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Childhood trauma interacts with ApoE to influence neurocognitive function in women living with HIV

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Abstract

HIV-associated neurocognitive disorder (HAND) describes a spectrum of behavioural, motor and cognitive disturbances that can occur secondary to HIV infection. Less severe forms of the disorder persist despite advances in antiretroviral medication efficacy and availability. Childhood trauma (CT) may predispose individuals to developing HAND. As genetic variation in human apolipoprotein E (ApoE) has been implicated in cognitive decline and may mediate the development of long-term health outcomes following CT, we investigated the influence of ApoE and CT on cognitive function in the context of HIV. One hundred twenty-eight HIV-positive Xhosa women completed the Childhood Trauma Questionnaire-Short Form (CTQ-SF) as well as the HIV Neurobehavioral Research Center neurocognitive test battery. rs7412 and rs429358 were genotyped using KASP assays, and this data was used to determine the ApoE isoform. Baseline differences in demographic and clinical variables according to CT exposure were calculated. Analysis of covariance was used to assess the contributions of CT and *ApoE* variants, as well as their interaction, to cognitive function. Eighty-eight participants reported experiencing CT. The rs7412 C allele protected against the harmful effect of CT on motor scores using an additive model. The interaction of ApoE ϵ 4 and CT was associated with worse attention/working memory scores. ApoE ϵ 4, alone and in combination with CT, is associated with poorer cognitive function. Further research into this gene-environment interaction may assist in identifying at-risk individuals for targeted interventions.

Keywords

ApoE; Childhood trauma; Cognitive function; HIV-associated neurocognitive disorder

Introduction

Approximately 36.7 million people worldwide were infected with human immunodeficiency virus (HIV) in 2016 (UNAIDS 2017). The majority of affected individuals reside in sub-Saharan Africa, where HIV/AIDS presents a serious public health burden (UNAIDS 2017). Among the complications of infection is the development of HIV-associated neurocognitive disorder (HAND), a term that encompasses a spectrum of behavioural, cognitive and motor disturbances consequent to HIV infection (Clifford and Ances 2013). HIV crosses the blood-

brain barrier early in the course of infection, where it can foster an inflammatory milieu with potentially neurotoxic effects (Ene 2018). Despite the success of combined antiretroviral therapy (cART) in reducing HIV-related morbidity and mortality, milder forms of HAND predominate comprising a mixed pattern of both cortical and subcortical features with varying degrees of functional impairment in activities of daily living (Saloner and Cysique 2017). Recent estimates suggest that as many as 50% of people living with HIV are affected by milder forms of HAND (Clifford and Ances 2013; Saloner and Cysique 2017). This is particularly concerning given that HAND is also associated with unemployment, reduced adherence to antiretroviral medication and poorer quality of life, thus heavily impacting affected individuals as well as broader society (Heaton et al. 2004; Woods et al. 2011).

Genetic variation in human apoprotein E (ApoE) has been identified as a possible risk factor for developing HAND, although this is still a subject of debate (Geffin and McCarthy 2018). The *ApoE* gene encodes a 34 kDa protein involved in transport and metabolism of both triglyceride and cholesterol (Bellosta et al. 1995; Mannila et al. 2013). Whilst ApoE is at its highest concentration in the liver, it is also found in the brain and cerebrospinal fluid, where it plays an important role in the redistribution of lipids and cholesterol within the central nervous system (Elshourbagy et al. 1985; Bellosta et al. 1995). Single nucleotide polymorphisms (SNPs) in exon 4 of *ApoE* encode base pair C/T transitions at rs7412 and rs429358, alternately giving rise to cysteine/arginine interchanges at residue positions 112 and 158 in the ApoE protein (Weisgraber et al. 1981). The combination of cysteine and arginine in turn determine the three primary ApoE isoforms, with Cys¹¹²-Cys¹⁵⁸, Cys¹¹²-Arg¹⁵⁸ and Arg¹¹²-Arg¹⁵⁸ designating ApoE ε2, ε3 and ε4 isoforms respectively (Mannila et al. 2013). The role of ApoE ε4 in neurocognitive impairment has been widely investigated, particularly in relation to Alzheimer's disease, a neurodegenerative disorder characterised by memory impairment (Strittmatter et al. 1993; Saunders et al. 1993; Liu et al. 2012). The functions of ApoE extend beyond its traditional involvement in lipid metabolism, and ApoE includes processes related to brain development, toxicity, inflammation, energetics, vasculature, as well as synaptic plasticity (Kim et al. 2009; Wolf et al. 2013). Consequently, ApoE may play a role in some of the pathophysiological mechanisms underlying the deleterious consequences of HIV in the brain (Corder et al. 1998). Studies that have investigated the link between genetic variation in *ApoE* and HAND have found evidence both for (Dunlop et al. 1997; Corder et al. 1998; Spector et al. 2010; Andres et al. 2011; Hoare et al. 2013; Mukerji et al. 2016; Wendelken et al. 2016) and against (Dunlop et al. 1997; Burt et al. 2008; Pemberton et al. 2008; Pomara et al. 2008; Sun et al. 2010; Joska et al. 2010; Morgan et al. 2013; Becker et al. 2015) its involvement in HAND. These contradictory findings may in part be due to the failure to assess the interaction of ApoE with other risk factors (Cooley et al. 2016).

