and with other factors. Simply accruing an ever-expanding library of single-nucleotide polymorphisms (SNPs) is unlikely to yield cumulative knowledge that will explain complex cognitive traits through a small set of additive genetic factors. However, genetic information can meaningfully inform studies of cognitive aging in several ways.

First, genetic variants that exert well-defined effects on specific enzymes, neurotransmitters and hormones are a gift of nature to those of us interested in how these biochemical agents influence brain and cognitive function in healthy humans. Experimentally controlling brain levels of dopamine (DA) through pharmacologic manipulation in reasonably large samples is difficult both ethically and logistically. Manipulating bioavailability of *BDNF*, APOE, key enzymes involved in ore-carbon or glucose metabolism cycles, and proinflammatory cytokines levels is impossible. Thus, relying on natural assignment to high-medium-low groups via genes, known as Mendelian randomization (Katan, 1986), is the only option. Instead of designing an experiment in the lab, we can avail ourselves of experiments of nature, and epidemiologists are doing so with increasing frequency (Lawlor et al., 2008)

Second, because the heritability of cognitive abilities increases with age (McClearn et al., 1997), it is expected that the influence of specific genetic variants will be also age-dependent, This (potentially bidirectional) influence of age and genes may inform about the reasons for significant individual differences in trajectories of cognitive aging. Especially if participants are selected to be normatively or optimally healthy at baseline, longitudinal studies of sufficient length and density of measurement are essential for allowing detectable influences of genetic (and other) risk factors to emerge. Such studies are still very rare and the future of understanding genetic influence on adult developmental change depends on increasing their number.

This leads to the third point: Considering the interactions between genes and other risk factors can provide insight into the pathways leading away from healthy or optimal cognitive aging, even in ostensibly healthy people. This is especially true in the case of cross-sectional studies, in which participation is predicated on the good (or even optimal) health of the participants, and the influence of a potentially risky allele that is the focus of the study may be counteracted by multiple favorable alleles and environmental factors that are not included in the models. To restate the conundrum: by selecting only healthy participants, we may often be selecting against the very variability we are asking genetics to account for, whereas by selecting broad population-based samples, we limit the number of variables from a large pool of risk factors that our statistical analyses can bear. Hence, the need for Gene × Gene or Gene × Physiological Risk studies. Examination of interactions between genetic variants and measurable physiological factor such as blood lipids (De Frias et al., 2007) or fasting glucose (Raz et al., 2008) adds more than specific information about biological markers. It introduces into consideration the multitude of environmental, lifestyle, and genetic influences that otherwise remain unmentioned. More importantly, this approach implicitly acknowledges the cumulative effects of multiple random events that contribute to the measured levels of physiological indices such as blood pressure or waist-to-hip ratio; that is, it gives a voice to otherwise silent random-walk life history. The problem inherent in this approach is that uncovering significant interactions calls for a greater statistical power than needed for establishment of the main effects.

The collection of articles presented in this Special Section illustrates the benefits of genetic association studies in cognitive aging, as well as the limitations and pitfalls of this approach to untangling the complex mesh of influences that determine life span trajectories of human cognition. Each of the papers elucidates one or more of the points enumerated above.

Four studies in this series demonstrate the usefulness of Mendelian randomization as a tool of studying the relationship between specific neurotransmitters and cognition in adult development. Two of these studies (Greenwood et al., 2014, pp. 363–373 and Papenberg et al., 2014, pp. 374–383) examine the effect of dopamine-related genes on age differences in cognition. The choice of genes is, of course, not random. Because decline in signal-to-noise ratio has been hypothesized as a core phenomenon of cognitive aging (Welford, 1981), and because this decline has been ascribed to a gradual failure of dopaminergic modulation (Li et al., 2001), genes associated with dopaminergic system are of particular interest in cognitive aging. Both Greenwood et al. and Papenberg et al. examine the effects of a common *Catechol-O-Metyltransferase* (*COMT*) VAL158MET polymorphism (rs4680), which affects dopamine availability in the prefrontal cortex, on measures of processing speed and memory. In addition, Greenwood and her colleagues test a Gene × Gene interaction between *COMT* VAL158MET and another DA-related genetic variant, *dopamine beta-hydroxylase* SNP (*DBH*; −1021C/T, and rs1611115) that controls availability of the eponymous enzyme, a catalyst of DA conversion into norepinephrine.

