Published in final edited form as:

Int J Geriatr Psychiatry. 2012 November ; 27(11): 1147–1154. doi:10.1002/gps.3759.

Gene by Neuroticism Interaction and Cognitive Function among Older Adults

Ilan Dar-Nimrod, Ph.D.¹, Benjamin P. Chapman, Ph.D., M.P.H.¹, John A. Robbins, M.D.², Anton Porsteinsson, M.D.³, Mark Mapstone, Ph.D.⁴, and Paul R. Duberstein, Ph.D.¹

¹Department of Psychiatry and Laboratory of Personality and Development, University of Rochester Medical Center, Rochester, NY, USA

²Department of Family and Community Medicine, University of California Davis School of Medicine, Sacramento, CA, USA

³Department of Psychiatry and Alzheimer's Disease Care, Research and Education Program, University of Rochester Medical Center, Rochester, NY, USA

⁴Department of Neurology and Alzheimer's Disease Care, Research and Education Program, University of Rochester Medical Center, Rochester, NY, USA

Abstract

Objectives—Both ApoE (apolipoprotein E) ϵ -4 allele(s) and elevated trait neuroticism, the tendency to experience distress, are associated with cognitive function among older adults. We predicted that neuroticism moderates the association between ApoE and cognitive function and also explored whether other personality dimensions (openness to experience, agreeableness, extraversion, and conscientiousness) affect the association between ApoE status and cognitive function.

Method—Five-hundred and ninety-seven older adults (mean age of 78) enrolled in the Ginkgo Evaluation of Memory (GEM) study completed the NEO-Five Factor Inventory of personality. Cognitive function was assessed via the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog), and a blood sample for ApoE genotyping was drawn.

Results—As hypothesized, regression analysis indicated that neuroticism moderated the relationship between the presence of ApoE ϵ -4 and cognitive function. Individuals with high neuroticism scores had significantly lower ADAS-cog scores compared with individual with low neuroticism scores, but this was true only among carriers of ApoE ϵ -4 (interaction effect $\beta = .124$, $p = .028$). There was scant evidence that other personality dimensions moderate the association between ApoE ϵ -4 and cognitive function.

Conclusions—Cognitive function may be affected by ApoE and neuroticism acting in tandem. Research on the underlying physiological mechanisms by which neuroticism amplifies the effect of ApoE ϵ -4 is warranted. The study of genotype by phenotype interactions provides an important and useful direction for the study of cognitive function among older adults and for the development of novel prevention programs.

Corresponding author: Ilan Dar-Nimrod, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, 300 Crittenden Blvd, Box PSYCH, Rochester, NY 14642, Phone: 585-273-4483, Fax: 585-276-2065, ilan_dar-nimrod@urmc.rochester.edu.

The authors have no disclosures to report.

Keywords

Older adults; G x E interaction; cognitive function; ApoE genotype; personality; neuroticism

Chronological age is often taken as a risk factor for cognitive decline associated with neurobiological aging. Yet age does not represent a causal mechanism itself—rather, it is a crude proxy for the accumulations of pathogenic processes occurring with age (MacDonald et al., 2011). The search for mechanisms that drive age-related diseases would therefore benefit from more refined analyses based on elements such as genetic predispositions, environmental influences, and psychosocial factors. Although there is a virtual scientific consensus that complex human phenomena involve interactive genetic and psychosocial processes (Institute of Medicine, 2006), research has traditionally focused on only one of these, seldom applying the interactive level of analysis (Dar-Nimrod and Heine, 2011). The present study is part of an increasing focus on the interactive approach to the study of cognitive function (e.g., Lee et al., 2011; Sachs-Ericsson et al., 2010).

Genes have been implicated in aging-related cognitive decline. Specifically, a number of studies identified an association between presence/absence of the apolipoprotein (ApoE) ϵ -4 allele on chromosome 19 and cognitive function in healthy adults (Reed et al., 1994; Woodard et al., 2010), with a meta-analysis (Small et al., 2004) indicating that the presence of the allele is associated with cognitive decline. The physiological mechanisms by which the presence of ApoE ϵ -4, an allele associated with elevated risk for cardiovascular diseases (Song et al., 2004) and Alzheimer's disease (Hardwood et al., 2010), may affect cognitive function remain unknown. The apparently modest effect size indicated by the meta-analysis (Small et al., 2004) highlight the variability in the magnitude of the association between ApoE ϵ -4 and cognitive decline and generate interest in potential moderators that affect the magnitude of this association. The physiological mechanisms, in which causal genetic indicators of complex phenotypes (such as cognitive function) affect phenotypes, are usually unknown (McCarthy and Hirschhorn, 2008). To address this weakness one must take into account that much of the expression of specific genes is dependent on environmental conditions (Johnson et al. 2009). More specifically, the cognitive-related, phenotypic expression of ApoE ϵ -4 has been shown to be affected by environmental stimuli in transgenic mouse models (Levi and Michaelson, 2007) and psychosocial elements have been shown to moderate the association between the presence of the allele and cognitive function among older adults (Lee et al. 2011). This study explores the moderating role of personality phenotypes.