Epidemiological research into environmental drivers of psychiatric disorders has identified childhood trauma (CT) as a risk factor for later psychopathology (Uher and Zwickler 2017; Hunt and Tomlinson 2018). Whilst the term “childhood trauma” encompasses a heterogeneous range of early life adversities of different timing, duration, severity and type, these experiences are unified by their potentially harmful consequences, including neurobiological effects on the developing central nervous systems and the possibility of long-term maladaptive mental health outcomes (Glaser 2002; Bick and Nelson 2016). The

exact mechanisms linking CT with later life psychopathology are not yet fully resolved, however several common pathophysiological mechanisms underlie both CT and HAND. Briefly, both developmental stress and HAND are associated with alterations to the hypothalamic-pituitary-adrenal axis stress response, heightened inflammation and increased oxidative stress (reviewed in Womersley et al. (2017)). Consequently, developmental stress-elicited alterations in these systems may increase allostatic load and essentially prime pathophysiological mechanisms underlying HAND. Accordingly, CT has been implicated in the development of HAND (Spies et al. 2012, 2016, 2017). In spite of strong evidence individually linking developmental stress and ApoE to HAND, as well as the likely role of gene-environment interactions in this disorder, the interaction of these two predictors (ApoE and CT) has not to our knowledge been investigated. Therefore, this study was conducted to examine how CT interacts with *ApoE* to influence neurocognitive function in HIV-positive South African women of Xhosa ethnicity. We hypothesised that carriers of the *ApoE* ϵ 4 isoform would perform worse on cognitive tests, and that these deficits would be further accentuated by a history of CT. Studies have associated *ApoE* ϵ 4 genotype with a range of cognitive effects in HIV including executive function, perceptual speed, verbal fluency, learning, memory and global cognitive function (Andres et al. 2011; Chang et al. 2011; Hoare et al. 2013; Panos et al. 2013; Mukerji et al. 2016; Wendelken et al. 2016). The interaction of CT and HIV has also been associated with a variety of cognitive impairments including diminished attention/working memory, executive function, language, motor skill and processing speed (Spies et al. 2016, 2017; Clark et al. 2018). Based on the broad spectrum of possible impairment, we thus decided to examine both global cognitive function as well as cognitive domains in our study.

Methods

Study design and participants

This analysis forms part of a larger investigation into the psychosocial and genetic determinants of HAND in South African women. We have previously reported on the role of HPA axis variants on neurocognitive function in this study group (Jacobs et al. 2018). Given the conflicting data on the role of ApoE in HAND, we also sought to investigate the role of *ApoE* variation. We apply a similar analytic approach, namely *ApoE* x CT interaction on HAND, in this paper. Briefly, participants were recruited from community health care clinics in and around Cape Town between 2008 and 2015. Consenting participants were screened for eligibility according to the following exclusion criteria: history of schizophrenia, other psychotic disorders, bipolar disorder; psychotropic medication use in the preceding month; current drug or alcohol abuse; previous head trauma; any current seizure disorder; and history of central nervous system infection, including hepatitis B and C infection. The study sought to recruit women living with HIV, between eighteen and 65 years of age, who were fluent in isiXhosa, English and/or Afrikaans and with a minimum literacy level commensurate with fifth grade. Consenting participants underwent a battery of neuropsychological tests administered by a trained research psychologist at the Stellenbosch University Faculty of Medicine and Health Sciences. This study was carried out in accordance with the recommendations of the Declaration of Helsinki with written informed

consent from all subjects. The protocol was approved by the Stellenbosch University's Human Health Research Ethics Committee (study reference number: N07/07/153).

