HHS Public Access

Author manuscript

Int J Geriatr Psychiatry. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Int J Geriatr Psychiatry. 2016 May ; 31(5): 502–509. doi:10.1002/gps.4355.

Apolipoprotein E and *Clusterin* can Magnify Effects of Personality Vulnerability on Declarative Memory Performance in Non-Demented Older Adults

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Abstract

Objectives—Recent research has linked psychological (personality) factors and specific genetic risk polymorphisms to performance on neurocognitive phenotypes. We examined whether episodic or semantic memory performance is associated with (a) three personality traits (i.e., neuroticism, extraversion, openness to experience), (b) two neurodegenerative-related polymorphisms (i.e., *Apolipoprotein E* (*APOE*; rs7412; rs429358), *Clusterin* (*CLU*; rs11136000)), and (c) cross-domain risk interactions (magnification effects).

Methods—Linear growth models were examined to test independent associations between personality traits and declarative memory performance, and potential interaction effects with *APOE* and *CLU* genetic risk. Normal older adults (n = 282) with personality and genetic data from the Victoria Longitudinal Study were included at baseline and for up to 14 years of follow-up.

Results—First, we observed that higher openness to experience levels were associated with better episodic and semantic memory. Second, three significant gene × personality interactions were associated with poorer memory performance at baseline. These synergistic effects are: (a) *APOE* allelic risk (ε4+) carriers with lower openness to experience levels, (b) *CLU* (no risk: T/T) homozygotes with higher extraversion levels, and (c) *CLU* (no risk: T/T) homozygotes with lower neuroticism levels.

Conclusions—Specific neurodegenerative-related genetic polymorphisms (i.e., *APOE* and *CLU*) moderate and magnify the risk contributed by selected personality trait levels (i.e., openness to experience, extraversion) on declarative memory performance in non-demented aging. Future research could target interactions of other personality traits and genetic polymorphisms in different clinical populations for predicting other neurocognitive deficits or transitions to cognitive impairment and dementia.

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Conflict of Interest

All authors confirm that there is no actual or potential conflict of interest.

Keywords

Personality traits; Genetic risk; *Apolipoprotein E*; *Clusterin*; Memory; Victoria Longitudinal Study

Introduction

The roles of both personality characteristics and genetic influences on non-demented cognitive aging and neurodegenerative diseases have been researched with growing breadth and clarity (Belsky *et al*, 2009; Harris *et al.*, 2011). Regarding genetic factors, research has linked risk polymorphisms with multifaceted clinical phenotypes (i.e., Alzheimer's disease (AD)) and neurocognitive performance in normal aging (Deary *et al.*, 2004). Arguably, the magnitude of risk conveyed independently by AD-related single nucleotide polymorphisms (SNPs) may have implications for the timing, trajectories, and potential for interactive or intensification effects in non-demented cognitive aging (Harris *et al.*, 2011; Lindenberger *et al.*, 2008). Specifically, neurodegenerative-related polymorphisms may influence cognitive performance and change in normal aging not only independently but also in particular constellations of interactions, especially those that involve combinations of risk from more than one factor (Belsky *et al.*, 2009; Sapkota *et al.*, 2015). Personality traits constitute an important (but understudied) domain of influence on cognitive performance and decline in non-demented aging. Conceivably, some vulnerability traits may also operate interactively with genetic or environmental factors to magnify the deleterious effects of biological influence in older adults (Eaton *et al.*, 2012; Lindenberger *et al.* 2008). In the present study, we examine three personality traits and two AD-related SNPs for their independent and interactive effects on declarative memory performance among older adults.

Consistently linked genetic risk factor for sporadic AD is the *Apolipoprotein E* (*APOE*; rs7412; rs429358) gene. *APOE* ε4 allele is connected with increased risk of AD-related dementia (Farrer *et al.*, 1997), but also normal cognitive decline (Small *et al.*, 2004) and mild cognitive impairment (MCI) (Brainerd *et al.*, 2011). We examine a second SNP prominently linked to AD and normal cognitive aging, *Clusterin* (*CLU*; rs11136000). Although more commonly associated with AD, in a recent study, cognitive normal *CLU* C+ carriers showed steeper memory decline than non-carriers who converted to MCI (Thambisetty *et al.*, 2013) and *APOE* may influence CLU levels in the frontal lobe in AD (Harr *et al.*, 1996; Nuutinen *et al.*, 2009; Wu *et al.*, 2012). Although the mechanisms linking the two genes and cognition remain unclear (Nuutinen *et al.*, 2009), we hope to add to the literature by examining the two genes in the same study and in interaction with personality traits.

