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RESEARCH ARTICLE

Apolipoprotein E: the resilience gene

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Abstract The apolipoprotein E (apoE) gene has been implicated in various conditions, most notably Alzheimer's disease and coronary artery disease. A predisposing role of the apoE4 isoform and a protective role of apoE2 isoform in those diseases have been documented. Here we investigated the role of apoE in resilience to trauma. Three hundred and forty-three US veterans were genotyped for apoE and were assessed for their lifetime trauma exposure (trauma score, *T*) and severity of posttraumatic stress disorder symptoms (PCL). The ratio PCL/T indicates sensitivity to trauma; hence, its inverse indicates resilience, *R*, to trauma. We found a significantly higher resilience in participants with apoE genotype containing the E2 allele (E2/2, E2/3) as compared to participants with the E4 allele (E4/4, E4/3). In addition, when the categorical apoE genotype was reexpressed as the number of cysteine residues per apoE mole (CysR/mole), a highly significant positive association was found between resilience and CysR/mole, such that resilience was systematically higher as the number of CysR/mole increased, from zero CysR/mole in E4/4 to four CysR/mole in E2/2. These findings demonstrate the protective role of the CysR/mole apoE in resilience to trauma: the more CysR/mole, the higher the resilience. Thus, they are in accord with other findings pointing to a generally protective role of increasing number of CysR/mole (from E4/4 to E2/2) in other diseases. However, unlike other conditions (e.g., Alzheimer's disease and coronary artery disease), resilience to trauma is not a disease but an adaptive response to trauma. Therefore, the effects of apoE seem to be more pervasive along the CysR/mole continuum, most probably reflecting underlying effects on brain synchronicity and its variability that we have documented previously (Leuthold et al., Exp Brain Res 226:525–536, 2013).

Keywords ApoE · Trauma · Resilience

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Introduction

Apolipoprotein E (apoE) is a plasma lipoprotein produced in the brain and peripherally (primarily in the liver) that plays a critical role in the transport and metabolism of cholesterol and other lipids, among various other roles (Mahley 1988; Mahley and Huang 2012). ApoE has been linked to diseases affecting the periphery and brain including cardiovascular disease (Mahley and Rall 2000) and Alzheimer's disease (Corder et al. 2000; Mahley et al. 2006), and has been implicated in various functions involved in brain health including neural development, regeneration, neuroprotection, and plasticity (Mahley 1988). The human apoE protein exists in three primary isoforms—E2, E3, and E4—that differ in terms of the presence of cysteine or arginine at two positions (residues 112 and 158) of the 299 amino

acids that comprise the protein (Weisgraber et al. 1981). These differences affect the structure and function of the apoE isoforms, promoting risk or resilience for various diseases. Presence of the E4 allele, for instance, is a strong genetic risk factor for Alzheimer's disease (AD) whereas the E2 allele is protective against AD (Farrer et al. 1997) but associated with Type III hyperlipoporteinemia (HLP) (Zannis et al. 1981) in homozygous E2 carriers in the presence of additional environmental or genetic vulnerabilities (Mahley and Rall 2000). The E3 allele is the most common and is generally considered neutral in terms of disease risk and protection.

In terms of diseases affecting the central nervous system, the E4 allele is most commonly implicated as it has been linked to various conditions that impact cognitive functioning including mild cognitive impairment (Pa et al. 2009), posttraumatic stress disorder symptoms (Peterson et al. 2015), and has been associated with poorer outcomes following traumatic brain injury (Zhou et al. 2008). The E4 allele has also been shown to affect neural interactions in healthy human brains (Leuthold et al. 2013) and in developing brain cultures in vitro (Christopoulos et al. 2015) and to promote accelerated cognitive decline among healthy individuals (Caselli et al. 2004, 2007). Relative to E3, E4 is generally considered to enhance risk of CNS disease whereas E2 is considered to enhance protection.