Individuals' personality affects much of their psychosocial environment (McAdams and Pals, 2006). Personality characteristics have also been linked to cognitive performance and function (Robinson and Tamir, 2005; Williams et al. 2010). In research on personality and health, the Five Factor Taxonomy of personality (FFT) has been utilized extensively (Smith and Williams, 1992; Chapman et al., 2009). The FFT enumerates primary domains of personality, the Big 5 (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness), which emerge in a variety of populations, languages and cohorts (McCrae and Costa, 2008). These personality dimensions are considered to be phenotypes shaped by a combination of environmental and genetic input (Institute of Medicine, 2006).

Increased neuroticism, the propensity to experience anxiety, distress, and negative affect, is predictive of cognitive decline associated with age (Chapman et al. in press; Crowe et al., 2006; Wilson et al., 2005). To the extent that Neuroticism is a phenotypic marker of an underlying process that drives age-related cognitive decline, older individuals with elevated neuroticism who are also carriers of ApoE ϵ -4 would be expected to be characterized by a

distinct pattern of cognitive aging, characterized by more precipitous decline. From a physiological perspective, an allostatic load framework supports the prediction that neuroticism moderates the association between ApoE ϵ -4 and cognitive function. It is well-established that increased HPA axis activity is associated with cognitive function (Lupien et al., 1998). Previous findings indicate increased HPA axis activity among individuals with ApoE ϵ -4 (Peskind et al., 2001) and among individuals high on neuroticism (Mangold et al., 2006). Double-dysregulation of the HPA axis resulting from a combination of the presence of ApoE ϵ -4 and increased neuroticism may exacerbate cognitive decline. Empirical findings are also consistent with the moderation prediction. Caselli et al. (2004) showed that trait anxiety, a facet subsumed by neuroticism, moderated associations between the presence of ApoE ϵ -4 homozygous genotype and a specific cognitive function (problem solving) among healthy adults. Several additional studies found that depression moderated the association between the presence of ApoE ϵ -4 and cognitive function among older adults. These studies identified interactions between depression and the presence of ApoE ϵ -4 affecting cognitive decline (Niti et al., 2009) and increased incidence of Mild Cognitive Impairment (MCI: Geda et al., 2006). As neuroticism is considered a strong predictor of depression (Duberstein et al. 2008) these findings may have portrayed a narrow picture focusing on particular symptoms and overlooking the broader phenomenon encompassed by neuroticism.

To provide a direct test of the hypothesized moderating influence of neuroticism, we conducted a primary analysis of data collected in the Ginkgo Evaluation of Memory (GEM) study (Dekosky et al., 2008). In addition, as empirical research indicated associations between cognitive function and other personality dimensions such as openness to experience (Chapman et al., in press; Wilson et al., 2005), extraversion (Chapman et al., in press; Crowe et al., 2006), and conscientiousness (Chapman et al., in press; Wilson et al., 2007) we included the interactions between ApoE genotype and these personality dimensions in the analysis for exploratory purposes. We also included an interaction term for ApoE ϵ -4 by agreeableness, which represents the last main facet of personality for which no previous research indicates association with age-related cognitive function.

Method

Sample

The sample consisted of older individuals enrolled in the Ginkgo Evaluation of Memory (GEM) study. Details of the sample (Dekosky et al., 2008; Duberstein et al., 2011) and recruitment (Dekosky et al., 2006) have been previously published. The study was conducted under an investigational new drug application with the Food and Drug Administration under the auspices of the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute on Aging (NIA). Eligible subjects were recruited at 4 sites between 2000 and 2002. Key enrollment criteria in GEM included: age 72 years or older (down from the initial 75 years cutoff to stimulate minority recruitment), English as usual language, and absence of significant morbidity. Among the exclusion criteria: anti-Parkinson medications, tricyclic antidepressants, antipsychotics, or other medications with significant psychotropic or central cholinergic effects.

Among the subjects enrolled at the University of California, Davis (UCD) site, a sub-study was conducted examining the relationship between cognitive function and personality dimensions (Chapman et al., in press). At this site, 2234 potential subjects participated in an initial screening telephone interview: 551 (24.7%) were ineligible; 761 (34.1%) refused to participate; and 922 (41.3%) attended the baseline study visit. Of these, 916 (99.3%) were randomized. Subjects at the UCD site had characteristics similar to those at the other sites. Because this sub-study was initiated after the start of the main GEM study, only 771

(84.2%) of the 916 enrolled subjects completed the personality inventory and are included in the current analyses. Finally, apolipoprotein E (ApoE) genotyping was obtained on 80% of subjects, and 597 (77.1%) of those completing the personality inventory and the cognitive function measure. This sample ranged in age from 72–91 years. Subjects did not significantly differ on demographic variables (age, minority race, and education) by whether or not they completed the personality inventory or by whether or not ApoE genotyping was completed. However, differences in body mass index (BMI) and waist circumference between participants with at least one ApoE ϵ -4 allele ($M = 26.38$, $SD = 4.28$; $M = 94.98$ cm, $SD = 13.75$ respectively for BMI and waist circumference) and those without the allele ($M = 27.36$, $SD = 4.29$; $M = 98.68$, $SD = 12.48$) emerged ($F(1, 596) = 5.49$, $p = .02$; $F(1, 589) = 8.69$, $p = .003$). Note that the intervention had no effect on outcomes (Dekosky et al., 2008; Snitz et al., 2009).