Demographic and clinical measures

Sociodemographic data were collected for all participants and included information on age, education, relationship status, self-declared ethnicity and employment. The MINI-International Neuropsychiatric Interview-Plus (M.I.N.I.-Plus) was used to screen for any psychiatric diagnoses (Sheehan et al. 1998). HIV seropositivity was confirmed by an enzyme-linked immunosorbent assay.

Childhood trauma and depression assessments

The Childhood Trauma Questionnaire – Short Form (CTQ-SF) (Bernstein, DP and Fink, L 1998) and Center for Epidemiological Studies – Depression Scale (CES-D) (Radloff 1977) were used to measure self-reported experience of CT and depressive symptomatology, respectively. Briefly, the CTQ-SF is a well-validated 28-item questionnaire that examines the experience of trauma prior to 18 years of age and provides information on five trauma subtypes, namely emotional, physical and sexual abuse, and emotional and physical neglect. For categorical analyses, the threshold CTQ-SF total score was set at 41 (indicative of low-to-moderate severity) (see Spies et al. 2016). The CES-D is a 20-item screening measure of depression in the past 7 days.

Neurocognitive assessment

All participants completed the HIV Neurobehavioral Research Center (HNRC) battery (Heaton et al. 2008). This battery consisting of seventeen tests uses Western neuropsychological measures that have been culturally adapted for the South African context (Spies et al. 2017). The tests tap into seven domains of cognitive function, namely motor ability, processing speed, verbal fluency, learning, delayed recall, attention/working memory and executive function. Raw test scores were subjected to regression analyses, using age and education as predictor variables, and test scores as the outcome. The resultant residuals were in turn used to calculate a studentized residual. The studentized residuals from relevant tests were then summed to create a domain Z-score. Finally, the mean of the seven domain Z-scores was calculated and provided an age- and education-adjusted composite global cognitive score (Spies et al. 2012).

Genotyping

DNA was extracted from whole blood using a phenol-chloroform procedure and the concentration and purity of the extracted DNA was checked using a NanoDrop 2000c spectrophotometer (ThermoFisher Scientific, Walton, MA, USA). Samples were genotyped for the two SNPs of interest, rs7412 and rs429358, using Kompetitive Allele Specific PCR (KASP) genotyping chemistry at LGC (Middlesex, UK). Briefly, the KASP assay makes use of a polymerase chain reaction-based technique to allow biallelic discrimination of SNPs (LGC 2013).

Statistical analysis

Shapiro-Wilk W tests were used to assess the distribution of the data and indicated that all variables, except CTQ-SF, CES-D and motor scores, were normally distributed. Descriptive statistics for parametric and non-parametric data are reported as mean $\pm$ standard deviation (SD) and median and interquartile range (IQR) respectively, whilst data for dichotomous variables are represented as counts and percentages. Independent sample t-tests, Mann-Whitney U tests and Pearson's chi-squared tests were used as appropriate to determine differences in demographic and clinical variables by CT exposure.

As a previous study has suggested that rs7412 and rs429358 may have distinct effects on dementia risk, beta amyloid deposition and lipid metabolism (Bennet et al. 2010), we conducted three parallel analyses to assess the contributions of each SNP, as well as ApoE isoform, on cognitive function. Regression analyses examining rs7412 and rs429358 assumed additive models. Genotyping for rs7412 (*T>C*) and rs429358 (*T>C*) was successfully performed for 128 and 126 participants respectively. Thus, analyses examining the influence of rs429358 on cognitive function are limited to the results of 126 women for which genotyping results were available. Regression models examining the influence of ApoE isoform on cognitive function also assumed additive models, with study participants receiving scores based on the number of ϵ 4 alleles carried (i.e. scores of 0, 1 or 2 for non-carriers, heterozygous and homozygous participants respectively). Of the 126 participants for which both rs7412 and rs429358 genotype information was available, thirteen were *C/T* heterozygotes at both SNPs. As these participants may carry either ϵ 1/ ϵ 3 or ϵ 2/ ϵ 4 combinations, our ApoE isoform analyses were limited to the 113 participants with definitive ApoE results.