However, human apoE is determined by two alleles resulting in six possible genotypes (E4/E4, E4/E3, E4/E2, E3/E3, E3/E2, E2/E2) that vary in terms of the number of cysteine residues per mole (Zannis et al. 1982). Specifically, E4/E4 has zero cysteine residues per mole (CysR/mole), E4/E3 has one CysR/mole, E4/E2 and E3/E3 have 2 CysR/mole, and E2/E2 has 4 CysR/mole. Thus, although the E4 allele has been associated with brain function and various diseases, its effect may be enhanced or moderated by the second allele and corresponding number of CysR/mole. Indeed, we have demonstrated that the effects of apoE on neural functioning are graded in an orderly manner according to CysR/mole with the greater number of CysR/mole (E2/E2) reflecting enhanced brain health and the fewest CysR/mole (E4/E4) reflecting decreased brain health (Leuthold et al. 2013). Although the specific mechanisms are as of yet unknown, the functional and structural changes conferred by each additional CysR/mole appear to increase neuroprotection and promote brain resilience.

In the present study, we examine the association between CysR/mole and brain resilience as it relates to mental health symptoms. Epidemiological studies have demonstrated that a minority of individuals who are exposed to potentially traumatic events develop PTSD or other related mental health conditions (Kessler et al. 1995; Breslau et al. 1998) and that, instead, resilience is the modal outcome (Bonanno and Mancini 2012). We examined the association between apoE CysR/mole and resilience and hypothesized that resilience would be associated with CysR/mole in a graded manner such that those with more Cys/mole would evidence greater resilience.

Materials and methods

Study participants

A total of 343 US veterans participated in the study as paid volunteers. The sample included 309 men (age: 56.44 ± 14.41 years, mean ± SD) and 34 women (age: 42.46 ± 13.67 years, mean ± SD). Diagnostic status was obtained via structured clinical interviews [Clinician Administered PTSD Scale for DSM-IV-TR (Blake et al. 1995) and Structured Clinical Interview for DSM-IV-TR (First et al. 2002)]. From that, it was determined that 147 participants were healthy controls. Of the remaining 196 participants, 168 met criteria for current or history of PTSD, 70 met criteria for a depressive disorder, 19 met criteria for non-PTSD anxiety disorder, 6 met criteria for alcohol dependence, and 13 met criteria for some other disorder (e.g., adjustment disorder, binge eating disorder, etc.). The study protocol was approved by the appropriate Institutional Review Board and participants provided written informed consent prior to participating in the study.

Resilience

Study participants completed self-report questionnaires assessing symptoms of posttraumatic stress disorder [PTSD Checklist; PCL; (Blanchard et al. 1996)] and lifetime trauma exposure [Deployment Risk and Resilience Inventory; DRRI; sum of endorsed items on Predeployment Stressors, Combat, and Postdeployment Stressors scales (King et al. 2006)]. To account for a small number of missing items, a standardized trauma score T was computed by dividing the total items endorsed by the number of items that were answered; the range of this score was 0–1. Trauma scores widely overlapped between the control and psychopathology groups. We computed a resilience score as follows. First, we define sensitivity to trauma S as the ratio of PCL score over the trauma score:

$$S = \frac{\text{PCL}}{T}. \quad (1)$$

Next, we define resilience R as the inverse of S:

$$\text{Resilience} = R = \frac{1}{S} = \frac{T}{\text{PCL}}. \quad (2)$$

The distribution of R was skewed to the right (Fig. 1), suggesting the need for a transformation.