Measures

Predictors—The *NEO-Five Factor Inventory* (NEO-FFI) is a 60-item self-report questionnaire (Costa and McCrae, 1992) measuring neuroticism (e.g., “I often feel tense and jittery”), openness to experience (e.g., “I often enjoy playing with theories and abstract ideas”), extraversion (e.g., “I really enjoy talking with people”), agreeableness (e.g., “I generally try to be thoughtful and considerate”), and conscientiousness (e.g., “I work hard to accomplish my goals”). Each domain is measured by 12 items. Response options comprise a 5-point Likert scale ranging from Strongly Disagree to Strongly Agree. Item scores ranged from 0 to 4 and were summed to yield a total score for each trait that ranged from 0 to 48, with higher scores indicating more of the trait. The NEO-FFI’s use in research in gerontology and geriatric psychiatry attests to its reliability and applicability to older samples (Archer et al., 2006; Duberstein et al., 2011). Internal consistency for the five subscales in the current study was adequate (Cronbach’s α ’s .75 – .82).

To establish participants’ ApoE genotype DNA was extracted with a Puregene Kit (QUIAGEN; Valencia, CA). ApoE genotyping was performed utilizing the TaqMan genotyping assays (Applied Biosystems; Foster City, CA) in a method described in detail elsewhere (Kuller et al., 1998). ApoE genotype was dichotomized to indicate the presence of the ϵ -4 allele.

The crux of the current article is testing personality moderation of the ApoE - cognitive function relationship. Five interaction terms were calculated as products of individuals’ ApoE ϵ -4 status and scores on each of the NEO- FFI subscales. Each of these products represented a specific Gene x Personality interaction term.

Covariates—Covariates were selected to maximize compatibility with prior similar studies (Chapman et al., in press; Duberstein et al., 2011), and included age, gender, race (minority vs. white), education (years of schooling), self-rated health (excellent, very good, good, fair, poor) and self-reported myocardial infarction, congestive heart failure, diabetes, angina, osteoporosis, stroke, transient ischemic attack (TIA), and cancer in the last 5 years. Scores on the 10-item version (Irwin et al., 1999) of the Center for Epidemiological Studies Depression scale (CES-D; Radloff, 1977), relevant (e.g., Gustafson et al., 2010) metabolic phenotypes (BMI [Kg/m^2] and waist circumference), current smoking status, alcohol consumption (i.e., number of standardized alcoholic drinks per week), and treatment group membership were also covaried.

Outcome Measures—Trained evaluators administered the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS- cog; Rosen et al., 1984), a well-validated measure of cognitive function (Wouters et al., 2009). The ADAS-cog was comprised of

evaluation items and tasks assessing spatial and temporal orientation, memory (short, long, and working), praxis (construal and ideational), language (following commands, naming, speaking, finding words, and comprehending) and general orientation. Higher scores reflect poorer cognitive function (increased number of errors).

Analyses

A hierarchical regression analysis was performed predicting cognitive function as measured by the ADAS-cog. At the first step all the covariates were entered simultaneously (Model 1). In the next step the presence of ApoE ϵ -4 genotype was added to the model (Model 2). Lastly, personality domain scores and their two-way interactions with ApoE genotype status were entered simultaneously to explore their overall contribution to the prediction of variance in ADAS-cog as well as their individual associations with this criterion. As the inclusion of openness to experience, extraversion, conscientiousness, agreeableness, and their interactions with the presence of ApoE ϵ -4 was exploratory rather than theoretically derived, we repeated the analysis eliminating these variables from the third step. Data were analyzed using SPSS (Version 18, IBM, Sommers, New-York).

Results

Table 1 presents complete data for the participants. Overall, ADAS-cog scores ranged from 1 to 23. Mean (SD) scores on the measure were $M = 6.62$ (2.86). NEO-FFI neuroticism scores ranged from 0 to 37, $M = 14.9$ (6.3).