Genetic association studies have been useful in identifying the degree of risk associated with some alleles in selected SNPs for cognitive changes with aging (Kremen *et al.*, 2011). However, for many neurocognitive phenotypes, the consideration of personal attributes and lifestyle activities may supplement or modify the observed roles of biological (genetic) factors (Runge *et al.*, 2014; Sachs-Ericsson *et al.*, 2010; Shanahan *et al.*, 2005). Personality traits encompass a wide range of behaviors as typically summarized in a specific set of dimensions or patterns characteristic to given individuals and they are generally stable in adulthood (Soubelet and Salthouse, 2011). Personality trait differences also determine how

older adults manage psychological stress (Grant and Langan-Fox, 2007), which is associated with hippocampal atrophy (Gallagher *et al.*, 1996) and accelerated aging due to dysregulation of the hypothalamus-adrenal cortex (McEwen, 1998). Thus, among older adults with personality trait differences similar stressors may result in wide range of behaviors and nervous system changes (Grant and Langan-Fox, 2007). For example, adults with higher neuroticism levels are at increased susceptibility to suicide (Wiktorsson *et al.*, 2013) or depression (Duberstein *et al.*, 2008). Low neuroticism with high extraversion levels has also been linked to lower dementia incidence among some older adults (Wang *et al.*, 2009). A recent study compared cognitive function in older adults with the *APOE* risk genotype (ε4+) as moderated by personality trait (Dar-Nimrod *et al.*, 2012a). Notably, *APOE* ε4+ allele carriers with higher neuroticism scores performed lower on the cognitive portion of the AD assessment scale (ADAS) as compared to *APOE* ε4+ carriers with lower neuroticism scores. In a subsequent study, *APOE* ε4+ carriers with high levels of neuroticism and extraversion showed worse performance on the ADAS (Dar-Nimrod *et al.*, 2012b). Personality traits linked to clinically significant depression (Duberstein *et al.*, 2008) may be involved in cognitive decline. Examining personality traits by genes may help clinicians identify older adults who are at a magnified risk for both cognitive decline and psychiatric conditions (Byers and Yaffe, 2011).

Three research questions were examined in the present study. First, are levels of neuroticism, extraversion, and openness to experience (openness) associated with baseline performance and longitudinal change in declarative memory? We predicted that (a) higher levels of neuroticism would be associated with poorer memory performance. In contrast, higher levels of (b) extraversion and (c) openness would be associated with better memory performance. Second, do allelic risk carriers for *APOE* ε4+ and *CLU* C+ perform poorly on memory tasks more than their lower genetic risk counterparts? Third, will specific gene × personality interactions influence initial and longitudinal memory performance? We expected *APOE* ε4+ and *CLU* C+ carriers with higher levels of neuroticism, and lower levels of extraversion and openness to have the worst overall performance compared to their counterparts. To our knowledge, this is the first study to examine personality by genetic interactions for declarative memory performance and change in non-demented older adults.

Method

Participants

Participants from the Victoria Longitudinal Study (VLS), a large-scale and multifactorial investigation of biomedical and neurocognitive aspects of aging were enrolled through advertisements and received a small honorarium for their participation. Written informed consent was obtained from all participants and all VLS data are collected with the approval from the human/institutional research ethics board. Our subsample is comprised of surviving members of two VLS cohorts who were present for the VLS genetic initiative in 2009–2011 (Supplementary Table S1). We linked eligible participants' newly obtained genetic, existing personality, and five-wave (14-year) longitudinal memory data. Specifically, we combined volunteers from Sample 1 and Sample 2 (n = 282; baseline age: 64.88 (5.45) years; 65.6% female) (Table 1). Mean interval between all waves for Sample 1 was 3.10 years and Sample

2 was 3.92 years. Participants with any missing cognitive data were included and handled using maximum likelihood in Mplus 7 (Muthén and Muthén, 1998–2012). Further information regarding the general VLS participant recruitment and testing procedures (Dixon and de Frias, 2004a) and personality assessment (Small *et al.*, 2003) are available.