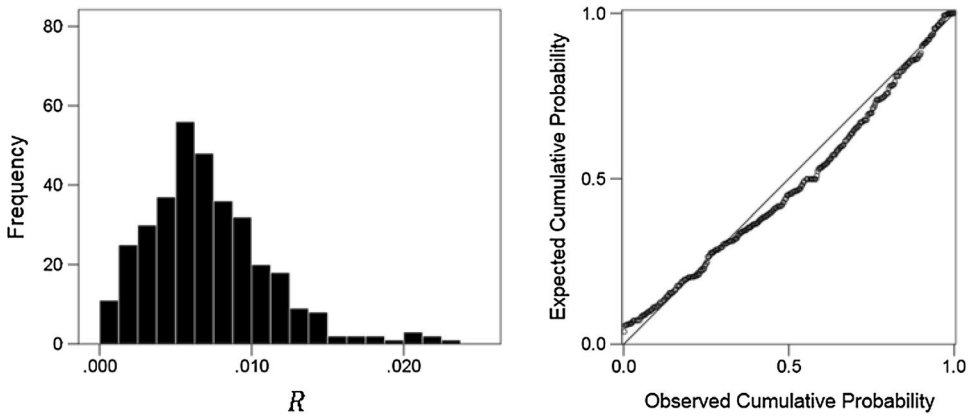

Fig. 1 *Left panel* frequency distribution of *R*. *Right panel* probability–probability (P–P) plot of the same data to show deviation from normality (*diagonal line*)

To find the appropriate transformation, we calculated the Box–Cox exponent (Box and Cox 1964), λ, namely the exponent to which R should be raised to normalize its distribution.

$$R_i'(\lambda) = \frac{R_i^{\lambda} - 1}{\lambda}, \tag{3}$$

where $i = 1, N$ ($N = 343$ R values available). Next, we computed the normal score of each R_i, i.e., its expected value of order statistic from a normal distribution, using the Blom (1958) version, as follows. Let K_i be the rank of R_i, such that $1 \leq K_i \leq N$. The scaling transformation for the rank is

$$q_i = \frac{K_i - 3/8}{\mathrm{N} + 1/4} \tag{4}$$

and the Blom normal score corresponding to the observation with rank K_i is:

$$B_i = \Phi^{-1}(q_i), \tag{5}$$

where $\Phi()$ is the normal cumulative distribution function.

To find out the value of λ which is most appropriate to transform R_i to $R_i'(\lambda)$ such that the distribution of the latter is closest to normal, we varied λ systematically from −5.00 to +5.00 in 1/100 steps and computed the Pearson correlation coefficient between $R_i'(\lambda)$ and B_i. This coefficient indicates the closeness of the distribution of $R_i'(\lambda)$ to a normal distribution. The outcome of this procedure is shown in the "normality plot" of Fig. 2 which plots the correlation coefficient above against λ. It can be seen that the distribution is unimodal with a peak at $\lambda = 0.46$ (correlation = 0.996264). This value is very close to 0.5 (the correlation at $\lambda = 0.5$ was 0.996083); hence, a square-root transformation was dictated.

$$R' = R^{0.5} = \sqrt{R}. \tag{6}$$

Indeed, a square-root transformation made the distribution of R' more symmetric and closer to normal (Fig. 3). Hence, the square-root-transformed resilience R' was used in all statistical analyses.

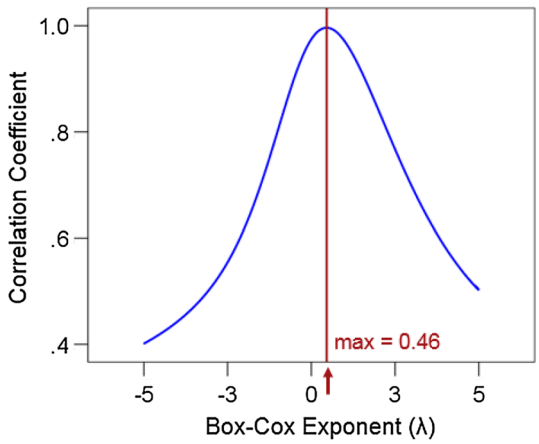

Fig. 2 Box–Cox normality plot. The correlation coefficient between the data raised to the Box–Cox exponent λ in the abscissa and Blom's normal score is plotted against the exponent λ. The maximum value of the distribution of the correlation (*vertical line*) indicates the exponent to which data values should be raised to approximate a normal distribution as close as possible (see text for more details)