Hierarchical regression analysis was performed to identify potential moderation roles for personality on the relationship between the presence of ApoE ϵ -4 and cognitive function. At the first step all the covariates were entered as predictors of ADAS-cog. They explained 14.1% of the variance in ADAS-cog ($R^2 = .155$, $F(19, 470) = 4.53$, $p < .001$). In the second step ApoE genotype status was added, improving the explained variance by 1.9% ($R^2 = .174$, $\Delta F(1, 469) = 10.96$, $p = .001$). In the third step all the personality scores and their interaction terms with the presence of ApoE ϵ -4 were simultaneously added. These additional variables contributed 3.4% to the explained variation in ADAS-cog scores ($R^2 = .208$, $\Delta F(10, 459) = 1.97$, $p = .035$). Table 2 presents the results of this last model. The analysis revealed neuroticism interaction with the presence of ApoE ϵ -4 ($B = .140$, $SE = .063$, $p = .028$) indicating that, controlling for the covariates, a carrier of at least one ApoE ϵ -4 allele who is 1 standard deviation (SD) above the mean in neuroticism would have, on average, an ADAS-cog score that is roughly 1.70 points (about 60% of a SD difference) higher than an ApoE ϵ -4 carrier who is 1 SD below the mean in neuroticism (see Fig. 1). In the absence of this allele, a person who is 1 SD above the mean in neuroticism would have, on average, an ADAS-cog score that is trivially lower (0.06 points or about 2.5% SD difference) compared with a person who is 1 SD below the mean in neuroticism.

The regression analysis did not indicate any additional significant personality by ApoE genotype interactions (see Table 2). One interaction term, Openness to experience by ApoE ϵ -4, approached statistical significance ($B = .066$, $SE = .047$, $p = .068$). This suggestive finding indicated that a person who is 1 SD above the mean in openness would have, on average, an ADAS-cog score that is roughly 0.76 points (about a quarter of a SD) higher than a person who is 1 SD below the mean in openness, when the ApoE ϵ -4 is present. In the absence of this allele, a person who is 1 SD above the mean in openness would have, on average, an ADAS-cog score that is roughly 0.44 points (about 15% of a SD) lower compared with a person who is 1 SD below the mean.

To explore the effect of the hypothesized moderation effect excluding the exploratory variables, an additional hierarchical regression was conducted in which the first 2 steps were

identical to the previous analysis but in the third step only neuroticism and its interaction with the presence of the ϵ -4 allele were retained. The inclusion of these elements significantly increased the explained variance in cognitive function ($R^2 = .19$, $\Delta F(2,468) = 4.32$, $p = .014$). Similar to the inclusive analysis, the ApoE ϵ -4 association with cognitive function was retained ($B = .989$, $SE = .285$, $p = .001$) but this effect was moderated by neuroticism ($B = .130$, $SE = .052$, $p = .013$). Neuroticism was not an independent predictor of ADAS-cog in this model ($B = .013$, $SE = .025$, $p > .50$).

Discussion

We examined the hypothesis that neuroticism moderates the association between ApoE and cognitive function in a sample of 597 older adults. Our results provided support for this prediction. Higher levels of neuroticism were associated with poorer cognitive function only among individuals with at least one ApoE ϵ -4 allele. Among people with other genotypes no indication for an association between neuroticism and cognitive function was found. This study was also designed to explore whether there is an empirical indication for other personality by ApoE interaction effects on cognitive function, which was not a-priori hypothesized. We found no conclusive evidence for additional interactions. However, our findings for openness to experience, albeit tentative, warrant replication.

As previous research found moderating effects of depression on the association between the presence of ApoE ϵ -4 and cognitive function or neurodegenerative disorders among older adults (Irie et al., 2008; Geda et al., 2006; Niti et al., 2009), the present analyses controlled for depressive symptom severity. We showed that neuroticism interacts with the presence of the allele to exacerbate cognitive decline above and beyond its association with depression.

It makes sense theoretically that neuroticism moderates the relationship between the presence of ApoE ϵ -4 allele and cognitive function. A logical next step is to begin to search for the physiological mechanisms involved in amplifying the pathogenic effects associated with the presence of the ApoE ϵ -4 allele. Developmental neuroendocrinology may provide a clue. Increased neuroticism is characterized by an elevated propensity to experience negative affect, including anxiety and a more negative evaluation of intrapersonal, interpersonal, and external environments, increasing subjectively experienced distress. As the HPA-axis is responsive to environmental input, it is not surprising that neuroticism is associated with increased HPA axis activity (Mangold et al., 2006). Thus, elevated neuroticism may be viewed as a behavioral marker of HPA dysregulation, and over the course of a lifetime, allostatic load. The presence of ApoE ϵ -4 is also associated with increased HPA axis activity (Peskind et al., 2001). This combined proclivity for elevated HPA activity represents a potential neuroendocrinologic process that may affect cognitive function by exacerbating hippocampal degeneration (Fuchs and Flügge, 1998) or other proximal mechanisms. Although glucocorticoids represent a promising future direction for research, inflammatory and metabolic processes associated both with neuroticism (Sutin et al., 2010a, 2010b), and ApoE ϵ -4 (Lynch et al. 2003) may be at play as well. Future research is needed to further explore the physiological systems involved in this effect.