DNA Extraction and Genotyping—Saliva was collected according to standard procedures from Oragene-DNA and stored at room temperature in Oragene® disks until DNA extraction. Genotyping was carried out using a PCR-RFLP strategy to analyze the allele status for *APOE* (rs7412, rs429358) and *CLU* (rs11136000) (Mcfall et al., 2013; 2015). Both genotype frequencies were in Hardy-Weinberg equilibrium: *CLU* ($\chi^2 = 0.21$, $p = 0.6457$) and *APOE* ($\chi^2 = 0.065$, $p = 0.799$). For purposes of analyses, we included two allelic combinations (risk and no risk) with past reports showing that being a carrier of one allelic risk is considered to be at risk (Harold *et al.*, 2009): *APOE* (risk: ε4+; no risk: ε4−) and *CLU* (risk: C+; no risk: T/T).

Measures

Episodic Memory: Word List Recall—From a pool of six equivalent lists, two different but comparable lists of 30 English words (Dixon *et al.*, 2004b) were used. Participants were given two minutes to study the list and five minutes to write down their answers. The total numbers of words correctly recalled from each list was averaged and used as the final score.

Semantic Memory: Vocabulary—The total number of correct answers from three 18-items series of tests in the Educational Testing Service kit (Ekstrom *et al.*, 1976) with 54 multiple-choice vocabulary questions was obtained for a final score.

NEO-PI—The NEO-PI (Costa *et al.*, 1985) was used at baseline for all participants to assess the five domains of personality traits: neuroticism, extraversion, openness, conscientiousness, and agreeableness. Based on previous literature (Dar-Nimrod *et al.*, 2012a), we examined neuroticism, extraversion, and openness traits for the present study. The full questionnaire consisted of 181 statements. Participants were required to answer based on how much they agreed with each statement from strongly disagree to strongly agree on a 5-point Likert scale. The present study used a subset of participants from the Small *et al.* (2003) study, which reported high Cronbach's alpha for all three traits in both samples.

Statistical Analyses

Descriptive statistics and means were calculated using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) (Table 1; Table 2). Linear growth models were used to analyze all research questions in Mplus 7. All missing values for cognitive measures were assumed to be missing at random and handled using maximum likelihood. Missing predictor values were handled using list-wise deletion. Only one participant was missing genetic information for *CLU* and 14 adults with *APOE* ε2/ε4 alleles were excluded. Risk alleles were coded as −0.56 and no risk alleles as 0.44 to avoid multicollinearity with gene by personality predictors. Age was entered as a continuous variable to rule out differences in cognitive performance and changes associated with baseline age.

We established a latent growth model of change over five waves for word recall and vocabulary by examining the best fitting growth models in a recommended order (McFall *et al.*, 2014): (a) a fixed intercept model, (b) a random intercepts model, (c) random intercept, fixed slope model, (d) random intercept, random slope model, and (e) random intercept, random slope, fixed quadratic model. The best fitting baseline change model was determined by examining several fit statistics. The chi-square test of model fit (χ^2; $p > .05$) allowed for an overall indication of good model fit. Additional absolute/comparative fit indices were also examined (Kline, 2011; Little, 2013): root mean square error of approximation ≤ .05, comparative fix index ≥ .95, and standardized root mean square residual ≤ .08. Following the examination of model fit, the χ^2 difference statistic was calculated to detect an improvement in fit with the addition of free parameters at each step. The best baseline model of change for word recall and vocabulary was obtained with the random intercept, random slope, and fixed quadratic model (Supplementary Table S2).

Next, each of the three personality traits and two SNPs were added as a time invariant predictor to test the independent effect of personality trait and allelic risk on intercept and slope. Baseline age was added as a covariate on intercept and slope in all analyses. A total of two models for each cognitive domain were examined for personality trait and SNP associations (Research Questions 1 and 2). Intercept and slope were regressed on both SNPs and personality traits. Unstandardized regression coefficients of each predictor were examined. For gene × personality interactions (Research Question 3), we calculated product terms in Mplus 7 to represent the SNP × personality trait interaction. Subsequently, intercept and slope were regressed simultaneously on personality trait, SNP, SNP × personality, and age in each model (Supplementary Table S3c). A total of twelve models were analyzed for Research Question 3.