ApoE genotyping

Participants provided a blood sample that was used for genetic testing. DNA samples were genotyped using PCR amplification followed by restriction enzyme digestion. Each amplification reaction contained PCR buffer with 15 mmol/L $MgCl_2$ ng amounts of genomic DNA, 20 pmol apoE forward (5N TAA GCT TGG CAC GGC TGT CCA AGG A 3N) and reverse (5T ATA AAT ATA AAA TAT AAA TAA CAG AAT TCG CCC CGG CCT GGT ACA C 3N) primers, 1.25 mmol/L of each deoxynucleotide triphosphate, 10% dimethylsulfoxide, and 0.25 µL Amplitaq DNA polymerase. Reaction conditions in a thermocycler included an initial denaturing period of 3 min at 95 °C, 1 min at 60 °C, and 2 min at 72 °C; followed by 32 cycles of 1 min at 95 °C, 1 min at 60 °C, and 2 min at 72 °C; a final extension of 1 min at 95 °C, 1 min at 60 °C, and 3 min at 72 °C. PCR products were digested with HhaI

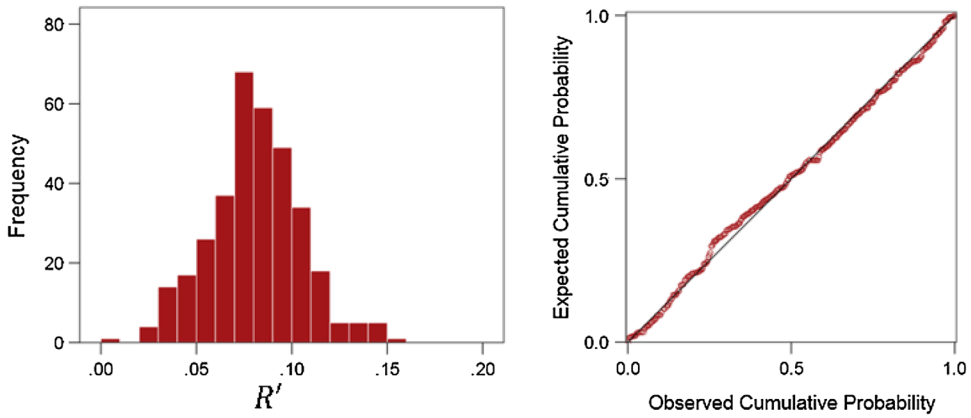

Fig. 3 *Left panel* frequency distribution of R'. *Right panel* probability–probability (P–P) plot of the same data to show closeness normality (*diagonal line*)

and separated on a 4% agarose gel which was stained with Ethidium Bromide. Known apoE isoform standards were included in the analysis.

Data analysis

Standard statistical analyses were carried out using the IBM SPSS statistical package (version 24). ApoE genotype was recorded into a new variable to reflect the corresponding number of CysR/mole: E2/E2 = 4 CysR/mole (n = 4); E3/E2 = 3 CysR/mole ($n = 38$); E4/E2 = 2 CysR/mole ($n = 9$); E3/E3 = 2 CysR/mole ($n = 209$); E4/E3 = 1 CysR/mole ($n = 78$); E4/E4 = 0 CysR/mole ($n = 5$). To examine the influence of apoE CysR/mole on resilience, we conducted a linear regression in which the number of CysR/mole, gender, and age were used as predictors of resilience. Initial analyses showed that neither age nor gender had a statistically significant effect, hence all subsequent analyses [analysis of variance (ANOVA), linear regression] were performed directly on R' as the dependent variable without covariates. Finally, we also performed an ANOVA to evaluate differences in resilience according to presence of E2 (E2/2, E2/3) and E4 (E4/4, E3/4) alleles.