HIV infection can produce a range of cognitive impairments with marked variation in the course, severity and the domains that are affected (Woods et al. 2009). Therefore, we included both global cognitive scores and the seven domain scores in our analyses. The association between cognitive scores (domain and global cognitive scores) and each of the two SNPs, rs7412 and rs429358, as well as ApoE isoforms, were assessed using general linear models. We used analyses of covariance (ANCOVA) to test the contribution of genotype and CT to global and cognitive domain scores. Briefly, generalised linear models with cognitive function as the dependent variable, and genotype and CTQ-SF scores as predictors, were generated. Analysis of variance and chi-squared tests were used to determine whether including the genotype $\times$ CTQ-SF interaction explained more of the variance in cognitive scores. CES-D scores and ARV treatment were included as covariates in all models. Our linear models generated an overall p-value, as well as p-values for the main and interaction effects. Due to the fact that these results stem from the same, rather than independent, models, correcting for multiple testing was not required.

All analyses were conducted using functions from R (R Development Core Team 2018) and the associated packages *SNPassoc* (González et al. 2014) and *HardyWeinberg* (Graffelman et al. 2018). An alpha value of 0.05 was used to determine significance.

Results

This study enrolled 128 HIV-positive South African women ranging from 21 to 50 years of age (mean age = 33.2 years). More than 68% ($n = 88$) of participants reported a history of CT. Women who reported CT had higher CES-D scores ($p = 0.010$) but did not otherwise differ from controls in respect to age, education, marital status, employment or ARV treatment. Demographic and clinical characteristics, as well as comparisons based on CT exposure, are reported in Table 1.

The most common genotype within our population was *CC* and *TT* for rs7412 and rs429358 respectively. Both SNPs were in Hardy Weinberg equilibrium in our sample (Table 2). Our analyses indicated no association between rs7412 genotype and global cognitive score under codominant, dominant, recessive, overdominant or log-additive models, whilst rs429358 was not associated with global cognitive score under a codominant model ($p = 0.062$, data not shown).

Regression analysis indicated a trend towards an association between reduced verbal fluency and rs7412 genotype ($p = 0.081$), with each *C* allele corresponding to a reduction in verbal fluency score. A generalised linear model to assess the influence of CT and rs7412, and their interaction, on motor scores revealed that increasing CT experience was associated with lower motor function ($p = 0.012$) whilst rs7412 was not associated with motor function ($p = 0.061$). However, the interaction between the rs7412 *C* allele and CT was associated with significantly lower motor function ($p = 0.018$), and including the rs7412 x CTQ-SF interaction in the model explained significantly more of the variance in motor function than these two factors acting individually ($p = 0.017$) (Table 3 and Fig. 1).

Regression models analysing the effect of CT and rs429358, including their interaction, on attention/working memory indicated a trend towards an increase in attention/working memory score with CT ($p = 0.069$). However, the interaction between the rs429358 *C* allele and CT was not associated with a reduced score in this domain ($p = 0.079$). Lastly, including the interaction between rs429358 and CTQ-SF score in the model produced a trend towards explaining more of the variance in attention/working memory ($p = 0.076$).

Of the 113 participants for whom we have ApoE isoform genotyping data, 40 carry the $\epsilon 4$ allele (33 heterozygous and 7 homozygous participants). The prevalence of the $\epsilon 4$ isoform did not differ according to CT exposure (Table 4). Our analyses indicated that the interaction between the isoform and CTQ-SF score was predictive of worse attention/working memory ($p = 0.021$), and that including this interaction in the model explained more of the variance in this domain ($p = 0.019$) (Table 5 and Fig. 2). The calculated Cohen's f^2 value for the CTQ-SF x ApoE $\epsilon 4$ isoform interaction on attention/working memory was 0.09, indicating a small effect size. The interaction between ApoE $\epsilon 4$ and CTQ-SF score was also nominally associated with reductions in executive function ($p = 0.094$) and global scores ($p = 0.071$), with these interactions producing trends towards explaining more of the variance in the executive function and global scores ($p = 0.091$ and $p = 0.068$ respectively).