Identification of psychosocial moderation of genetic correlates, such as the one tested in this study, offers potent and possibly cost-effective approaches for interventions. Although recent decades have seen exciting advances in our knowledge of genetics, hopes for treatments following the identification of genetic etiology for diseases have been dashed – and this is true even of diseases with overwhelming penetrance such as early onset Alzheimer's disease, Huntington disease, or Tay-Sachs (see for example Pearson, 2009 for a detailed case for Cystic Fibrosis). In the vastly more common cases in which genetic predispositions, age-related physiological processes and psychosocial elements act in

concert to affect risk for adverse health outcomes, the translational issues are even more pronounced.

Despite almost 2 decades of research that indicates association between the presence of ApoE ϵ -4, Alzheimer disease, and cognitive function, the physiological mechanism remains unknown. As a result the identification of the gene as a risk factor has yet to lead to viable interventions. Focusing on moderating variables such as neuroticism may offer a potentially alternative route for interventionists targeting individuals with elevated genetic risk for AD, even in the absence of a precise understanding of the physiological mechanism. If the current findings are replicated, it may be useful to consider ways in which neuroticism levels could be reduced. Neuroticism is stable over intermediate spans of time in the absence of intervention, but somewhat mutable when subjected to intervention (Chapman, et al., 2011; Krasner et al., 2009). Previous research indicated that neuroticism can be successfully reduced using behavioral interventions (Brosschot et al., 2006), meditation (Gaylord et al., 1989) and pharmacological treatment (Costa et al., 2005; Tang et al., 2009).

Several limitations and strengths of the present study deserve mention. The non-experimental nature of the study poses a methodological limitation on causal inferences. Then again, it is not possible to randomize genotypes or personality dimensions. In addition, the data used in the study are cross-sectional providing a “snap shot” of cognitive function at a particular point. A longitudinal design and analyses would provide stronger evidence for causal processes. However, cross-sectional designs offer valuable information often providing beneficial methodological aspects (reducing response biases for example: Rindfleisch et al., 2008). Along with these limitations the study possesses strengths. To our knowledge, this is the first report to explore genetic by personality interactions among older adults. Anchored in the interactionist perspective, this study underscores the importance of a biopsychosocial interactionist approach to understanding of aging-related disease. The findings may also offer initial empirical evidence that identify a specific population (i.e., ApoE ϵ -4 carriers with elevated neuroticism) for which existing interventions have the potential to ameliorate aging-related cognitive changes.

Acknowledgments

This research was supported in part by grants T32MH18911, K08AG031328 from the National Institute of Aging and U01 AT000162 from the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements. Additional support was provided by the National Heart, Lung, and Blood Institute, and the National Institute of Neurological Disorders and Stroke. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the NCCAM or the National Institutes of Health.

References

- Archer N, Brown RG, Boothby H, Foy C, Nicholas H, Lovestone S. The NEO FFI is a reliable measure of premorbid personality in patients with probable Alzheimer’s disease. *Int J Geriatr Psychiatry*. 2006; 21:477–484. [PubMed: 16676294]
- Caselli RJ, Reiman EM, Hentz JG, Osborne D, Alexander GE. A distinctive interaction between chronic anxiety and problem solving in asymptomatic APOE ϵ 4 homozygotes. *J Neuropsychiatry Clin Neurosci*. 2004; 16:320–329. [PubMed: 15377739]
- Chapman BP, Duberstein PR, Tindle HA, Sink KM, Robbins J, Tancredi DJ, Franks P. Personality predicts cognitive function over seven years in older persons. *Am J Geriatr Psychiatry*. in press.
- Chapman BP, Roberts B, Duberstein P. Personality and longevity: knowns, unknowns, and implications for public health and personalized medicine. *J Aging Res*. 2011
- Chapman BP, Shah M, Friedman B, Drayer R, Duberstein PR, Lyness JM. Personality traits predict emergency department utilization over 3 years in older patients. *Am J Geriatr Psychiatry*. 2009; 17:526–535. [PubMed: 19461261]