Results

Effect of ApoE on resilience

Resilience was higher in the presence of the E2 than the E4 allele ($P = 0.008$; Fig. 4). More specifically, there was a systematic increase in resilience from the E4/4 genotype to E2/2 genotype (Fig. 5). This suggested that the number of CysR/mole could be a good predictor of resilience. This was confirmed by the results of a linear regression analysis which yielded a positive and highly statistically significant

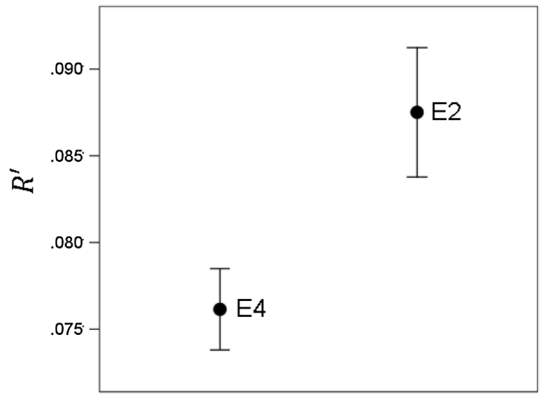

Fig. 4 Means ± SEM of R' of participants with the apoE2 allele (E2/2 and E2/3 genotypes, $N = 42$) and apoE4 allele (E4/4 and E3/4 genotypes, $N = 83$)

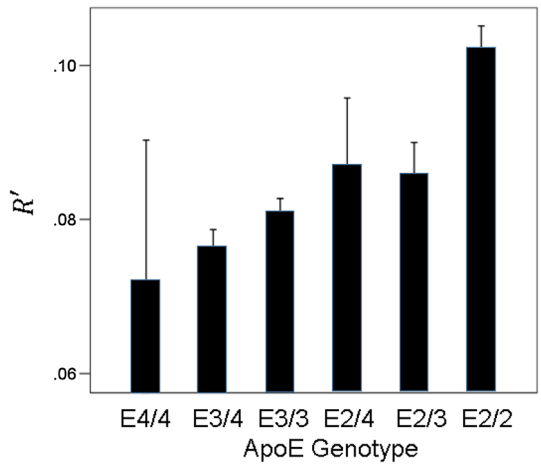

Fig. 5 Means ± SEM of R' for the stated apoE genotype

effect of CysR/mole on R': $b = 0.005$, $\beta = 0.147$, $P = 0.006$, where b is the regression coefficient for R' and β is the

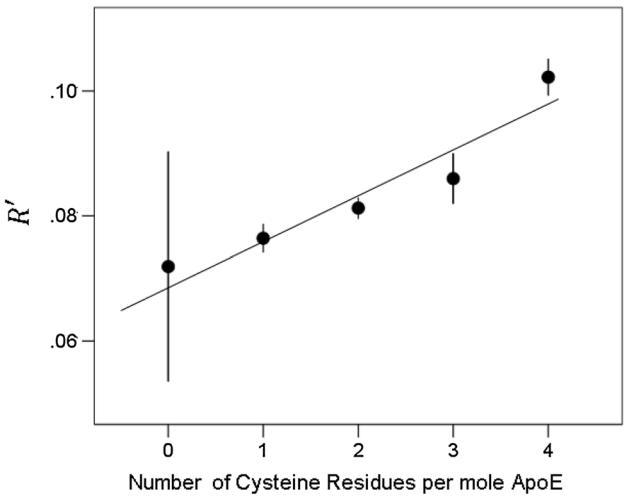

Fig. 6 Means ± SEM of R' for the stated number of apoE CysR/mole (see text for details)

corresponding standardized regression coefficient. This effect is illustrated in Fig. 6.