Discussion

Our study sought to determine whether the combination of CT and genetic variation in *ApoE* contributes to cognitive function in women living with HIV in South Africa. More than two-thirds of the sample reported experiencing trauma before the age of 18 years. This high proportion of women with childhood trauma is in keeping with previously published reports in South Africans (Jewkes et al. 2010; Gibbs et al. 2018; Womersley et al. 2018), including the results of a community-based study by Meinck et al. (2016), which found that 68.9% of the 3515 children interviewed had experienced physical, sexual or emotional abuse. Self-reported depressive symptomology was significantly higher in our study participants who reported CT. A similar link between depression and CT has been previously reported in studies of HIV-positive South African women (Spies and Seedat 2014; Spies et al. 2018). With respect to *ApoE* genotyping data, 35.4% of the 113 participants were found to carry the $\epsilon 4$ isoform.

Our model analysing the individual contributions of rs7412 and CT to motor scores, indicated that CT experience was significantly associated with reduced motor function. The interaction between rs7412 and CTQ-SF also interacted to influence motor scores, with the *C* allele protecting against worse motor function in the presence of CT. Similar harmful effects of CT on cognitive function have been previously reported. A neuroimaging study investigating the contribution of HIV and early life stress to HAND, found that HIV-positive women with a history of CT had poorer performance on motor tests compared to HIV-positive women who did not report experience of CT (Spies et al. 2016). To the best of our knowledge, rs7412 has not been previously associated with motor function. However, this may in part be because the effects of rs7412 alone on cognitive function have yet to be studied. Though our finding of a negative association between CT and motor scores is in keeping with the literature, why, or how, developmental stress interacts with genetic predisposition to affect specific domains of cognitive function is not yet clear.

Our findings indicated that *ApoE* $\epsilon 4$ and CT interacted to reduce attention/working memory. Previous studies have suggested that *ApoE* variation may moderate the association between developmental stress and later psychological health. In a study that examined the role of *ApoE* genotype and adverse childhood experiences on depressive symptoms in older adults (50 – 70 years of age), early life stress was associated with increased depressive symptoms in carriers of the $\epsilon 4$ isoform compared to non-carriers (Park et al. 2015), suggesting that $\epsilon 4$ carriers may be more sensitive to stress than non-carriers or, alternatively, may be more vulnerable to the deleterious effects of early life adversity on later mental health (Park et al. 2015). A study of patients with bipolar disorder indicated that CT, specifically childhood sexual abuse, interacted with *ApoE* $\epsilon 4$ to reduce memory performance, as measured by a composite score of tests to assess visual recall memory, total verbal learning and recognition memory (Savitz et al. 2007).

Following initial infection, HIV crosses the blood-brain-barrier and can produce diffuse neuropathology, affecting both cortical and subcortical grey matter as well as white matter tracts linking different brain regions (Janssen et al. 2015; van Zoest et al. 2017; O'Connor et al. 2018; Li et al. 2018; Oh et al. 2018). This non-localised pattern of infection may explain

why HAND is characterised by a broad range of possible impairments (Woods et al. 2009). Indeed, though multiple HAND diagnostic criteria have been developed, they share the requirement of a comprehensive test battery that assesses multiple domains of function (Tierney et al. 2017). The presentation of HAND has also changed with advances in antiretroviral medication. Prior to the advent of cART, impairment in motor, speed of information processing, and verbal fluency domains predominated whereas more recent patterns of impairment primarily reflect difficulties with learning and executive function (Heaton et al. 2011). Our study group was recruited between 2008 and 2013, and thus are likely to have experienced changing ARV availability and efficacy following South Africa's development of an antiretroviral rollout programme and improving ARV regimens (Evans 2013; Meintjes et al. 2017). The variable presentation of HAND thus guided our decision to examine the interactive effects of CT and *ApoE* on global as well as cognitive domain scores.