Results

Mean level memory results for all five waves before any statistical analyses are displayed in Table 2. Age was a significant covariate in all models for Research Questions 1–3. This indicates that we accounted for interindividual differences in declarative memory performance at baseline and any changes as a result of baseline age. For Research Question 1, we observed three significant personality-memory associations. Higher openness scores were significantly associated with higher word recall (β = 0.041; SE = 0.013; $p = .002$) and vocabulary (β = 0.145; SE = 0.018; $p < .001$) performance at baseline. Higher extraversion scores predicted lower vocabulary performance (β = −0.099; SE = 0.020; $p < .001$) at baseline. However, we did not observe any significant associations with neuroticism. We observed stability of personality-declarative memory associations over five waves (Supplementary Table S3a). For Research Question 2, independent effects of *APOE* and *CLU* did not significantly predict baseline or change in memory performance (Supplementary Table S3b).

The key analyses were conducted for Research Question 3. We observed four significant gene by personality interactions at baseline. First, a significant interaction between *APOE* and openness predicted vocabulary performance. Not only did the adults with lower openness levels have poorer vocabulary performance but this effect was magnified for *APOE*

ε4+ carriers (β = −0.088; SE = 0.040; p = .029) (Figure 1a). The remaining significant interactions involved the *CLU* polymorphism with neuroticism and extraversion. Second, the *CLU* × neuroticism interaction significantly predicted word recall and vocabulary performance. Specifically, *CLU* T/T homozygotes with higher neuroticism levels had the best word recall (β = 0.078; SE = 0.028; p = .005) (Figure 1b) and vocabulary performance (β = 0.134; SE = 0.042; p = .001) (Figure 1c). In contrast, *CLU* homozygotes with lower neuroticism levels had the worst performance. Third, a *CLU* × extraversion interaction significantly predicted vocabulary performance. In this interaction, *CLU* T/T homozygotes with lower extraversion levels had the best vocabulary performance. In contrast, *CLU* homozygotes with higher extraversion levels showed the worst performance (β = −0.118; SE = 0.050; p = .018) (Figure 1d). Longitudinally, we observed stability in SNP × personality trait associations on memory (Supplementary Table S3c).

Discussion

We examined interactive associations of three targeted personality traits with *APOE* and *CLU* genotypes for baseline performance and change on episodic and semantic memory in non-demented older adults. Although previous studies have observed significant independent associations of personality traits (Grahman *et al.*, 2012) and SNPs (Small *et al.*, 2004; Thambisetty *et al.*, 2013) with memory, we addressed the integration (Dar-Nimrod *et al.*, 2012a) of these two trends. We expected patterns of association that would be consistent with the magnification of vulnerability effects, whereby lower memory performance would be associated with combined risk from both domains. We review the patterns below.

For the three-targeted traits (neuroticism, extraversion, openness), we observed three independent personality-memory associations consistent with the vulnerability hypothesis. Specifically, adults with lower scores on the openness trait had lower baseline word recall and vocabulary performance. Openness-memory associations may also mediated by different cognitive activity levels (Hogan *et al.*, 2012) so lifestyle activities should be examined with the openness trait in future investigations of personality influences on cognitive performance.

Less directly affiliated with the vulnerability hypothesis was the result with extraversion. Higher extraversion levels were associated with worse performance on vocabulary at baseline. Previous studies have reported that older adults with higher extraversion levels have faster performance on speed tasks (Pearman, 2009) but poorer performance on semantic memory (Baker and Bichsel, 2006) or global cognition (Chapman *et al.*, 2012). In the latter two cases, remembering and recall are required, whereas speed is typically a fluid-type reaction time performance. Thus, high extraversion levels may predispose older adults to be more alert in situations requiring quick performance but do not support performance on tasks requiring correct recall of new or cultural information, as observed in our study. Observation of vulnerability effects for extraversion may be dependent on the neurocognitive domain involved or other aspects of the performance situation.