Discussion

In the present study we document the effect of apoE on resilience to trauma. Our findings highlight protective effects of apoE2 and complement previous research demonstrating systematic effects of apoE CysR/mol on brain health (Leuthold et al. 2013).

ApoE and resilience

In the present study, resilience to trauma was significantly higher among E2 carriers (E2/E2, E2/E3) than among E4 carriers (E3/E4, E4/E4), and systematically decreased from the E2/E2 genotype to the E4/E4 genotype. These findings suggest that the E2 allele plays a protective role and promotes resilience to trauma. The differential effects of the E2 and E4 alleles observed here are in accord with a vast literature evaluating associations of apoE genotype and AD. It is well established that ApoE genotype is a robust determinant of AD risk, with homozygous E4 carriers at considerably higher odds of developing AD than heterozygous E4 carriers and other allelic variations; conversely, ApoE2 is associated with decreased risk of AD and is considered neuroprotective (Corder et al. 1993; Farrer et al. 1997). The present results suggest that the neuroprotective effects of the E2 allele extend beyond AD risk and may promote overall brain health.

Neuroprotection and CysR/mole

The neuroprotective effects of the E2 allele may be conferred, at least in part, by the presence of additional cysteines relative to other isoforms. The three ApoE isoforms are distinguished by the presence of either a cysteine or arginine residues at two loci (Weisgraber et al. 1981); the E2 isoform has two cysteines, the E3 has one cysteine and one arginine, and the E4 has two arginines. These single amino acid substitutions confer significant structural and functional differences including differences in conformational stability, ability to bind to lipoprotein receptors, and binding and clearance of amyloid-beta peptides, as well as differential effects on synaptic functioning and neurogenesis, among others (Hatters et al. 2006; Liu et al. 2013; Mahley and Rall 2000). For instance, relative to E3 (1 CysR/mole), the E4 (0 CysR/mole) is associated with decreases in synaptic function, vascular and mitochondrial function, lipid glucose metabolism, neurogenesis, and amyloid-beta clearing, and increases in brain atrophy, neuronal toxicity, amyloid-beta aggregation, tangle formation, and aberrant brain activity, all of which are related to AD pathogenesis (Liu et al. 2013). Even among cognitively healthy women, differences in the number of CysR/mole are systematically associated with differences in synchronous neural interactions, with the 4-CysR/mole (E2/E2) reflecting optimal brain health (Leuthold et al. 2013). Here, we demonstrated that resilience to trauma increases systematically as cysteines increase from 0-CysR/mole (E4/E4) to 4-CysR/mole (E2/E2). We have previously demonstrated that among healthy individuals, but not those with posttraumatic stress disorder, resilience to trauma is characterized by neural plasticity (James et al. 2013); it is possible that enhanced neural plasticity observed in that study may be partially determined by apoE.

Neuroprotective mechanisms

Considerable effort has been placed on understanding the mechanisms that contribute to neurodegeneration in E4 carriers; as summarized by Mahley et al. (2009), these include increased amyloid-beta production, destabilization of membranes and apoptosis, and proteolytic cleavage resulting in tangle-producing fragments and disruptions to mitochondria. In contrast, the specific neuroprotective mechanisms of the E2 allele (and additional CysR/mole) are not well understood. Mahley and Rall (2000) suggest that the relative superiority of E2 (and E3) over the E4 allele stems from enhanced ability to repair neuronal damage and protect against damage via neurite outgrowth and cytoskeletal effects, respectively. Recent research also concluded that enhanced ApoE2 cortical abundance (relative to E3 and E4) coupled with its inability to bind to

low-density lipoprotein receptors may promote clearance of amyloid-beta (Conejero-Goldberg et al. 2014). Given the neurodegenerative effects of E4 and neuroprotective effects of E2, various apoE-targeted strategies are being developed to promote health and reduce risk of various neurodegenerative diseases (Liu et al. 2013). One line of work is aimed at converting apoE4 to other isoforms that may preserve brain health and provide protection against various insults (including trauma) to the brain.