ApoE may contribute to HAND via a range of mechanisms including infection, immunosuppression, inflammation, oxidative damage, and synaptic plasticity. Firstly, genetic variation in *ApoE* may directly affect HIV infection and replication in the brain. A basic science study found that incubating cells in media containing the binding fragment of ApoE reduced HIV infection (Dobson et al. 2006). Interestingly, susceptibility to infection is dependent on ApoE isoform, with viral attachment to the cell membrane and fusion with the target cells more likely when cells were incubated in the presence of ApoE ϵ 4, compared to ϵ 3 (Burt et al. 2008). In addition to a more rapid rate of infection, ϵ 4 carriers have less efficient efflux of cholesterol from cells. Consequently, more cholesterol is available to support the plasma membrane lipid rafts required for HIV viral assembly and budding, with a study finding that greater membrane or viral envelop cholesterol increases the infectivity of HIV (Burt et al. 2008). The low-density lipoprotein receptor-related protein (LDLR), is responsible not only for the uptake of ApoE into neurons, but also the uptake of HIV-1 transactivator (Tat), a neurotoxic viral protein which has released by cells infected with HIV (Liu et al. 2000). The genetic variation in *ApoE* encoding cysteine/arginine transitions at residues 112 and 158, occurs in close proximity to the LDLR receptor binding region. As a result, the different tertiary structures of ApoE ϵ 3 and ϵ 4 proteins may affect their ability to bind to the LDLR and competitively inhibit LDLR-mediated Tat uptake into neurons (Dobson et al. 2006; Mahley et al. 2009). Altered tertiary structure of the ApoE protein may also impact the production of enzymes involved in the response to oxidative stress, thereby explaining the increased sensitivity of the ϵ 4 carriers to the damaging effects of oxidative stress, including that induced by Tat (Miyata and Smith 1996; Pocernich et al. 2004; Urfer-Buchwalder and Urfer 2017).

ApoE influences the immune response to infection with the results of basic science experiments indicating an immunosuppressive effect on lymphocyte proliferation (Cardin et al. 1988). A more recent functional genomics investigation in HIV-exposed cultured astrocytes and neurons, found ApoE isoform-dependent effects on gene expression with ϵ 3 genotype cultures displaying increased expression of genes related to interferon-induced responses and antigen presentation, both indicators of a more robust innate immune response to HIV challenge (Geffin et al. 2013). Using a similar methodology in a later study, the authors found that HIV exposure in human neural progenitor cells decreased expression of

genes involved in neurogenesis in recombinant $\epsilon 4$ cells, suggesting that HIV potentiates the harmful effects of this isoform on neurogenesis and possibly neuronal survival (Geffin et al. 2017). Despite these immunosuppressive effects, $\epsilon 4$ has also been linked to increased inflammatory processes, a key feature of HIV-related neuropathology (Hong and Banks 2015). Compared to ApoE $\epsilon 3$, the $\epsilon 4$ protein is more likely to undergo proteolytic cleavage, which increases the level of circulating $\epsilon 4$ fragments. These fragments in turn have been found to increase gene expression of interleukin 1 beta, a pro-inflammatory cytokine, as well as protein levels of matrix metalloproteinase 9, a cytokine-regulated metalloproteinase implicated in neuroinflammation, though the mechanism responsible for this effect has not yet been resolved (Dafnis et al. 2012). A neuroimaging study examining the role of ApoE on HIV-related differences in cognitive capacity and brain metabolism, found that HIV-positive $\epsilon 4$ carriers had higher frontal white matter levels of myoinositol, a glial marker associated with neuroinflammation, which was in turn associated with poorer fine motor speed (Chang et al. 2014). HIV-positive $\epsilon 4$ carriers also performed significantly worse on tests of executive function compared to HIV-negative controls without the $\epsilon 4$ allele. The authors suggested that these results may point to a synergistic effect of HIV infection and ApoE $\epsilon 4$ on neuroinflammation with downstream detrimental effects on cognitive function (Chang et al. 2014).

Finally, this ApoE isoform may influence neuronal remodelling and synaptic plasticity (Bellosta et al. 1995). Compared to $\epsilon 3$, the $\epsilon 4$ isoform has been linked to reduced growth of new projections in developing neurons as well as lower density of dendritic spines, the specialised synaptic contacts sites whereby neurons receive excitatory and inhibitory input (Bellosta et al. 1995; Nathan et al. 2002; Ji et al. 2003). These deficits limit compensatory mechanisms in the brain, such as neuronal remodelling, synaptic replacement, and dendritic outgrowth, and may underlie the increased vulnerability to age-related brain degenerative processes in $\epsilon 4$ carriers (Fagan et al. 1996). Thus ApoE $\epsilon 4$ may further decrease synaptodendritic integrity, the decline of which has been implicated as a means by which HIV infections drives cognitive decline (Levine et al. 2016).