- Costa JPT, Bagby RM, Herbst JH, McCrae RR. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J Affect Disord.* 2005; 89:45–55. [PubMed: 16203041]
- Costa, PT.; McCrae. Revised NEO personality inventory and NEO five-factor inventory: Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc; 1992.
- Crowe M, Andel R, Pedersen NL, Fratiglioni L, Gatz M. Personality and risk of cognitive impairment 25 years later. *Psychol Aging.* 2006; 21:573–580. [PubMed: 16953718]
- Dar-Nimrod I, Heine SJ. Some thoughts on essence placeholders, interactionism, and heritability: Reply to Haslam (2011) and Turkheimer. *Psychol Bull.* 2011; 137:829–833. [PubMed: 21859183]
- DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. *Contemporary clinical trials.* 2006; 27:238–253. [PubMed: 16627007]
- DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, Lopez OL, Burke G, Carlson MC, Fried LP. Ginkgo biloba for prevention of dementia. *JAMA.* 2008; 300:2253. [PubMed: 19017911]
- Duberstein PR, Chapman BP, Tindle HA, Sink KM, Bamonti P, Robbins J, Jerant AF, Franks P. Personality and risk for Alzheimer's disease in adults 72 years of age and older: A 6-year follow-up. *Psychol Aging.* 2011; 26:351. [PubMed: 20973606]
- Duberstein P, Palsson S, Waern M, Skoog I. Personality and risk for depression in a birth cohort of 70-year-olds followed for 15 years. *Psychol Med.* 2008; 38:663–672. [PubMed: 18237453]
- Fuchs E, Flügge G. Stress, glucocorticoids and structural plasticity of the hippocampus. *Neurosci Biobehav Rev.* 1998; 23:295–300. [PubMed: 9884123]
- Geda YE, Knopman DS, Mrazek DA, Jicha GA, Smith GE, Negash S, Boeve BF, Ivnik RJ, Petersen RC, Pankratz VS. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: a prospective cohort study. *Arch Neurol.* 2006; 63:435. [PubMed: 16533972]
- Gustafson D, Melchior L, Eriksson E, Sundh V, Blennow K, Skoog I. The ACE Insertion Deletion polymorphism relates to dementia by metabolic phenotype, APOE4, and age of dementia onset. *Neurobiol Aging.* 2010; 31:910–916. [PubMed: 18838196]
- Harwood DG, Kalechstein A, Barker WW, Strauman S, St George-Hyslop P, Iglesias C, Loewenstein D, Duara R. The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *Int J Geriatr Psychiatry.* 2010; 25:511–518. [PubMed: 19750560]
- Institute of Medicine. Genes, behavior, and the social environment: Moving beyond the Nature/Nurture debate. Washington, DC: National Academies Press; 2006.
- Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, Launer LJ. Enhanced risk for alzheimer disease in persons with type 2 diabetes and APOE {varepsilon} 4: The Cardiovascular Health Study Cognition Study. *Arch Neurol.* 2008; 65:89. [PubMed: 18195144]
- Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Arch Intern Med.* 1999; 159:1701–1704. [PubMed: 10448771]
- Johnson W, Turkheimer E, Gottesman I, Bouchard T. Beyond heritability: twin studies in behavioral research. *Cur Directions Psycholog Sci.* 2010; 18:217.
- Kim KW, Youn JC, Jhoo JH, Lee DY, Lee KU, Lee JH, Woo JI. Apolipoprotein e4 allele is not associated with the cognitive impairment in community-dwelling normal elderly individuals. *Int J Geriatr Psychiatry.* 2002; 17:635–640. [PubMed: 12112161]
- Krasner MS, Epstein RM, Beckman H, Suchman AL, Chapman B, Mooney CJ, Quill TE. Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. *JAMA.* 2009; 302:1284–1293. [PubMed: 19773563]
- Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, Burke GL, Tracy R, Bhadelia R. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke; A Journal Of Cerebral Circulation.* 1998; 29:388–398.
- Lee BK, Glass TA, James BD, Bandeen-Roche K, Schwartz BS. Neighborhood Psychosocial Environment, Apolipoprotein E Genotype, and Cognitive Function in Older Adults. *Arch Gen Psychiatry.* 2011; 68:314. [PubMed: 21383266]