For the neuroticism trait, we observed no significant associations with memory. Past studies with non-demented older adults have reported mixed findings including no associations

between neuroticism and crystalized intelligence (Baker and Bichsel, 2006) and three-year global cognitive decline (Jelicic *et al.*, 2003). Conceivably, the range of neuroticism levels in the present study may have been restricted and fairly low, at least compared with the cognitively impaired groups, dementia populations, or groups with existing personality disorder or increased risk for psychiatric conditions (Meins and Dammast, 2000; Wiktorsson *et al.*, 2013). Further, we examined only neuroticism at baseline (Small *et al.*, 2003), so future work could test changes in aging. Although healthy older adults are relatively stable in their personality traits (Soubelet and Salthouse, 2011) and the larger sample from which the present subsample was derived showed relatively little change in personality traits over two waves (Small *et al.*, 2003), longitudinal studies with larger and more diverse samples for personality-cognition associations are encouraged in the future. We acknowledge that our personality trait measure was only tested at baseline and used to predict longitudinal change in memory, which may have limited our results.

We turn now to the key analyses including gene × personality interactions. We observed four interesting and novel cross-domain associations with memory performance at baseline. First, memory performances by adults with higher openness levels at baseline were not affected by *APOE* genotype. In contrast, *APOE* ε4+ carriers with lower openness levels showed poorer memory performance than the *APOE* ε4− group (Figure 1a). Prior research has linked higher hypothalamic-pituitary-axis activity levels to cognitive deficits (Lupien *et al.*, 1998) in *APOE* ε4+ carriers (Peskind *et al.*, 2001) and lower openness levels to poor cognitive performance (Grahman *et al.*, 2012). This linkage directly supports our vulnerability-related interpretation. Positive correlations between openness levels and memory even in the presence of genetic vulnerability (*APOE* ε4+) suggest that higher openness levels may serve as a potential protective factor for cognitive decline. Adults with higher openness levels have been associated with more social lifestyle and cognitive engagement (Grahman *et al.*, 2012). Therefore, the protective effects observed for adults with higher openness levels may be modified through their social and cognitive lifestyle.

Second, *CLU* T/T homozygotes were protected from the vulnerability associated with high neuroticism levels on word recall and vocabulary at baseline. Adults with *CLU* T/T and high neuroticism levels had the best word recall (Figure 1b) and vocabulary (Figure 1c) performance. Previous reports have shown that neuroticism levels discriminate between healthy aging and early-stage AD (Duchek *et al.*, 2007), and an active lifestyle may act as a buffer against the negative effects of high neuroticism in at-risk adults (Wang *et al.*, 2009). The present sample may have benefited from both healthy aging, with lower neuroticism levels, and a relatively advantaged socially engaged lifestyle (Runge *et al.*, 2014). Whether lifestyle activities play a specific role in this gene-personality dynamic should be tested in future studies.

Third, *CLU* T/T homozygotes with lower extraversion levels had better vocabulary performance than those with higher extraversion levels. In contrast, extraversion levels did not influence vocabulary performance for *CLU* C+ carriers (Figure 1d). Similarly, previous studies have linked high extraversion levels to poorer memory performance (Baker and Bichsel, 2006; Luchetti *et al.*, 2015). Adults with *CLU* allelic risk may already be at a disadvantage on memory tasks (Braskie *et al*, 2011) but *CLU* T/T homozygotes in our

sample were at a magnified risk for poor vocabulary performance if they had higher extraversion levels.

We note briefly that we observed no significant independent gene-memory associations at baseline or longitudinally. Past studies are mixed but some have also shown no cognitive associations with *APOE* ε4+ risk carriers in non-demented populations (Bunce *et al.*, 2014; Jorm *et al.*, 2007; Juva *et al.*, 2000). Similarly, cognitive decline has only been observed among *CLU* C+ risk carriers who eventually reached MCI status (Thambisetty *et al.*, 2013). Different health and environmental risk factors may influence *APOE* and *CLU*-memory associations in older adults. Previous studies have reported moderation effects with gender (Mortensen and Høgh, 2001), vascular health (McFall *et al.*, 2015), gene synergistic effects and effect modifications (Sapkota *et al.*, 2015), or more prevalence in the dementia population (Elias-Sonnenschein *et al.*, 2008). We conducted post-hoc analyses (a) to examine the remaining two personality traits (conscientiousness; agreeableness) independently and in interaction with *APOE* and *CLU*, and (b) re-analyze our results to test for any differences with the inclusion of *APOE* ε2/ε4 as risk, and gender and baseline education as covariates. We observed three significant findings, and no difference in our result with *APOE* ε2/ε4, gender, and education. First, high conscientiousness levels were associated with poor baseline word recall performance (β = −0.055; SE = 0.026; $p = .035$). Second, higher agreeableness scores were associated with steeper 12-year decline in vocabulary (β = −0.019; SE = 0.009; $p = .035$). Third, *APOE* risk carriers with high agreeableness scores had the worst word recall performance at baseline (β = 0.177; SE = 0.080; $p = .028$).