Greenwood and colleagues (2014) found that a combination of advanced age and two genetic markers of low DA bioavailability (*COMT* VAL158 and *DBH* C/C Homozygocity) were associated with particularly low WM scores. This study is a useful illustration of amplification of age-related differences by genetically controlled variations in relevant neurotransmitter, as predicted by the inverted-U model of life span DA trajectory (Goldman-Rakic et al., 2000), its relation to WM performance (Cools & D'Esposito, 2011) and age-related increases in heritability of cognitive ability (McClearn et al., 1997).

Papenberg and colleagues (2014) take advantage of genetic variability in the bioavailability of prefrontal DA and demonstrate a significantly stronger association between age and memory among older low-DA individuals than among those who had genetic propensity for higher DA levels. The authors conclude that dedifferentiation of memory functions in older VAL homozygotes suggests that suboptimal dopaminergic modulation may underlie memory declines during aging. A notable feature of this study is that the investigators treated cognitive variables on the level of construct and not, as unfortunately is a common practice, on the level of individual indicators. Thus, they can credibly conclude that their findings indicate age-related modification of relationship between cognitive abilities, such as working and episodic memory.

Two studies in this Special Section examined the effects of another common polymorphism in a gene that control the expres-

sion of a protein with a very wide array of functions, *brain-derived neurotrophic factor* (*BDNF* VAL66MET, rs6265). *BDNF* plays important role in synaptogenesis, membrane maintenance and repair, and various metabolic processes (Lipsky & Marini, 2007). Ghisletta et al. (2014, pp. 284–392) test the effects of *BDNF* variation on cognitive decline, and Das et al. (2014, pp. 393–403) ask a similar question, including potential interactions with *COMT* VAL158MET.

Ghisletta and colleagues (2014) investigated the effects of genetic variation in *BDNF* expression on individual differences in age-related decline in perceptual speed. In a unique sample of the Berlin Aging Study, they found that octogenarians, who were followed up for 13 years and contributed up to 11 measurement occasions, exhibited more pronounced slowing on perceptual-motor tasks if they carried at least one MET allele of the *BDNF* VAL66MET polymorphism. No association between perceptual speed and *BDNF* genotype was noted as baseline. Das and colleagues (2014) investigated the effect of *COMT* VAL158MET and *BDNF* VAL66MET polymorphisms and their interaction on 8-year change in speed and found no effect of either SNP on change in reaction time (RT) or individual variability therein. They did find, however, that homozygotes for the *COMT* VAL158 and *BDNF* 66MET allele, that is, individuals with low bioavailability of DA and lower expression of *BDNF*, had significantly slower and more variable RT than the rest of the sample. On the Symbol Digit Modalities Test, which was probably the most similar to the Ghisletta et al. index of perceptual speed, Das et al. observed no significant effects, neither on baseline values nor on change.

What may account for the differences in these two studies is unclear. For example, the difference in results may reflect the lack of overlap in the age ranges of the samples (almost 84 years old in Ghisletta et al. study and under 64 in Das et al., 2014). In other words, those in Das et al. may not yet have reached the age at which genetics begins to bend the longitudinal performance curve on these measures. This comparison illustrates the difficulty of compiling a cumulative record of findings in genetics of cognitive aging and the need for a greater uniformity in the design of future investigations. The use of single tasks or indicators here, rather than analysis at the construct level, may have also contributed to the apparent discrepancy and the lack of uniformity of the single indicators may illustrate the heterogeneity of heritability problem highlighted by Kremen and his colleagues (2014, pp. 404–417).