- Lee BK, Glass TA, Wand GS, McAtee MJ, Bandeen-Roche K, Bolla KI, Schwartz BS. Apolipoprotein E genotype, cortisol, and cognitive function in community-dwelling older adults. *Am J Psychiatry*. 2008 appi. ajp. 2008.07091532 v07091531.
- Levi O, Michaelson DM. Environmental enrichment stimulates neurogenesis in apolipoprotein E3 and neuronal apoptosis in apolipoprotein E4 transgenic mice. *J Neurochem*. 2007; 100:202–210. [PubMed: 17074063]
- Lupien SJ, de Leon M, De Santi S, Convit A, Tarshish C, Nair NPV, Thakur M, McEwen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci*. 1998; 1:69–73. [PubMed: 10195112]
- Lynch JR, Tang W, Wang H, Vitek MP, Bennett ER, Sullivan PM, Warner DS, Laskowitz DT. APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. *J Biol Chem*. 2003; 278:48529. [PubMed: 14507923]
- Macdonald SWS, Decarlo CA, Dixon RA. Linking biological and cognitive aging: toward improving characterizations of developmental time. *J Gerontology Series B, Psychol Sci Soc Sci*. 2011; 66(Suppl 1):i59–i70.
- Mangold DL, Wand GS. Cortisol and adrenocorticotrophic hormone responses to naloxone in subjects with high and low neuroticism. *Biol Psychiatry*. 2006; 60:850–855. [PubMed: 16950229]
- McAdams DP, Pals JL. A new Big Five: Fundamental principles for an integrative science of personality. *Am Psychol*. 2006; 61:204. [PubMed: 16594837]
- McCarthy MI, Hirschhorn JN. Genome-wide association studies: potential next steps on a genetic journey. *Hum Mol Genet*. 2008; 17:R156. [PubMed: 18852205]
- McCrae, RR.; Costa, PT, Jr. The five-factor theory of personality. In: John, OP.; Robins, RW.; Pervin, LA., editors. *Handbook of personality psychology: Theory and research*. 3. New York, NY US: Guilford Press; 2008. p. 159-181.
- Niti M, Yap KB, Kua EH, Ng TP. APOE- 4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2009; 64:306.
- O'brien J, Ames D, Schweitzer I, Mastwyk M, Colman P. Enhanced adrenal sensitivity to adrenocorticotrophic hormone (ACTH) is evidence of HPA axis hyperactivity in Alzheimer's disease. *Psychol Med*. 1996; 26:7–14. [PubMed: 8643765]
- Pearson H. Human genetics: One gene, twenty years. *Nature*. 2009; 460:164–169. [PubMed: 19587741]
- Peskind ER, Wilkinson CW, Petrie EC, Schellenberg GD, Raskind MA. Increased CSF cortisol in AD is a function of APOE genotype. *Neurology*. 2001; 56:1094–1098. [PubMed: 11320185]
- Pomara N, Greenberg WM, Branford MD, Doraiswamy PM. Therapeutic implications of HPA axis abnormalities in Alzheimer's disease: review and update. *Psychopharmacol Bull*. 2003; 37:120. [PubMed: 14674372]
- Radloff LS. The Ces-D scale. *Applied psychological measurement*. 1977; 1:385.
- Reed T, Carmelli D, Swan GE, Breitner J, Welsh KA, Jarvik GP, Deeb S, Auwerx J. Lower Cognitive Performance in Normal Older Adult Male Twins Carrying the Apolipoprotein E {varepsilon} 4 Allele. *Arch Neurol*. 1994; 51:1189. [PubMed: 7986172]
- Rindfleisch A, Malter AJ, Ganesan S, Moorman C. Cross-sectional versus longitudinal survey research: concepts, findings, and guidelines. *Journal of Marketing Research*. 2008; 45:261–279.
- Robinson MD, Tamir M. Neuroticism as Mental Noise: A Relation Between Neuroticism and Reaction Time Standard Deviations. *J Pers Soc Psychol*. 2005; 89:107–114. [PubMed: 16060749]
- Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984; 141:1356. [PubMed: 6496779]
- Sachs-Ericsson N, Corsentino E, Collins N, Sawyer K, Blazer DG. Problems meeting basic needs moderate the association between the APOE 4 allele and cognitive decline. *Aging Mental Health*. 2010; 14:138–144. [PubMed: 19946803]
- Saklofske D, Kelly I, Janzen B. Neuroticism, depression, and depression proneness. *Personality and individual differences*. 1995; 18:27–31.

- Sandström A, Peterson J, Sandström E, Lundberg M, Nystrom I-LR, Nyberg L, Olsson T. Cognitive deficits in relation to personality type and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in women with stress-related exhaustion. *Scand J Psychol.* 2011; 52:71–82. [PubMed: 20964695]
- Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging.* 2004; 19:592. [PubMed: 15584785]
- Smith TW, Williams PG. Personality and Health: Advantages and Limitations of the Five Factor Model. *J Pers.* 1992; 60:395–425. [PubMed: 1635048]
- Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, Saxton J, Lopez OL, Dunn LO, Sink KM. Ginkgo biloba for preventing cognitive decline in older adults. *JAMA.* 2009; 302:2663–2670. [PubMed: 20040554]
- Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med.* 2004; 141:137. [PubMed: 15262670]
- Sutin AR, Terracciano A, Deiana B, Naitza S, Ferrucci L, Uda M, Schlessinger D, Costa P. High Neuroticism and low Conscientiousness are associated with interleukin-6. *Psychol Med.* 2010a; 40:1485–1493. [PubMed: 19995479]
- Sutin AR, Terracciano A, Deiana B, Uda M, Schlessinger D, Lakatta EG, Costa PT. Cholesterol, triglycerides, and the Five-Factor Model of personality. *Biol Psychol.* 2010b; 84:186–191. [PubMed: 20109519]
- Williams PG, Suchy Y, Kraybill ML. Five-Factor Model personality traits and executive functioning among older adults. *Journal of Research in Personality.* 2010; 44:485–491.
- Wilson RS, Bennett DA, Mendes de Leon CF, Bienias JL, Morris MC, Evans DA. Distress proneness and cognitive decline in a population of older persons. *Psychoneuroendocrinology.* 2005; 30:11–17. [PubMed: 15358438]
- Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Arch Gen Psychiatry.* 2007; 64:1204. [PubMed: 17909133]
- Woodard JL, Seidenberg M, Nielson KA, Smith JC, Antuono P, Durgerian S, Guidotti L, Zhang Q, Butts A, Hantke N. Prediction of cognitive decline in healthy older adults using fMRI. *J Alzheimer's Dis.* 2010; 21:871–885.
- Wouters H, van Gool WA, Schmand B, Zwinderman AH, Lindeboom R. Three sides of the same coin: measuring global cognitive impairment with the MMSE, ADAS cog and CAMCOG. *Int J Geriatr Psychiatry.* 2010; 25:770–779. [PubMed: 19946861]

Figure 1.