Several limitations of the present study should be mentioned. First, we included a non-demented homogenous group of older Caucasians from Canada. Personality traits and heritability of genes may differ among nationalities (Allik and McCrae, 2004). Future studies should test differences in socioeconomic backgrounds (Costa *et al.*, 2001) and compare clinical populations and different ethnicities. Second, we observed a potential limitation of power as our post-hoc power analyses (Preacher and Coffman, 2006) revealed a medium effect size for all models (Supplementary Table S4). Third, although the presence of up to 14 years of longitudinal data was a design strength, the stability associated with personality and semantic memory during this period may have restricted variability in change. Conceivably, a larger sample could provide significant longitudinal results and should be examined.

Selective personality trait levels independently affected cognitive performance in non-demented aging. Moreover, cross-domain interactions showed that personality trait effects on declarative memory were moderated by *APOE* and *CLU* allelic risk. Ongoing efforts to better evaluate the potential synergistic effects of non-clinical personality characteristics and genetic risk conveyed from leading AD-related genotypes may lead to improved understanding not only of non-demented cognitive aging but also potentially earlier detection of individuals at risk for exacerbated memory decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the volunteer participants and the VLS staff for their many contributions. More information about the VLS may be found at: http://www.ualberta.ca/~vlslab/.

Financial support

This work was supported by grants from (a) the National Institutes of Health (National Institute on Aging; R01 AG008235) to Roger A. Dixon, and (b) Alberta Health Services (University Hospital Foundation) to David Westaway, Jack Jhamandas, and Roger A. Dixon. Dr. Dixon is also supported by the Canada Research Chairs program. The funding source did not have a role in the study design, data collection, statistical analysis, results interpretation, report writing, or submission decisions.

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Key Points

1. In non-demented older adults, lower openness to experience is associated with worse episodic and semantic memory.
2. *APOE* ε4 allelic risk magnifies this association.