The results of this study need to be interpreted in the light of several limitations. The results of several investigations into the genetic contributions to HAND suggest that the harmful effects of ApoE $\epsilon 4$ on cognitive function may be likely to be expressed at a later age (Valcour et al. 2004; Pomara et al. 2008; Panos et al. 2013; Mukerji et al. 2016; López et al. 2017). Such a temporally mediated effect could explain some of the divergent literature findings regarding the role of ApoE in HAND. Indeed Chang et al. (2011) propose an antagonistic pleiotropy theory of ApoE $\epsilon 4$ in HIV, suggesting an interaction between HIV, ApoE $\epsilon 4$ and age such that HIV-positive individuals carrying the $\epsilon 4$ allele may be vulnerable to accelerated brain aging. If *ApoE* variants do produce age-dependent effects, it is likely that the full scope of ApoE-mediated impairment in our study group would not yet be apparent, due to their relatively younger age (mean age = 33.2 years). Furthermore, our study was limited to women and thus the results may not be directly applicable to men. Sex-specific effects of ApoE were found in a study of language ability in 1000 Chinese individuals with harmful effects of rs7412 and rs429358 *C/T* genotypes limited to male participants (Zhen et al. 2017). Alternatively, in a study of mild cognitive impairment, ApoE $\epsilon 4$ was predictive of worse cognitive function in women but not in men (Altmann et al.

2014). With respect to neuropsychological scores, our analyses did not account for the possibility of trauma subtype-dependent cognitive effects. The results of a study examining the effect of childhood neglect, physical abuse and sexual abuse on cognitive function in adults, indicated that neglect was associated with a worse impact on cognition than physical and sexual abuse, suggesting that different forms of abuse may have specific consequences on neurocognitive function (Perez and Widom 1994). Furthermore, the duration of abuse is an important consideration. In a study of college-attending women, individuals with a history of sexual abuse during childhood performed worse on tests of scholastic aptitude and displayed poorer inhibitory responding in comparison to controls, with worse performance in short-term, verbal, visual and global memory scores associated with the duration of abuse (Navalta et al. 2006). Furthermore, though the CTQ-SF has shown robust validity, it is necessary to bear in mind that assessment of CT experience in adults relies on retrospective self-report and thus could be influenced by memory recall bias (Bernstein et al. 2003; Carpenter et al. 2009). Notwithstanding that our study examined global and domain scores of cognitive function, it is possible that assessing associations with individual test measures may yield different results. The small sample precluded multiple comparison of individual test scores. Indeed, a South African study on the contributions of ApoE isoform to HAND in a Xhosa population only found differences on the Hopkins Verbal Learning Test Delayed Recall component of the HIV Neurobehavioral Research Center test battery (Hoare et al. 2013). Finally, the relatively small sample size used for this investigation does limit the conclusions which can be drawn.

Despite these limitations, the findings of our pilot study examining the role of *ApoE* and CT on cognitive function in an HIV sample of relatively young women are intriguing. The field of gene-environment interactions holds great promise for elucidating the pathophysiology underlying complex neuropsychiatric conditions. However, it is important to remember that the findings documented here may be more specific to the population investigated, as ethnicity-dependent effects of ApoE on cognitive function have previously been reported (Barnes et al. 2013). Further studies examining the contribution to HAND in low- and middle-income country populations that bear the greatest burden of HIV infection, such as South African women, are needed. Our results require replication in larger and more diverse samples of male and female participants across the age range. However, the mechanisms underlying our observations can only be elucidated through functional studies, which were beyond the scope of our investigation. Finally, if ApoE is found to mediate the development of HAND, ApoE-targeted treatment strategies that are being investigated in Alzheimer's Disease could offer exciting possibilities for intervention in HAND (Asensi 2015; Zhao et al. 2018).

Conclusion

The phenotypic characteristics of HAND have evolved with research indicating a complex phenotype with genetic and environmental contributions. Our results indicate that genetic variation in *ApoE* influences different cognitive domains, and moreover acts synergistically with CT to worsen cognitive function in South African women living with HIV.

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Fig. 1.

The combination of rs7412 and childhood trauma influences motor function. Under an additive model, the interaction between rs7412 and childhood trauma is associated with lower motor domain Z-scores ($p = 0.018$). Including the interaction between rs7412 and childhood trauma explained significantly more of the variance in motor domain Z-score than genotype or CTQ-SF score alone ($p = 0.018$). A score of greater than or equal to 41 on the CTQ-SF was used as the cut-off value for the presence of childhood trauma.

Fig. 2.