Cognitive Function (ADAS-cog) as a Function of Neuroticism and the Presence of ApoE ϵ -4

* Notes: ADAS = Alzheimer's Disease Assessment Scale- cognitive, ApoE = apolipoprotein E genotype. Neuroticism scores centered (mean = 0).

Table 1

Characteristics of participants (N = 597).

	M (SD) or %
<u>Demographics</u>	
Age (years)	78.6 (3.1)
Male %	58.1
White, non-Hispanic, %	91.8
Education (years of schooling)	14.9 (3.2)
<u>Conditions %</u>	
Myocardial infraction	9.3
Congestive heart failure	3.0
Angina	10.5
Diabetes	7.5
Cancer	21.4
Osteoporosis	12.1
Stroke	3.5
TIA	7.8
Self-rated health (%)	
Excellent	9.8
Very good	42.0
Good	43.1
Fair	4.7
Poor	0.4
BMI (Kg./m ²)	27.1 (4.3)
Waist circumference (cm)	97.8 (12.9)
CES-D	3.8 (3.6)
Current smoker	2.2
Alcohol	5.38 (8.0)
<u>Variables of Interest</u>	
APOE ε4 allele present, %	22.8
<i>Personality Factors*</i>	
Neuroticism	14.9 (6.3)
Conscientiousness	32.6 (5.6)
Extraversion	27.9 (5.4)
Openness to experience	29.6 (6.9)
Agreeableness	34.7 (5.0)

Notes: The sample ranged in age from 72–91 years; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; Alcohol = Amount of weekly alcoholic drinks consumption; APOE = apolipoprotein E genotype. Mean in category unless otherwise noted. Standard deviations shown in parentheses

* NEO-FFI = NEO Five Factor Inventory's raw scores.

Table 2
Hierarchical Regression Analysis Predicting Cognitive Function (ADAS-cog)-Final Step

Predictor	B	SE	t	p	.95 CI for B	
					Lower Bound	Upper Bound
Intercept	6.536	1.256	5.205	<.001	4.068	9.004
<u>Demographics</u>						
Age	.149	.041	3.645	<.001	.069	.229
Gender (female reference)	.790	.314	2.515	.012	.173	1.408
Education (years)	-.048	.042	-1.132	.258	-.131	.035
White race (minority reference)	.951	.555	1.712	.088	-.141	2.042
<u>Physical health conditions (no condition reference)</u>						
Myocardial infarction	.065	.490	.132	.895	-.899	1.028
Congestive heart failure	.911	.758	1.201	.230	-.579	2.401
Angina	.259	.449	.578	.564	-.623	1.142
Osteoporosis	.400	.389	1.027	.305	-.365	1.165
Diabetes	.514	.459	1.120	.263	-.388	1.415
Cancer (past five years)	-.238	.305	-.780	.436	-.836	.361
Stroke	1.045	.707	1.478	.140	-.345	2.434
Tia or small stroke	1.478	.491	3.011	.003	.513	2.442
<u>Other covariates</u>						
Subjective health evaluation	.211	.185	1.145	.253	-.151	.574
BMI (body mass index)	.013	.047	.274	.784	-.079	.105
Waist circumference	-.015	.016	-.919	.359	-.046	.017
CES-D	.093	.038	2.455	.014	.019	.168
Current smoker ('non' reference)	-1.058	.835	-1.267	.206	-2.699	.583
Alcohol use	.002	.015	.155	.877	-.028	.033
Treatment (control reference)	.006	.239	.027	.979	-.464	.477
<u>Variables of interest</u>						
ApoE status*	1.045	.290	3.599	<.001	.474	1.615
Neuroticism (N)	-.005	.028	-.176	.860	-.061	.051
Openness (O)	-.032	.022	-1.460	.145	-.074	.011

Predictor	B	SE	t	p	.95 CI for B	
					Lower Bound	Upper Bound
Extraversion (E)	.024	.029	.824	.411	-.033	.080
Agreeableness (A)	-.046	.030	-1.515	.130	-.105	.014
Conscientiousness (C)	-.002	.029	-.083	.934	-.060	.055
ApoE x N interaction	.140	.063	2.198	.028	.015	.264
ApoE x E interaction	.066	.063	1.047	.296	-.058	.191
ApoE x O interaction	.087	.047	1.828	.068	-.006	.180
ApoE x C interaction	-.031	.057	-.541	.589	-.142	.081
ApoE x A interaction	.002	.070	.035	.972	-.135	.140

Notes: ADAS-cog = Alzheimer's Disease Assessment Scale- cognitive, CES-D = Center for Epidemiologic Studies Depression Scale. Alcohol use = number of alcoholic drinks consumed in a week. Personality scores centered (mean = 0). Age centered on sample mean of 78.

* ApoE (apolipoprotein E genotype) e-4: absent coded as (0), present coded as 1.