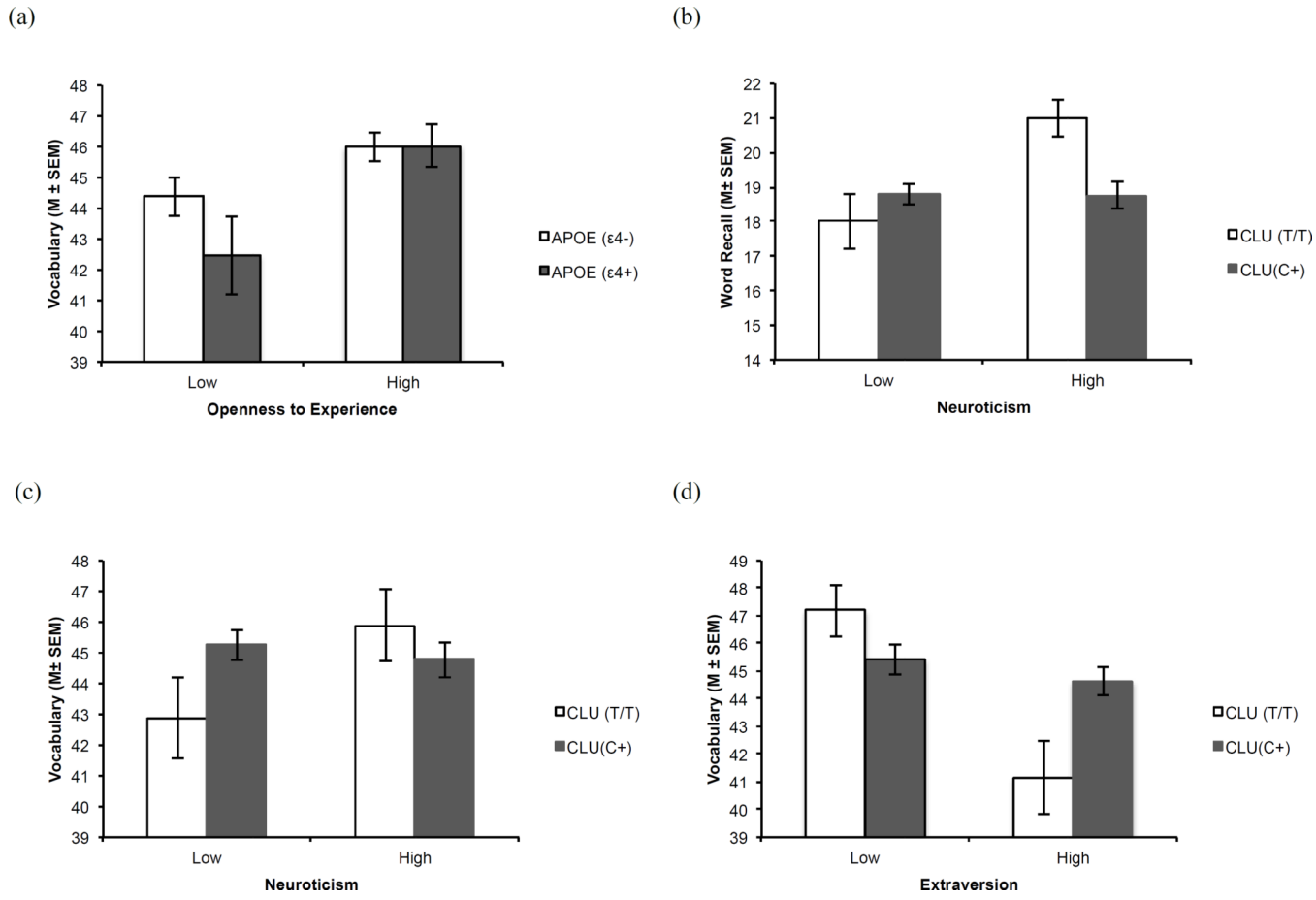

Figure 1.

Personality by gene interaction effects for baseline declarative memory performance: (a) Adults with low openness to experience levels had poorer vocabulary performance and this effect was magnified for those with *APOE* allelic risk (ε4+). (b) *CLU* T/T homozygotes in the low neuroticism group had poorer word recall performance than *CLU* T/T homozygotes in the high neuroticism group. (c) *CLU* T/T homozygotes in the low neuroticism group had poorer vocabulary performance than *CLU* T/T homozygotes in the high neuroticism group. (d) *CLU* T/T homozygotes in low extraversion group had the best vocabulary performance, whereas those in the high extraversion group had the worst performance.

(Note: High and low represent those above and below the mean personality trait score).

Table 1

Descriptive characteristics (mean and standard deviation) for personality trait and genetic measures.

	Total
n	282
Age (years)	64.88 (5.45)
Education (years)	14.89 (3.05)
Gender (M/F)	97/185
Personality	
Neuroticism	77.17 (20.72)
Extraversion	101.25 (16.57)
Openness to Experience	115.50 (17.64)
Genes	
APOE	ε4− = 202; ε4+ = 66
CLU	T/T = 42; C+ = 239

n, Total number; *APOE*, *Apolipoprotein E* (ε4− = no risk/ ε4+ = risk); *CLU*, *Clusterin* (T/T = no risk/C+ = risk).

Table 2

Descriptive characteristics (M and SD) for word list recall and vocabulary for all five waves.

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
n	282	266	255	239	200
Episodic Memory					
Word List Free Recall	18.86 (3.75)	19.12 (3.82)	18.64 (3.90)	17.89 (4.28)	16.62 (4.78)
Semantic Memory					
Vocabulary	44.89 (5.78)	44.96 (5.33)	44.75 (5.31)	44.29 (5.18)	43.90 (5.32)

n, Total number; M, Mean; SD, Standard deviation.