The combination of ApoE $\epsilon 4$ isoform and childhood trauma influences attention/working memory. Under an additive model, the interaction of ApoE $\epsilon 4$ copy number and childhood trauma is associated with worse attention/working memory ($p = 0.021$). Including the interaction between $\epsilon 4$ and childhood trauma explained significantly more of the variance in attention/working memory domain Z-score than ApoE $\epsilon 4$ copy number or CTQ-SF score alone ($p = 0.019$). A score of greater than or equal to 41 on the CTQ-SF was used as the cut-off value for the presence of childhood trauma. CTQ-SF Childhood Trauma Questionnaire Short Form.

Table 1:

Demographic and clinical characteristics of study participants according to childhood trauma exposure

Variable	Childhood trauma exposure				
	No (<i>n</i> = 40)	Yes (<i>n</i> = 88)	<i>t</i>	χ^2	<i>p</i>
Mean age in years (SD)	32.0 (6.8)	33.7 (6.7)	-1.33	-	0.191
Mean years of education (SD)	10.5 (1.3)	10.0 (1.8)	1.70	-	0.091
Marital status, <i>n</i> (%)			-	0.79	0.477
Single/separate/widowed	30 (29.4)	72 (70.6)			
Married/cohabiting	10 (38.5)	16 (61.5)			
Unemployed, <i>n</i> (%)	24 (60.0)	61 (69.3)	-	1.07	0.319
On antiretroviral medication, <i>n</i> (%)	14 (31.1)	41 (46.3)	-	1.51	0.251
Median CES-D score (IQR)	4 (0 – 11.8)	14 (0 – 48.1)	-3.70		0.010 *
Median CTQ-SF score (IQR)	32.5 (29.0 – 36.0)	61.5 (53.0 – 77.5)	-18.09		< 0.001

CES-D Center for Epidemiological Studies - Depression Scale

* a significant different between participants with and without childhood trauma exposure.

Table 2:

Distribution of *ApoE* rs7412 and rs49358 genotypes amongst HIV-positive black South African female participants

SNP	Overall, <i>n</i>	<i>C/C</i> , <i>n</i> (%)	<i>C/T</i> , <i>n</i> (%)	<i>T/T</i> , <i>n</i> (%)	HWE p-value
rs7412	128	80 (62.5)	42 (32.8)	6 (4.7)	0.931
rs429358	126	7 (5.6)	46 (36.5)	73 (57.9)	0.886

HWE Hardy Weinberg Equilibrium, *SNP* single nucleotide polymorphism

Table 3:

Predictive value of CTQ-SF x rs7412 interactions on motor scores

Model	Degrees of freedom of residuals	Deviance of residuals	Degrees of freedom	Dev	Pr(>Chi)
rs7412 + CTQ-SF	123	145.19			
rs7412 + CTQ-SF + rs7412 * CTQ-SF	122	138.68	1	6.51	0.017

All models included antiretroviral treatment and Center for Epidemiological Studies – Depression Scale as covariates. *CTQ-SF* Childhood Trauma Questionnaire-Short Form.

Table 4:Prevalence of *ApoE* ε4 isoforms amongst 113 HIV-positive black South African female participants

	All participants (<i>n</i> = 113)	Childhood trauma exposure			
		No (<i>n</i> = 34)	Yes (<i>n</i> = 79)	χ^2	<i>p</i>
ApoE ε4 isoform carrier status				0.60	0.739
Non-carrier, <i>n</i> (%)	73 (64.6)	21 (61.8)	52 (65.8)		
Heterozygous, <i>n</i> (%)	33 (29.2)	10 (29.4)	23 (29.1)		
Homozygous, <i>n</i> (%)	7 (6.2)	3 (8.8)	4 (5.1)		

ApoE apolipoprotein E

Table 5:

Predictive value of CTQ-SF x ApoE ε4 interactions on attention/working memory

Model	Degrees of freedom of residuals	Deviance of residuals	Degrees of freedom	Dev	Pr(>Chi)
ApoE ε4 + CTQ-SF score	108	80.45			
ApoE ε4 + CTQ-SF score + ApoE ε4 * CTQ-SF score	107	76.54	1	3.91	0.019

All models included antiretroviral treatment and Center for Epidemiological Studies – Depression Scale as covariates. *CTQ-SF* Childhood Trauma Questionnaire - Short Form