The study by Kremen and colleagues (2014) is the only one in this collection that applies twin-study methodology to an age-sensitive ability, episodic memory. The study makes the point that there is also complexity in the abilities that show genetic variation and a need to examine that complexity at the level of constructs, rather than individual indicators of abilities. Kremen and his colleagues report that a relative large portion of genetic variance is measured at the level of individual tests (i.e., the California Verbal Learning Test vs. Wechsler Memory Scale) rather than a more general episodic memory factor. Thus, genetic influence may act not on a cognitively salient commonality that unites disparate indicators but on the cognitive processes that distinguish between them. The Kremen et al. findings make a case for examining the sources of variability and commonality in each sample before starting the search for specific genetic effects.

The Greenwood et al. (2014) and Das et al. (2014) studies show the importance of Gene × Gene interactions, and three other studies in this collection examine the influence of Gene × Physiological Risk factors. In particular, common age-related vascular and metabolic risk factors play an important role in modifying genetic influences on cognition, and specifically, vascular risk contributions to *COMT* effects on episodic and working memory (Raz et al., 2009, 2011). Two studies in this collection focus on this important interaction.

McFall and colleagues (2014, pp. 418–430) examined the conjoint effect of genetically determined differences in ability to metabolize insulin (indexed by insulin-degrading enzyme polymorphism, IDE rs6583817) and a surrogate measure of arterial stiffness, pulse pressure. They measured changes in executive functions (determined on a latent construct level) over at least three measurement occasions and found that not only was a lower ability to degrade insulin associated with steeper declines in executive functions, but the effect was exacerbated by increased pulse pressure. de Frias and colleagues (2014, pp. 431–439) studied the effects of APOEε4 in probably the oldest longitudinal sample of healthy adults—the Seattle Longitudinal Study—and found a combined effect of the risky allele of APOE and hypertension on several indices of cognitive performance.

Finally, one study in this Special Section investigated whether positive lifestyle factors can reduce the effects of genetic risk. In a sample of older adults, Ferencz and colleagues (2014, pp. 440–449) found that whereas elevated genetic risk for Alzheimer's disease conveyed by four polymorphisms, (*PICALM* [s3851179 G allele, rs541458 T allele], *BIN1* [rs744373 G allele], and *CLU* [rs11136000 T allele]), was associated with poor episodic memory performance, self-reported levels of physical activity mitigated these detrimental genetic influences.

In summary, the collection of articles presented in this Special Section converges on the importance of examining epistatic and additive effects of genetic variants and physiological biomarkers as the means of explaining age-related variance in cognitive performance. The reported findings clarify that although it is highly unlikely that single genetic variants determine the trajectories of cognitive aging, they definitely can give a nudge in positive or negative direction. Moreover, these findings, especially those of Ferencz and colleagues (2014), give rise to hope that manipulation of the nongenetic components of the observed relationships may lead to interventions that will be able to offset the genetically unfavorable conditions.

In this quest for harnessing the accumulating genomic knowledge, students of cognitive aging may do well by acknowledging an emerging elephant in the room: epigenetics. The idea that gene expression can be modified in the most fundamental way by variation in social and biological environments is not new, and the extant literature has some stellar examples of epigenetic effects on cognitive and affective properties of model organisms (e.g., Kosik et al., 2012; Rudenko & Tsai, 2014; Sweatt, 2010). It seems only natural to extend the current approach, which targets interactions between genetic variants and markers of physiological risk, to focusing on factors that affect gene expression and action at the source. The problem is that such environmental factors are myriad. Some are random and uncontrollable: occasional trauma, infection, or stressful events. Others are pervasive and desperately awaiting intervention: environmental pollution, radiation, and poor living conditions. They all affect the expression, maintenance, and repair of genes. Thus, we should learn to live with the "fundamental randomness" (Smith, 2011), but we can put more effort into understanding the intricate mutual influence between genetic variants and the environmental agents that affect their

expression. In other words, to understand the genetics of aging, a process that unfolds in time, we should "embrace interactionalism" (Turkheimer, 2004) and epigenetics as its most fundamental manifestation. The hopes for all-explaining genes may be fading but the evidence for genetic influence on cognitive aging, nudge-by-nudge, continues to accumulate. Although this may be a challenging scenario from a scientific perspective, as Turkheimer (2000) also notes, it is an encouraging one from the human perspective: Although our genes may nudge us, we can often nudge back.

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Received April 14, 2014
Accepted April 15, 2014 ■