ApoE: beyond the brain

Although the role of ApoE in risk and protection for neurodegenerative disorders is highly investigated, the effects of ApoE extend beyond the CNS. Indeed, ApoE is highly involved in cardiovascular disease (Mahley and Rall 2000; Anand et al. 2009), and has been shown to play a role in susceptibility to parasitic, bacterial, and viral infections (Mahley et al. 2009) and immunoregulation (Mahley and Rall 2000). In most of these cases, examination into the effects of different isoforms has not been explored. However, similar to the present findings, research on cardiovascular disease has determined that "apoE2 may actually be the most beneficial apoE isoform (in the absence of type III hypolipoproteinemia), while E4 carries the most risk" (Mahley and Rall 2000, p. 518), as confirmed later (Anand et al. 2009; Bennet et al. 2007; Ward et al. 2009). The protective role of E2 (or, for that matter, of higher number of CysR/mole) beyond neurodegeneration and mental health resilience is an active area of research.

Resilience: mechanisms and measurement

Resilience reflects the ability to maintain psychological and physical health in the face of adversity. Evidence from animal and human studies suggests that resilience involves a complex interplay of behavioral, neural, molecular, and hormonal mechanisms (Russo et al. 2012). Research investigating genetic influences on resilience is limited although some studies have demonstrated associations with genes involved in the functioning of the hypothalamic–pituitary–adrenal axis and various monoamine systems, and genes encoding for neuropeptide Y (as reviewed by Feder et al. 2009). In addition, animal studies have revealed evidence of epigenetic changes underlying variability in stress responses (Meaney and Szyf 2005). The present study adds to the relatively limited research regarding genetic basis for resilience and suggests that apoE may play a critical role in one's stress response.

Another issue concerns the measurement of resilience. Most often, self-report questionnaires are utilized to characterize resilience. Typically, such measures evaluate intrinsic factors such as personality characteristics (e.g., hardiness, sensitivity) and/or extrinsic factors such as social support or familial cohesion. A recent methodological review of 19 resilience measurement scales concluded that many existing scales were conceptually and theoretically questionable and that none could be considered a "gold standard" for measuring resilience (Windle et al. 2011). We took a different approach. Here, we measured resilience directly by evaluating PTSD symptoms in relation to lifetime trauma exposure rather than using proxy measures derived from personality and social characteristics. Our approach may benefit future investigators as it likely reflects a more accurate quantification of resilience than current approaches.

Concluding remarks

The results of this study bring forth two important points. First, they support our previous hypothesis (Leuthold et al. 2013) that the protection (or susceptibility) conferred by the apoE molecule is exerted along the continuum of number of CysR/mole, and is not categorical as the common reference to the apoE genotype might suggest. Second, the focus on resilience to trauma suggests that a "resilience" framework is a more suitable platform regarding effects of apoE than the traditional susceptibility/protection dichotomy. More specifically, we postulate that the number of CysR/mole confers a variable resilience to insults of various kinds, depending on the domain (e.g., the brain, the cardiovascular system, blood lipids, etc.). The concept of resilience is overarching and transcends specific organ systems. As in the case of trauma and the reaction to it, it would be useful to define the corresponding entities (insult and reaction to it) in other systems. For example, the role of apoE in coronary artery disease (CAD) (Anand et al. 2009) presupposes factors (e.g., dietary "insults") and reactions to those factors (e.g., formation of atherosclerotic plaques) that lead to the development of CAD. A "cardiovascular resilience" could be quantified in a similar way as in this study, if the insults and the reactions to them were quantified. Then the relation of this cardiovascular resilience to the number of CysR/mole apoE could be rigorously evaluated: we predict that an effect similar to the one found in this study would be found there too. We believe that this fairly general, domain-independent framework, would unify the multifaceted effects of apoE in different systems and would allow comparisons of the effects across various organ systems.

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